Anesthesiological Aspects of Awake Craniotomy

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Anesthesiologische aspecten
van de wakkere craniotomie

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PREPARATION
vocal ANESTHESIA
STRESS
ANXIETY
ANALGESIA
SAFETY
SEDATION
local ANESTHESIA
MEMORY
COMFORT
PAIN
TRUST

I

Introduction and outline of the thesis

I. INTRODUCTION AND OUTLINE OF THE THESIS

To understand the current practice of awake craniotomy and the challenges and options linked to this procedure, this introduction will address the historic development of awake craniotomies, some general ideas behind the resection of brain tumors and some general ideas of patient centered care. These three aspects create the fundament on which the research presented here is founded.

The historic development from trepanations to today's awake craniotomies:

The history of awake craniotomy actually starts with trepanations, perhaps the oldest form of neurosurgery. Whilst a classic trepanation is just a burrhole, craniotomy is defined as the removal of a bone-flap. The oldest trepanned skull (estimated 7000 years old) was found at a Neolithic burial site of Ensisheim in France. Because the brain itself does not have nociceptors, this quite invasive procedure in principle can be performed with local anesthesia only.

Therefore, it is not surprising that skulls with evident signs of "successful" (the patient survived the procedure long enough to show even some kind of wound-healing of the skull) have been found in almost all cultures: Mesoamerican Indians, Ancient Egyptians, Romans, Greeks and Chineses.

Even Hippocrates (460-370 BC) has published some ideas about trepanation as therapy for fractures and/or contusions of the skull in his manuscript "on the injuries of the head". Hippocrates also described the fact, that brain and body are linked in a crossing manner: damage to the right hemisphere causes functional damage to the left part of the body and vice versa.

On the way to today's awake craniotomies some side-paths have been followed: Eristratus (about 290 BC) claimed that there exists a relationship between the number of gyri and sulci in the brain and the intelligence of the person. Galenus (129-199 AC) believed, that there was no relevant function located in the brain cortex. In his ideas, the "soul" of humans was located around the heart and the diaphragm and up to the 17th century many people considered the brain cortex just as a protective layer without a relevant function.

The operation of Trepan, from Illustrations of the Great Operations of Surgery: Trepan, Hernia, Amputation, Aneurism and Lithotomy, by Charles Bell, 1815. (John Martin Rare Book Room at the Hardin Library for the Health Sciences, University of Iowa.)

On the other hand, the Dutch-Flemish painter Jan Sanders van Hemessen painted between 1550-1555 his famous scene "The surgeon or The Extraction of the Stone of Madness" (©Prado-collection), which depicts a frontal awake craniotomy for the treatment of psychiatric derangement:

We also find clear instructions how to perform trepanations and craniotomies in the "Armamentarium Chirurgicum" by Johannes Scultetus, published 1655:
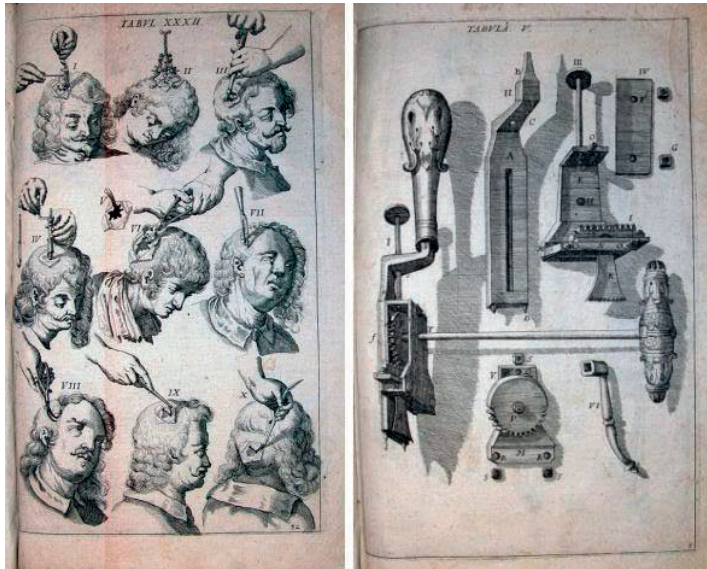
However, it finally lasted up to 1861, when Paul Broca discovered by autopsy of a patient with a well described motoric aphasia, that his gyrus frontalis inferior (later referred to as "Broca's area") was not well developed:
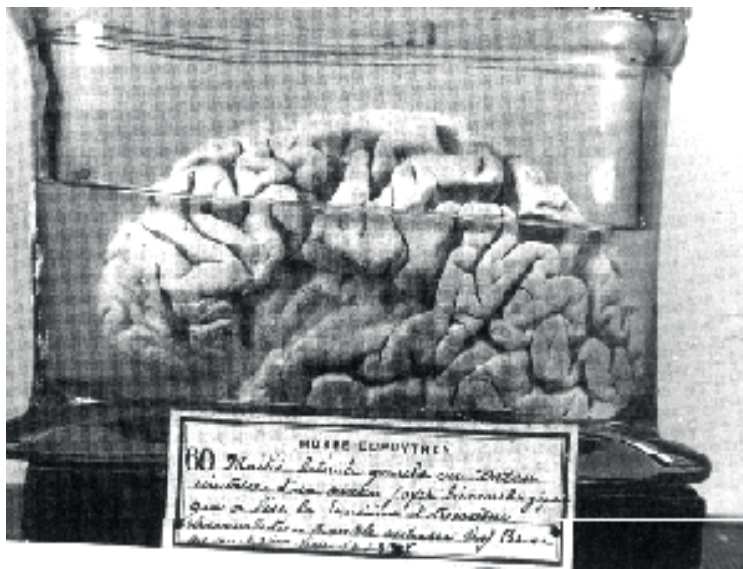
This can be considered as first scientific demonstration of the fact, that a certain brain function - in this case: being able to speak - is linked to a certain area of the brain.

After Broca's finding a lot of research was done under - with our view from today - unethical circumstances. The papers of Bartholow (1874)[1], Foerster (1926)[2] and Penfield (1937)[3] must be named as the milestones to our current understanding of the somatotopic organization of the cerebral cortex. Dr. Wilder Penfield finally described the *homunculus* illustrating the motor and sensory representation of the body within the brain cortex.

The following picture shows a figure created by Sharon Price-James. This figure is an attempt to visualize the relationship between different parts of the body and the cortical surface they are representing. Obviously, not the actual size of a part of the body, but the complexity of the sensory (and motor, respectively) functions determines the size of the cortical representation.

Whilst the principle findings of Penfield are still valid today, we know that there exists a lot of variation between patients, making it mandatory that every single patient operated awake undergoes his personal cortical brain mapping to identify the functional relevant areas of the brain.

In the early years of neurosurgery, an awake craniotomy was a standard procedure due to a lack of anesthesiological alternatives. It was also performed in cases, where being awake did not provide an advantage for the patient's neurological outcome, except of avoiding a possibly dangerous general anesthesia. In the 20th century, driven by the development of modern anesthetics and anesthesia machines, most craniotomies were performed under general anesthesia, which provided much more comfort to the patient and the surgical team. It took until the late 1990's, when awake craniotomies started their "*renaissance*" on the neurosurgical OR as a conscious choice for selected patients. The pharmacokinetic properties of propofol enabled the anesthesiologist to control the patient's level of sedation with a previously unknown precision and predictability, which finally encouraged the neurosurgeons to operate on brain tumors they would not dare to resect under general anesthesia.

Brain tumor resection:

In general, brain tumors can be treated by surgery, chemotherapy and or radiation. Common feature of all axial tumors (growing from neuronal tissue like astrocytoma, oligodendroglioma or glioblastoma) is the disappointing fact that a complete resection without risk of recurrence of the tumor is quite impossible. Therefore, brain tumor resection aims to resect as much as possible of the tumor - because cytoreduction is linked to a better effect of the subsequent chemo- and/or radiotherapy and thus a longer survival of the patient[4] -, but this cytoreduction should create a minimal risk of neurological damage to maintain the quality of life for the patient as high as possible.

Brain tumors can occur in all lobes of the brain, and the majority of tumors can be removed safely under general anesthesia. However, if a brain tumor is located close to functional, eloquent areas of the brain, which cannot be monitored during general anesthesia like speech or the whole motor cortex, many neurosurgeons will hesitate to perform a tumor resection under general anesthesia, because of the risk of neurological damage to the patient.

Before the technique of awake craniotomy became more popular, a common approach to these tumors was "wait and see". Some neurosurgeons performed small biopsies in these tumors to get a clear diagnosis of the type of tumor, but even a biopsy could cause fatal neurological damage to the patient.[5,6]

The technique of awake brain tumor resection with brain mapping enables the neuro-surgeon to resect brain tumors in or close to these eloquent areas with the intention of a maximum cytoreduction on the one side and a minimal risk of neurological damage for the patient on the other side. Tumors which have been considered surgically untreat-able 20 years ago have become at least partially resectable by awake craniotomy, and the indications for awake craniotomies are still growing.[7,8]

Patient centered care:

Being awake whilst undergoing brain tumor resection is an idea which spontaneously causes unpleasant feelings for the majority of the patients. However, the role of the patient is crucial for the success of this procedure, because only a cooperative, alert patient can interact with the whole team in a way that makes safe tumor resection possible. Therefore, the importance of a good preparation and guidance of the patient throughout the perioperative period cannot be underestimated. Coping with the fact of suffering from a malignant brain tumor, being exposed to the OR-environment which can be experienced as hostile and feeling the need to cooperate as good as possible for a successful resection is just a rough summary of the psychodynamics in patients undergoing awake craniotomies for brain tumor resection. These special feelings and needs must be addressed by the medical team, and exactly this is a great example of "patient-centered care". All measures taken have two priorities: safety and comfort of the patient – with safety being the absolute number one. The challenge to cooperate with the patients as a kind-of-member of the OR-team without asking too much of them physically, but especially mentally cannot be compared with any other type of surgery. However, most patients undergoing awake craniotomies are quite young and highly motivated to contribute to the success of the procedure. Canalizing this motivation and also coping with possible disappointments (e.g. incomplete resection, [temporary] neurological worsening) requires a special doctor-patient-relationship and also involve-ment of the patient's family.[9]

Outline of the thesis:

Based on the background described above, this thesis summarizes the research ques-tions and possible answers based on the clinical and scientific work of the author in more than 300 patients undergoing (awake) brain tumor resections during the last 22 years. The publications presented here are clustered around 5 key-questions:

Question 1: What are the pre-requisites for a successful awake craniotomy?

Chapter 1 reviews the role of the anesthetist in the perioperative care for patients undergoing awake craniotomies. From preoperative patient selection to perioperative management the most relevant issues are addressed in this invited review. Chapter 2 summarizes the use of local anesthetics for brain tumor resections. Furthermore, this review addresses the technique of infiltration (surgical field block vs. direct nerve/scalp-block).

Question 2: Is an awake craniotomy for the patient more or less stressful than a brain tumor resection under general anesthesia?

The research published in chapters 3, 4 and 5 focusses on the metabolic (and emotional) impact of an awake craniotomy on the patients. Because all patients with axial brain tumors are treated with dexamethasone perioperatively, measuring cortisol as the most physiological stress hormone was not feasible. Therefore, we decided do look at the plasma amino acid profile (chapter 3) and the inflammatory profile (chapter 4) as "objective", physiological markers of the subjective phenomenon stress. Chapter 5 is a review dealing with current options and concepts how to further improve the patient's experience for those undergoing awake craniotomy.

Question 3: The patients undergoing an awake craniotomy must be cooperative during the procedure, but: what do they remember of the perioperative period and how do they deal with it?

In chapter 6 we focus on the subjective experience of the patients undergoing an awake craniotomy and the quantity and quality of their memories of the perioperative period. In chapter 7 we applied the same questionnaire on another group of patients undergoing brain tumor resection not only awake, but also under general anesthesia. In this second study we also addressed aspects of anxiety and coping, both known to have an impact on the quality and quantity of memories. Furthermore, we were interested how anxiety in patients and their relatives is related and how it changes between the pre- and postoperative period.

Question 4: What is the added value of an awake craniotomy in selected patient populations?

In chapter 8 we give a detailed case-report of a 9-year-old boy who underwent an awake craniotomy for glioblastoma resection. From 2004-2017 this was the youngest patient ever published for this type of procedure. Chapter 9 focusses on patients undergoing a brain tumor resection in the insula. Brain tumor resections in this deep subcortical region are challenging and not frequently performed. However, we have been able to collect a relative big group of patients operated either awake or under general anesthesia and

have been able to compare these groups and their perioperative outcomes. Chapter 10 addresses the question, whether patients suffering from a (suspected) glioblastoma multiforme have advantage by an awake craniotomy. Considering the poor prognosis of this disease, a technique offering a maximum resection with a minimal risk of functional deficits might be of added value. Nevertheless, until today the majority of these patients is not operated awake.

Question 5: What is the adequate postoperative pain-treatment after an (awake) craniotomy?

Chapter 11 is an analysis of the efficacy of the postoperative pain management in neurosurgical patients in general with special attention for patients after craniotomies. In the final general discussion, we review the findings of the papers presented and address future perspectives.

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II

General aspects of awake craniotomy

Chapter 1

Awake craniotomy for brain tumor resection – what does the anesthesiologist do?

AWAKE CRANIOTOMY FOR BRAIN TUMOR RESECTION – WHAT DOES THE ANESTHESIOLOGIST DO?

Introduction:

From a historical point of view, awake craniotomy is more a quite old surgical technique experiencing a kind of renaissance, than it can be called an innovation of the 3rd millennium AC.

As we know, successful trepanations were performed centuries before the first anesthesia. We also know for about 100 years, that the sensory and motor cortex are organized by representation of the "homunculus" and that the Broca-motor speech area is located at the frontotemporal lobe.

This article describes the technique of awake craniotomy as it has been successfully performed by the authors for years in more than 200 cases.

Definition:

The term "awake craniotomy" for this procedure is actually not correct, because the craniotomy, the opening of the skull is performed with the patient under sedation. Once the craniotomy is performed, the special feature of this technique is that the patient will wake up and stay awake whilst the neurosurgeon is removing the brain tumor.

Indications:

Tumors close to functional relevant areas of the brain

The awake craniotomy has shown its added value in patients, where a tumor of neuronal tissue (e.g. glioma, astrocytoma) is located close to functional relevant brain areas (e.g. speech, motor function), and if the integrity of these areas cannot be monitored adequately during general anesthesia. (fig. 1)
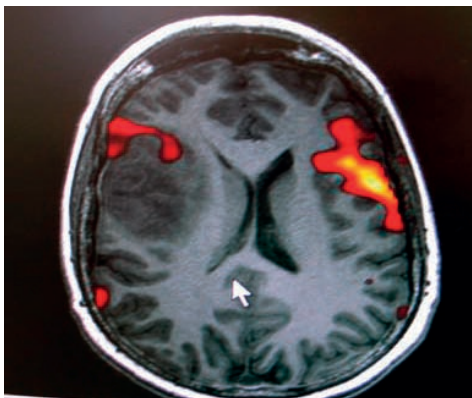
Figure 1: fMRI of a temporoparietal tumor close to functional relevant brain areas. The red color indicates an increase of perfusion / brain activity when the patient was asked to whistle.

Options:

In patients with these kind of tumors, the neurosurgeon in general has three options:

1) *Wait and see*: If the tumor is growing slowly, this can be done well for years.
2) *Taking a biopsy*: If the radiological picture suggests a primary brain tumor, we do not recommend taking a biopsy. Taking a biopsy from a tumor located close to functional relevant areas still includes the risk of a functional damage to the patient without the advantages of a tumor resection.
3) *Performing an awake craniotomy*: Aiming for a maximum of tumor resection with a minimal risk of functional damage.

Better prognosis for adjuvant therapies:

Recent literature provides good evidence that aiming for the most radical resection of the tumor improves the chances of all adjuvant therapeutic measures (chemotherapy and even more radiotherapy) and hereby can prolong the survival of the patient for up to 50% (e.g. in case of a glioblastoma multiforme 13 months in place of 8) [1-3].

Thus, the added value of an awake craniotomy for the patient is based on the prolongation of life with maintenance of the quality of life – and even re-craniotomies in case of possible tumor-recurrence are possible.

Patient selection:

When screening and selecting patients for an awake craniotomy we apply the following criteria:

*State of the patient***:**

The patient must have a maximum level of consciousness, must be cooperative and alert. A successful awake craniotomy requires a patient, who can communicate clearly and gives correct feedback about possible effects of the electrical stimulation during the cortical mapping ("I feel a warm wave in my left arm").

In general, patients are highly motivated to undergo an awake craniotomy. Most patients are quite young and they understand that this technique offers some extra options in their difficult situation. In contrast to almost all other types of surgery, the patient himself essentially contributes to the surgical result, and the majority of patients experiences this fact as much more motivating than threatening.

The patient should not have a predictable difficult airway, because a general anesthesia with orotracheal intubation is always the first alternative in case of an intraoperative emergency.

The patient should not have any coagulation disorder. In case of major bleeding intraoperatively, the risk of brain edema increases, but the options to treat this adequately are limited in this case of an acute emergency in a spontaneous breathing patient.

In the two weeks before the planned day of the procedure, the patient should not experience an epileptic *grand-mal* insult. This time-limit is somewhat arbitrary and not based on higher levels of clinical evidence, however, during the procedure the brain will become stimulated electrically. If this stimulation finds a brain in a level of higher excitability, the risk of a grand-mal insult on the operating table with a patient fixated in the Mayfield clamp will be increased. Smaller, focal insults are no arguments to postpone the procedure.

Age of the patient:

With an age of 9.5 years the authors have successfully treated one of the youngest patients worldwide ever undergoing an awake craniotomy for brain tumor resection. We consider the age as a number less relevant than the psychomotor and psychosocial development of the child. In our case, the father of the child has been present on the OR throughout the procedure and has significantly contributed to the smooth course of events [4].

Weight of the patient:

More interesting than age as a number, we consider the weight of the patient, because it defines the toxic upper limits for the amount of local anesthetics which can be used safely. This amount can be quite limited in older and cachectic patients, too.

In these situations, we recommend to perform a classic skull block on the relevant nerve-exit-points in place of the common surgical field block in the area of the planned incision. The amount of local anesthetics needed to perform the classic skull block in experienced hands should be less than for a field block (15 vs. 30 ml in average). We recommend the use of bupivacaine 0.375% with adrenaline 1:200.000.

Location of the tumor:

The tumor must be accessible for the neurosurgeon with the patient in the supine or lateral position or any position in-between. We do not perform awake craniotomies in prone or sitting positions. This is due to the increased risk of air embolism in case of spontaneous breathing patient in the sitting position and the difficult airway access and the limited patient comfort in case of 4-5 hours lying prone awake.

Tumors located in the insula are a special challenge for the patients and the medical team, but can be performed as an awake craniotomy. Before the beginning of the resection of the tumor the neurosurgeon has to perform a fissurotomy, which prolongs the duration of the procedure. This fissurotomy should be done with the patient sedated.

During the tumor resection from the insula, we see much more frequently exhaustion of the patients than in case of a cortical tumor resection.

Tumors located close to the temporobasal skull-base and dura can cause trigeminal nerve pain during the procedure. If the diathermic electrocoagulation is triggering the nerve, pain and vegetative reflexes (bradycardia) are possible. However, by good communication between neurosurgeon and anesthesiologist and the use of small amounts of remifentanil (0.5-1 µg/kg) these situations can be managed quite well.

Grade of the tumor:

In patients who had biopsy performed in other centers or the radiological findings were highly suggestive for a glioblastoma, some neurosurgeons are quite reluctant to perform an awake craniotomy. Also in our population about 65% of the patients have a low grade primary brain tumor.

However, based on the recent findings, showing an improved survival in case of an extended resection even in glioblastoma patients, we do not consider (suspected) glioblastoma as a contraindication to awake craniotomy [2,3].

Recurrent tumor:

Tumor recurrence is common in case of primary brain tumors. However, also the second and even third procedure can be performed as an awake craniotomy with suitable patients. In case of a second awake craniotomy in one patient, special attention for sufficient analgesia is mandatory. Due to scar formation, the spread of the local anesthetic in case of infiltration anesthesia of the surgical field can be limited. Furthermore, due to wound healing after the first procedure scar formation including a tight connection between the dura and the skull can have occurred, which makes a second craniotomy possibly more painful, and vagal reactions cannot be excluded.

Premedication / patient preparation:

Keystone of the anesthesiological preparation of the patient is an intensive (in average about 100 minutes lasting) dialogue between the anesthetist responsible for the procedure and the respective patient - and, if possible, at least one relative of the patient. During this dialogue, which in general takes place about two weeks before the operation, with slides and movies the whole course of events during the procedure is presented to the patient. Furthermore, the patient receives a collection of lay-journal articles about the awake craniotomy to be well informed and prepared. The following aspects are especially stressed during this dialogue:

Need to rest without moving on the operating table:

We have excellent experiences with letting the patients train the perioperative position at home. In general, we recommend 3 sessions of 3-4 hours each, so that the patient can already detect possible pressure points and choose the most comfortable position.

Furthermore, we also ask the patients in case of any itching not to scratch themselves, but to ask another person to do so, which will be the case on the OR, too. Our key message is: speaking is always possible, but any body movements should be avoided.

Possible sources of discomfort:

Pillows, jelly-matrasses and other means are used to make the patients lie as comfortable as possible. Urinary catheters induce a feeling of urge, especially in men. Once informed about the fact that this feeling is caused by the catheter, most patients are able to relax their pelvic muscles and to suppress this feeling. Infiltrating the skin for placement of the Mayfield clamp and infiltration of the surgical field are the most painful moments of the procedure. However, by administration of a small bolus of remifentanil (50-75 μg respectively), this can be managed very comfortably.

Glasses, false teeth, hearing aids:

During an awake craniotomy communication between the medical team and the patient must be intense and as unrestricted as possible. Patients who cannot talk clearly without their false teeth, patients who cannot identify the pictures of the aphasia test without glasses and patients who cannot understand the neuropsychologist without their hearing aids have to take these devices with them to the OR.

Fasting, use of alcohol and nicotine:

If the patients develops a state of substance withdrawal, the ability to cooperate is endangered. Coffee-withdrawal induces headache, nicotine-withdrawal induces coughing and agitation, alcohol-withdrawal can cause vegetative disturbances and psychomotor agitation. Therefore, all our patients undergoing an awake craniotomy are allowed to consume up to 60 minutes before anesthesia induction the substances they are used to consume at home during the early morning.

Drugs used for premedication:

Criteria for continuing or discontinuing the drugs the patients is used to take from home are not different from patients undergoing any other type of surgery under general anesthesia. If the patient is using antiepileptic drugs, continuing them is crucial [5].

On the evening before surgery the patient is offered 1-2 mg lorazepam p.o. for a good night rest. In the morning, about an hour before anesthesia induction, 25 mg promethazine and 7.5 mg piritramide are given intramuscularly. We have chosen this combination of drugs because the quality and duration of sedation of benzodiazepines in the morning of the procedure were too unpredictable (will the patient be awake, as soon as the dura is opened?)

Other aspects:

The possibilities to lower an increased intracranial pressure during an awake craniotomy are limited - the patient cannot be e.g. temporarily hyperventilated. Therefore, we ask the patients to sleep in the night before the procedure with an elevated head (20-30 degrees). Finally, all patients are given anti-thromboembolic stockings.

Anesthesia induction:

Limiting the stress:

All awake craniotomy-patients are planned as the first of the day, in order to keep the stress due to fasting and mental excitement as limited as possible. During the whole procedure "vocal anesthesia"- a distracting dialogue with the patient - next to clear announcements of all actions taken is essential for the success of the procedure.

For anesthesia induction, basic monitoring is connected. Patients receive an i.v. access (18 G) and a nasal oxygen probe (3 l/min). As soon as this is inserted, induction is performed with propofol (bolus of 0.5-1 mg/kg) and continued at a dose of about 4 mg/kg/h.

With the patient asleep, but spontaneously breathing we insert under local anesthesia (1% Lidocaine) an arterial catheter (radial artery), a central venous catheter (v. basilica) and the urinary catheter. After insertion of all these lines propofol-sedation is stopped.

The awake patient can help actively by finding the optimum position on the operating table. Afterwards the surgical field is shaved and prepared and local infiltration anesthesia is performed.

The agitated patient:

We found that especially young male patients who obviously had not yet coped sufficiently with the fact that they were suffering from a brain tumor showed a high level of agitation under the influence of propofol in the doses mentioned. Therefore, the need of a good emotional work-through, if necessary supported by a psychologist, is stressed during the preoperative dialogue. In case of agitation and unrest during sedation, a complete stop of propofol has turned out to be the better choice than even more sedation. As good local anesthesia alone is sufficient to undergo the craniotomy, gaining back consciousness will make the patient cooperative again. An increase of the propofol-dosages in case of agitation does not automatically stop the agitation, but might also cause a need of intubation with loss of neuropsychological monitoring.

Local anesthesia:

In our practice, we rely on the following combination of drugs:

For the local anesthesia of the three fixation points of the Mayfield clamp: 12-20 ml of a mixture of lidocaine 1% and bupivacaine 0.25% (final concentrations) with adrenaline

1:200.000. For the infiltration of the surgical field 25-40 ml bupivacaine 0.375% with adrenaline 1:200.000. The local anesthesia mixture is prepared by the anesthetist but injected by the neurosurgeon who is performing the painful procedures. A small bolus of remifentanil before the injections of the local anesthesia clearly increases patient comfort.

Craniotomy / trepanation:

Second period of sedation:
After the surgical field is anesthetized and all drapes and blankets are installed, the patient is sedated again with another bolus of propofol (0.5-1 mg/kg) followed by continuous infusion (average 4 mg/kg/h). Here we see a high variability between the patients, which can be explained by the use of antiepileptics and other (social) drugs.

During our first awake craniotomy procedures, we kept the patients sedated from the first iv-line until the opening of the dura mater. However, we saw frequently problems with patients who had difficulties to orientate themselves under the blankets, because they woke up in a completely different environment compared to the situation when sedation was started.

Airway management:
During craniotomy we keep the patient on spontaneous breathing; an oxygen nose-probe is the only kind of airway-management we use routinely. In case of emergencies, of course, all necessary anesthesia drugs and devices to perform intubation are prepared ready to use.

In literature, all possible alternative regimens of airway management are discussed (laryngeal mask, intubation-extubation, other supraglottic airway devices etc.) without any convincing evidence of a superiority of one technique above the others. An arterial blood gas analysis during this period can be useful to verify the adequacy of the spontaneous ventilation.

Fluid management:
We strive for normovolemia and rely on NaCl 0.9%, balanced crystalloid infusions and in case of blood loss above 300 ml also Hetastarch-solutions. Blood transfusions are extremely rare in these procedures.

Other drugs:
During craniotomy, we also give routinely 200 ml mannitol 15% in case of relevant brain edema formation. Furthermore, we give dexamethason 8 mg i.v. and pheytoine 250 mg i.v. The latter is given with the idea, that this dose is too low to suppress a proper

response on the cortical electrical stimulation, but high enough to suppress a secondary generalization of an epileptic insult which might be induced just by a cortical stimulation.

As soon as the dura mater is opened, the propofol-infusion is stopped and the patient's awakening is expected.

Brain mapping / neurostimulation:

Supported by a neuropsychologist / linguist, the patient has to undergo several psychological tests, which are adapted to the location of the tumor and possible preexisting neuropsychological deficits of the patient. During these tests, the neurosurgeon stimulates the cortical surface in the surgical field with an electrical tweezer. In case of a motor or sensory response to the electric stimulation, the cortical area is marked. The neurosurgeon tries to identify cortical zones without any response or interference with the tests, which enable him to approach the tumor safely.

This period of brain mapping can be challenging, if the neurosurgeon induces an epileptic insult by the electrical stimulation. In that case, a few milliliters of iced water, which must be kept available are applied by the neurosurgeon directly on the stimulated brain surface. This will stop a local insult in most cases. If the insult does persist or starts to generalize, intravenous thiopentone (0.5-1.5 mg/kg) will stop the epileptic activity, whilst keeping the patients able to breath spontaneously.

Management during tumor resection:

Keeping the patient awake:
After a safe approach to the tumor is found, the authors prefer to keep the patient awake with a distracting dialogue ("vocal anesthesia"). This enables an immediate stimulation of deeper located brain structures during the progress of the procedure, to identify safe resection margins. (Fig. 2)

During this dialogue, the patient is also instructed to announce if he wants some fluid on his lips or whether he would like to change position to avoid pressure sores. In coordination with the neurosurgeon this can be facilitated. In general, blood pressure during an awake craniotomy is higher than under general anesthesia, but it is only rarely necessary to decrease it actively by administering urapidil (0.2-0.5 mg/kg i.v.).

Tumor resection ends with a final control of all relevant neurological functions of the patient and hemostasis by the neurosurgeon.

Complications:

All patients survived the procedure and the early postoperative period. We have seen focal epileptic insults in several patients; 3 patients showed generalized grand-mal epileptic insults. All insults could be managed without intubating the patient.
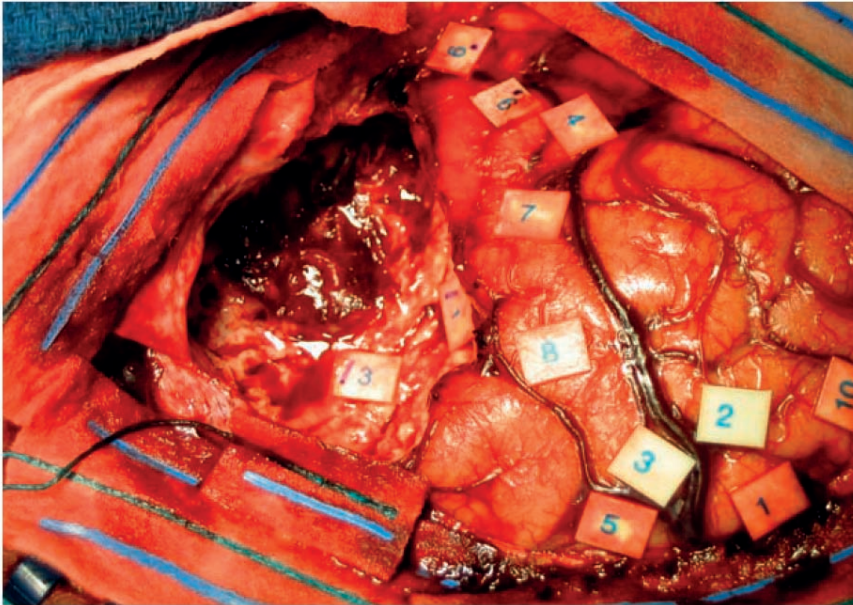
Figure 2: Surgical field after tumor resection: The sterile numbers indicate, where during cortical and sub-cortical stimulation functional brain areas have been identified.

No patient panicked on table or requested a switch to general anesthesia. In most of the cases with a less radical tumor resection than we preoperatively had hoped, this was due to the high risk of functional deficits based on the findings at (subcortical) electrical stimulation.

In 5 cases we had to stop the tumor resection before we reached these limits, because the patients became exhausted and/or less alert, which made reliable feedback during neurostimulation impossible.

No patient needed intubation and ventilation intraoperatively due to a respiratory problem. Two patients postoperatively developed severe generalized brain edema, which made an intubation on the 2nd or 3rd day postoperatively necessary.

Wound closure:

During the closure of dura, skull and skin patients are sedated again with propofol, bolus and continuous infusion. In general, lower dosages are needed than at the beginning of the procedure (initial dose -20%).

Skin closure is done with staples because they can be placed much faster than sutures without any disadvantage for the cosmetic result. After in average 3.5 hours time from incision to wound closure the procedure is finished and the administration of propofol is stopped.

Postoperative management:

All patients wake up whilst the wound bandage is placed and are transferred to our Post-Anesthesia-Care-Unit, which is more a high-care-unit than a recovery. The patients spend here the first 24 h postoperatively and undergo frequently neurological checks. Once arrived there, they are allowed to eat and drink. After 6 h postoperatively prophylactic low-dose heparines will be given, if the patient shows no neurological abnormalities. Postoperative mobilization starts just on the first postoperative day in order to keep the risk of postoperative bleeding low.

Analgesia:

Patients undergoing an awake craniotomy in general have only low pain scores. Once the local anesthesia has been faded, paracetamol and opioids are sufficient to provide excellent pain control [6].

Discussion:

The authors are aware of the fact, that the available literature is full of variations and alternatives on the regimen described here [7,8].
    These alternatives mostly affect
*   The technique of local anesthesia (field block vs. wound infiltration, choice of drugs and additives),
*   The airway management (from spontaneous breathing up to intubation/extubation), and
*   The technique of sedation (addition of continuous remifentanil, use of dexmedetomidine) [9].
In several studies we could demonstrate, that the subjective experience of patient comfort and patient satisfaction with our regimen is very positive. Also, when focusing on objectively measurable stress parameters, it meant clearly no higher level of stress for the patient than a tumor resection under general anesthesia [10,11].
    Because there is no evidence showing superiority of one technique above the other, we refrain from this discussion on a more detailed level.

Key messages:
*   Awake craniotomy is indicated for primary brain tumors located close to functional relevant brain areas.
*   When selecting the patients, careful attention to possible contraindications is mandatory and the specific aspects of the procedure must be kept in mind.
*   The intraoperative cooperation of the patient is based on an intensive preparation. A preoperative dialogue of 100 minutes is usual.

- The routine protocols for fasting and non-smoking must be applied liberally in this population.
- Bringing false teeth, glasses and hearing aids to the OR can be necessary to enable the neuropsychological monitoring.
- "Vocal anesthesia" – a distracting dialogue with the patient – is a keystone of the anesthesia regimen.
- The quite minimalistic airway management we practice for years (continuously spontaneous breathing patient with oxygen nose probe) is safe, feasible and successful.
- After an awake craniotomy – just like after all similar tumor resctions under general anesthesia – patients are treated for 24 hours on our PACU/High care unit.

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Chapter 2

Local anesthetics for brain tumor resections: current perspectives. (invited review)

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LOCAL ANESTHETICS FOR BRAIN TUMOR RESECTION: CURRENT PERSPECTIVES.

ABSTRACT

This review summarizes the added value of local anesthetics in patients undergoing craniotomy for brain tumor resection, which is a procedure that is carried out frequently in neurosurgical practice. The procedure can be carried out under general anesthesia, sedation with local anesthesia or under local anesthesia only. Literature shows a large variation in the postoperative pain intensity ranging from no postoperative analgesia requirement in two-thirds of the patients up to a rate of 96% of the patients suffering from severe postoperative pain. The only identified causative factor predicting higher postoperative pain scores is infratentorial surgery. Postoperative analgesia can be achieved with multimodal pain management where local anesthesia is associated with lower postoperative pain intensity, reduction in opioid requirement and prevention of development of chronic pain. In awake craniotomy patients, sufficient local anesthesia is a cornerstone of the procedure. An awake craniotomy and brain tumor resection can be carried out completely under local anesthesia only. However, the use of sedative drugs is common to improve patient comfort during craniotomy and closure. Local anesthesia for craniotomy can be performed by directly blocking the six different nerves that provide the sensory innervation of the scalp, or by local infiltration of the surgical site and the placement of the pins of the Mayfield clamp. Direct nerve block has potential complications and pitfalls and is technically more challenging, but mostly requires lower total doses of the local anesthetics than the doses required in surgical-site infiltration. Due to a lack of comparative studies, there is no evidence showing superiority of one technique versus the other. Besides the use of other local anesthetics for analgesia, intravenous lidocaine administration has proven to be a safe and effective method in the prevention of coughing during emergence from general anesthesia and extubation, which is especially appreciated after brain tumor resection.

Keywords: brain tumor, craniotomy, local anesthesia, neurosurgery, scalp block

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INTRODUCTION

Craniotomy for brain tumor resection is carried out frequently in neurosurgical practice. While about one-half brain tumors do not grow into neuronal tissue (like pituitary adenomas and meningiomas), the other half (e.g. oligodendrogliomas, astrocytomas, glioblastomas and metastases) do. Definitive cure of a tumor of this second group can be considered as impossible. On the other hand, it is known that a maximum of cytoreduction and tumor resection is associated with a better long-term survival. Therefore, these tumors are frequently resected by awake craniotomy with cortical (and subcortical) mapping, enabling a maximum of resection with a minimal risk of functional damage to the patient.[1,2]

If the patient is conscious and responsive at any time during the procedure, it is referred to as an awake craniotomy. An awake craniotomy can be carried out with three different forms of anesthetic care. In the sleep–awake–sleep technique, the patient is anesthetized during the placement of the skullpin head holder and the craniotomy whereafter consciousness must be regained in order to map cortical areas. Another option is to perform the procedure under monitored anesthetic care where the patient is mildly sedated to control anxiety and pain. Finally, the awake–awake–awake technique involves no sedation but only requires analgesia and special attention to non-pharmacological interventions such as hypnosis.[3] In all awake craniotomy techniques, the use of local anesthetics is mandatory.

Neurosurgical procedures cause more pain than anesthesiologists expect,[4] and post-craniotomy pain is not always well understood.[5] However, clinicians have become more aware of the incidence and intensity of post-craniotomy pain. There is a large variation in the occurrence of postoperative pain and the requirement of analgesic medication in neurosurgical patients. Pain scores have a large variation ranging from a visual analog score of approximately 15 to more than 60 in two large studies.[6,7] In a recent review of 26 studies assessing different aspects of postcraniotomy pain, 15 studies reported pain percentages in the first two postoperative days up to 60%–96%.[5] It is unclear why this great variation of the incidence of postoperative pain exists in craniotomy patients. Attributable factors could be the perioperative opioid and analgesic regiment used, the exact moment of the first postoperative pain score and the composition of the neurosurgical population. A recent review studied several factors such as age and gender, surgical site, surgical technique, psychological factors and tumor characteristics, but the results are conflicting and inconclusive.[8] The surgical site has turned out to be the only reliably identified factor: infratentorial surgery tends to be more painful and requires a higher cumulative opioid dose than supratentorial surgery, possibly because of the surgical-induced stretch and trauma of the neck muscle mass.[9,10] A review by de Gray and Matta provides further details about the pathogenesis of postoperative pain.[10]

The treatment of postoperative pain in neurosurgery is characterized by a balance between swift neurological assessment and the prevention of sedation, hypercapnia and opioid side effects such as vomiting on one side and patient comfort and the prevention of hypertension on the other side. Although opioids are frequently used in nonneurological surgery, their side effects raise caution to use these drugs in neurosurgical patients. Interestingly, these theoretical adverse effects have not been observed in studies using opioids.[11] Nevertheless, post-craniotomy pain should be treated by multimodal pain management where several classes of drugs are combined with local anesthesia.[11,12] Since patient-related factors that can predict the occurrence of serious postoperative pain are not known, it is recommended to provide on-demand analgesics that need to be administered with minimal delay to all craniotomy patients.[6] If an opioid drug is necessary, intermittent intravenous morphine provided on a medium- or high-care postoperative unit or via a patient-controlled system may be an effective option with less side effects compared to codeine or tramadol.[12,13]

Besides acute postoperative pain, craniotomy patients are prone to develop chronic post-craniotomy headache where the incidence varies between 0% and 65%.[9,14] Chronic pain can not only develop at the site of the incision but also develop as a moderate pressure sensation involving the entire head. In one study, 18% of the patients developed a severe throbbing sensation associated with nausea and vomiting.[15] Several preoperative factors associated with the development of chronic headache have been identified, such as depression, anxiety and temporomandibular disorders.[16]

Locoregional anesthesia has been shown to have an additional value in craniotomy patients, independent of the anesthesia technique used.[17] In the intraoperative phase, locoregional anesthesia diminishes the autonomic responses during the application of the skull-pin placement[18,19] as well as during dural closure and skin closure,[19] which due to the lack of a sensory innervation of the brain tissue itself are much more painful than tumor resection. Even under general anesthesia and after an opioid was administered, heart rate and blood pressure can increase by 15% and 43%, respectively, after application of the Mayfield clamp.[20] This effect can be largely diminished by preoperative application of local anesthesia, via either a scalp block or local infiltration,[20,21] leading to a more hemodynamically stable anesthesiological course.

In awake craniotomy patients, the use of local anesthesia is the cornerstone of the procedure and has been established as a standard of care.[21–23] If the local anesthesia is effective, no other analgesic drugs are necessary during the whole procedure. However, additional sedation is commonly used during craniotomy and closure, the steps of the procedure where the cooperation of the patient is not required. This combination en-

ables a comfortable emergence and adequate analgesia during the regain of consciousness. The combination of sedation and local anesthesia has also been proven effective in the pediatric population.[24,25] Sedation during craniotomy can be done with propofol or dexmedetomidine alone; it is much more a comfort measure than a medical need. The combination of local anesthesia with sedation has been used successfully in patients with a relative contraindication for a "typical" awake craniotomy, like fragile patients and patients with a poor neurological status, too.[26] However, in our practice, we would prefer to perform procedures in these groups of patients under general anesthesia because of the better anesthesiological control of the intraoperative situation.

It can be discussed whether there is a place for shortacting opioids like remifentanil just before the injection of the local anesthetics; it increases patient comfort by damping some of the pain intensity of the local injections. On the other hand, the same injections are routinely performed without additional opioids in patients who need to be sutured after minor head traumas.

Regarding the additional value of local anesthetics for the postoperative phase of all craniotomy procedures, the use of regional anesthesia leads to lower pain scores and a reduction of opioid consumption in the early postoperative period.[27] Local anesthetics can be injected as a dedicated regional scalp (or nerve) block or as a diffuse local infiltration of the surgical field. Studies using scalp blocks have been meta-analyzed. In an analysis published in 2013, seven studies with a total of 320 patients were systematically analyzed out of 20 studies that investigated the effect of regional scalp blocks.[27] Several authors performed the scalp blocks at different time points of the perioperative course: a scalp block was performed preoperatively, before incision and after wound closure. The analysis showed an overall reduction in pain score 1 hour postoperatively (mean difference: -1.61, 95% confidence interval: -2.06 to -1.15, P< 0.001). A reduction in pain scores up to 8 hours for a preoperative scalp block and up to 12 hours with a postoperative blockade was observed. Application of a scalp block reduced morphine consumption, although this effect was small (n= 6 trials, standardized mean difference: -0.79, 95% confidence interval: -1.55 to -0.03, P= 0.04).[27]

Studies using local infiltration instead of application of a regional skull block were analyzed in a meta-analysis by Hansen et al.[28] In total, there were five randomized trials including a total of 249 patients: Bloomfield et al described infiltration with bupivacaine 0.25% pre- and postoperatively showing a significant reduction in pain scores immediately on admission on the PACU that wears off after 1 hour.[19] Other studies in this review looked at the effect of infiltration before suturing and skin closure using either ropivacaine 0.75% or bupivacaine 0.5%. They found that infiltration reduces morphine

consumption in the early postoperative period.[29] Another study using ropivacaine 0.75% could not replicate this effect, but patients in the intervention group (with local anesthesia) showed significantly reduced pain scores in the early postoperative period.[30]

A recent study using a mixture of lidocaine and ropivacaine addressed the question whether pre- or postoperative infiltration is more effective in reducing postoperative pain. The authors found lower pain scores and a reduction of morphine consumption in the group that received infiltration before incision.[31] This supports the idea of "preemptive analgesia" by local anesthetics due to inhibition of the pain-signal transmission. However, despite this weak support for local infiltration, there is an urgent need for more scientific trials addressing this issue.

For infratentorial craniotomies, a recent randomized trial showed that the scalp block blunts the hemodynamic response better during application of the skull-pin. Patients also had a slightly lower pain intensity score in comparison to local infiltration only. Postoperative morphine consumption was equal in both groups.[32]

Several studies addressed the effect of local anesthesia on the development of chronic post-craniotomy pain. Batoz et al found in a randomized trial that postoperative local infiltration with ropivacaine significantly reduces persistent pain 2 months after craniotomy.[30] In a larger study with the same design, however, this effect was not found to be significant,[33] leaving the effect of local infiltration on the development of chronic pain uncertain.

One recent study found beneficial effects of intravenous lidocaine in craniotomy patients. Intravenous lidocaine has already been extensively described and reviewed, especially in visceral-abdominal surgery where it reduces pain in the early postoperative period.[34] In the study by Peng et al, craniotomy patients were randomized to receive a bolus (1.5 mg/kg) and a continuous infusion (2 mg/kg/h) of intravenous lidocaine or saline. No other local anesthetic application was used. The lidocaine group showed lower pain scores and a higher rate of absence of pain (NRS = 0) in the early postoperative period.[35] Further research is needed to answer the question how intravenous lidocaine compares to the application of local anesthesia in terms of postoperative pain and morphine requirement.

Taking this all together, there is sufficient support for the use of local anesthetics to prevent pain during awake craniotomy, to reduce pain and pain response in patients undergoing craniotomy under general anesthesia and to prevent chronic pain after craniotomy.

At this point, the technique of the local anesthesia itself must be studied further: must it be injected as a direct nerve/scalp block or is a local infiltration of the field sufficient, too?

INNERVATION OF THE SCALP AND DIRECT NERVE BLOCK

The scalp is innervated by six different nerves on both sides (**Table 1** and **Figure 1**). Excellent anatomical reviews have been published before describing in detail the location of the nerves in relation to the surface anatomy.[36–39] When applying a direct nerve block, several considerations need to be taken into account. While the landmarks where these nerves leave the skull are quite well defined, the area they cover shows an enormous variability. The supraorbital nerve has the medial iris as a reliable topographical landmark, where the location of the nerve is within 1 mm from the needle, small enough to be reached by a deposition of local anesthetic.[40] The supratrochlear nerve can also be reliably blocked at the point where it exits the orbita and before it enters the corrugator muscle.[41] The zygomaticotemporal branch of the trigeminal nerve shows a variation in anatomy and branches. It also has an intramuscular course in 50% of the cases.[42] Although the innervated area of the scalp of this nerve branch is small, identifying the exact blocking site of this nerve can be difficult and varies in the literature.

The auriculotemporal nerve runs between a distance of 8 and 20 mm anterior to the origin of the helix, so the recommended injection site is 10–15 mm from this point taking care not to inject the superficial temporal artery or to block branches of the facial nerve.[43] Both anatomical structures are of special importance in patients undergoing

Table 1 Nerves innervating the scalp

Nerve	Origin	Innervation	Anatomical landmarks	Special pitfalls on injection
Supraorbital nerve	Frontal nerve (ophthalmic division of trigeminal nerve)	Forehead to lambdoidal structure	Incisura supraorbitalis, right above pupil in a straight forward-looking patient	Direct nerve injection Eyelid injury Orbital injection
Supratrochlear nerve	Frontal nerve (ophthalmic division of trigeminal nerve)	Lower part of the forehead	Medial corner of the orbita, few millimeters lateral from the nasal apex	Not applicable
Zygomaticotemporal nerve	Zygomatic nerve (maxillary division of trigeminal nerve)	Small area of forehead and temporal areas	Half way between the supraorbital and the auriculotemporal nerve	Not applicable
Auriculotemporal nerve	Mandibular division of trigeminal nerve	Tragus, anterior portions of the ear, posterior portion of temple	15 mm ventral from the tragus of the ear. Close to arteria temporalis superficialis, cranial from the os zygomaticum	Proximity of artery and facial nerve. Intra-articular injection
Greater occipital nerve	C2/C3 (C1–C4) spinal nerves	Posterior part of the scalp to the vertex	End of the medial third of a line between protuberantia occipitalis externa and the lower end of processus mastoideus, close to arteria occipitalis	Arterial injection
Lesser occipital nerve	C2 spinal nerves	Lateral area of the scalp posterior to the ear	Beginning of the lateral third of a line between protuberantia occipitalis externa and the lower end of processus mastoideus	Not applicable

Note: Based on data from Kerscher et al.[36]
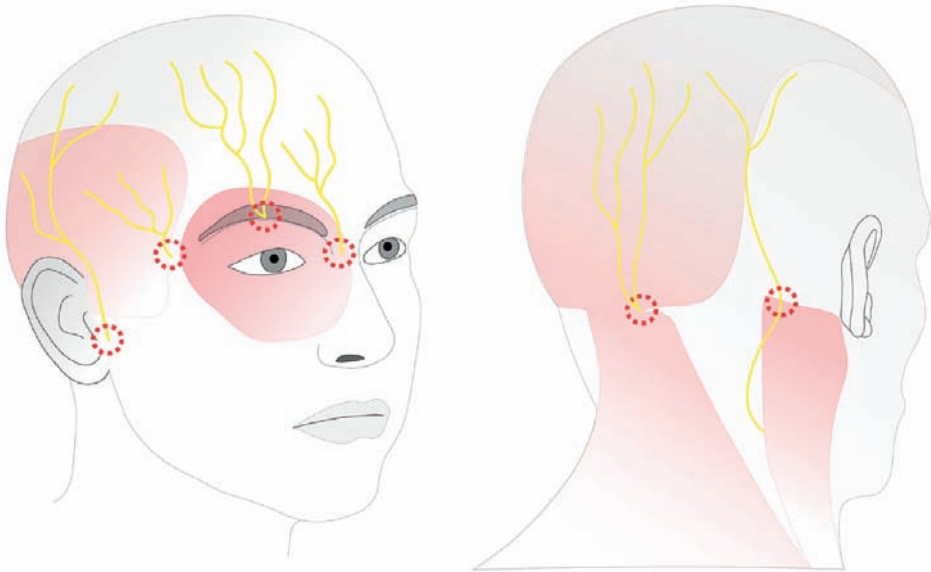
Figure 1 Sensory innervation of the skull and injection sites.
Notes: Nerves from left to right: auricotemporal nerve, zygomaticotemporal nerve, supraorbital nerve, supratrochlear nerve, greater occipital nerve and lesser occipital nerve. Injection sites are marked in red dotted circles.

awake craniotomies, as injecting in the first can cause epileptic seizures and blocking the second can cause (temporary) loss of nerve function, which can be confusing, if the surgeon operates near to neurons controlling facial function. More variation can be observed in the occipital nerves arising from the spinal plexus[44] where some authors advocate a precise localization of the two different nerves[36,39] while others recommend a field block approach to block the occipital nerves.[38] However, in many patients, both occipital nerves can be identified with ultrasound,[45] too, which enables a direct nerve block.

Recently, a new study describing the use of a maxillary block in craniotomy patients found better analgesia compared to a regional scalp block.[46] This innovative approach relies on the retrograde spread of the anesthetic along the maxillary nerve, leading finally to a complete block of all branches of the ipsilateral trigeminal nerve.

APPLICATION OF A FIELD BLOCK

When applying a field block, both the sites of the pins of the Mayfield clamp and the site of the incision must be infiltrated with local anesthetics. To improve patient comfort, it is our practice to precede the injection of the local anesthetic by a bolus injection of a short-acting opioid (we use about 0.8 μg/kg of remifentanil). For the Mayfield clamp, we routinely use an injection of 12–15 mL mixture of lidocaine 1% and bupivacaine 0.25% (final concentrations). Due to the fact that mostly there is only a short delay between the injection of the anesthetic and the placement of the clamp, we decided to add lidocaine for its fast onset. Epinephrine 1:200,000 can be safely added. We prefer the use of bupivacaine 0.25% over ropivacaine 0.75%. Although the local anesthetic duration of bupivacaine with added epinephrine and ropivacaine is comparable[29] and microvascular changes are identical,[47] the cumulative dose of local anesthetic is lower when equal volumes of either bupivacaine 0.25% or ropivacaine 0.75% are used.

For anesthesia of the incision site, an injection of up to 30 mL of bupivacaine 0.375% combined with adrenaline 1:200,000 is used. In our practice, the anesthetist prepares the local anesthetics, but the responsible neurosurgeon himself injects the local anesthetics to prevent misinterpretation between the planned surgical incision and clamp sites and the anesthetized scalp areas. To prevent local anesthetic toxicity, we recommend this technique only for patients with a minimal weight of 50 kg in order to avoid a bupivacaine dose exceeding 3 mg/kg. Mixing lidocaine and bupivacaine does not have a synergistic (supra-additive) effect on cardiotoxicity.[48]

Similar to other blocks, the same precautions must be taken into consideration when applying a cranial nerve block. Careful aspiration and slow injection to avoid intravascular injection are mandatory. Furthermore, a direct intraneural injection, which will cause immediate severe pain, must be stopped as soon as the patient complains. This risk is especially high in case of the supraorbital nerve block due to its anatomical position. When injecting to block the supraorbital nerve, care must be taken to prevent injury to the eyelid. When blocking the auriculotemporal nerve, injection in the temporomandibular joint, the superficial temporal artery and the facial nerve is a hazardous pitfall. The incidence of a transient facial nerve palsy after blockade of the auriculotemporal nerve has been described at up to 17%.[49]

Besides general complications of the local anesthetic such as overdosage and intranervous or vascular injection, there are specific complications described in the literature following a field or direct nerve block (Table 1). Direct injection of a local anesthetic in the cerebral ventricular system leading to a total subarachnoid block has been observed[50] which can be a direct lethal complication when not recognized and treated promptly by

protecting the airway and providing circulatory support. One must be aware of the risks of patients who have undergone craniotomy before or who have skull defects for other reasons like plasmocytoma. However, in a meta-analysis of seven studies of the scalp block, no adverse events were reported.[27]

Bilotta et al investigated the learning curve of seven residents in anesthesiology in order to achieve a "good–excellent" level of competence when applying a direct nerve block. The residents achieved an "excellent" rating after carrying out 10 procedures, concluding that a total of 11 procedures was sufficient to independently perform a direct nerve block in 95% of residents.[51]

To conclude, an infiltration of the surgical field by the neurosurgeon is a simple, reliable and safe technique for the vast majority of the patients. However, in patients with lower body weight, or in case of longer-lasting procedures (e.g. insula tumors), or in patients undergoing re-craniotomies (where scars inhibit the spread of the anesthetic in case of a surgical field block), but also for postoperative pain treatment, a direct nerve/scalp block (performed by an anesthetist) is a valuable alternative. It can be performed with a smaller total amount of local anesthetic, but with equal or possibly even longer-lasting effect. However, the direct nerve/scalp block is technically more challenging to perform and needs more training.

THE USE OF LOCAL ANESTHETICS TO DIMINISH AUTONOMIC RESPONSES

In this review, we already discussed the role of local anesthetics to provide analgesia when administered via a direct nerve block, a regional field block and via intravenous administration. Another indication for the use of local anesthetics in craniotomy patients is the reduction of autonomic responses such as coughing around extubation after general anesthesia for a craniotomy. Coughing produces a rapid rise in intracranial pressure,[52] which is an undesirable response in the early postoperative period. Several interventions have been studied in a study comprising 204 patients. The most effective strategies were the application of intracuff lidocaine and intravenous lidocaine (1.5 mg/kg at the end of surgery) significantly reducing the incidence of coughing.[53] Besides the prevention of coughing, lidocaine prevents the occurrence of a postoperative sore throat up to 30 hours after extubation.[54] In another randomized trial, spraying the supra- and subglottic areas with lidocaine 4% gave a significant reduction of cough during tracheal extubation.[55]

We recommend the use of intravenous lidocaine because the topical use of lidocaine spray might weaken laryngeal reflexes and thereby enable (silent) aspiration. Further-

more, the use of lidocaine to fill the cuff of the tube is not recommended by the producers of the tube and might cause liability problems in case of a cuff leak.

Besides lidocaine, a single bolus infusion of dexmedetomidine results in a reduction of coughing and an attenuation of hemodynamic parameters during emergence from anesthesia.[56] It is an interesting question how lidocaine compares to dexmedetomidine in the reduction of autonomic responses during emergence.

CONCLUSION

In summary, this review clearly shows the added value of local anesthetics in patients undergoing craniotomy for brain tumor resection: local infiltration of the surgical field or a direct nerve/scalp block is an effective measure to reduce postoperative pain. In case of the awake craniotomy technique, local anesthetics can be so effective that no other analgesics have to be given intraoperatively. There is insufficient scientific support to promote one local anesthesia technique as superior to the other. In our experience, both have their advantages. Infiltration of the surgical field is easy to perform, effective and safe in most patients. Direct nerve/scalp block has clear advantages in patients with lower body weight, longer-lasting (> 5 hours) procedures and possibly in re-craniotomies but requires more training and good anatomical knowledge. Finally, in case of general anesthesia for brain tumor resection, the intravenous application of lidocaine before extubation can help to suppress coughing and hemodynamic instability leading to a smoother and better recovery from anesthesia.

Future research should focus on 1) imaging techniques, which help with the identification of smaller nerves for direct nerve blocks, and 2) local anesthetics providing a long-lasting effect with low toxicity. Finally, studies directly comparing a surgical field block versus a direct nerve/scalp block are also highly required.

DISCLOSURE

The authors report no conflicts of interest in this work.

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ANALGESIA
SEDATION
local ANESTHESIA
COMFORT
ANXIETY
vocal ANESTHESIA
SAFETY
MEMORY
PAIN
TRUST

III

**Comfort, stress and metabolic effects
of an awake craniotomy**

Chapter 3

Inflammatory profile of awake function-controlled craniotomy and craniotomy under general anesthesia.

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INFLAMMATORY PROFILE OF AWAKE FUNCTION-CONTROLLED CRANIOTOMY AND CRANIOTOMY UNDER GENERAL ANESTHESIA.

ABSTRACT

Background. Surgical stress triggers an inflammatory response and releases mediators into human plasma such as interleukins (ILs). Awake craniotomy and craniotomy performed under general anesthesia may be associated with different levels of stress. Our aim was to investigate whether those procedures cause different inflammatory responses.

Methods. Twenty patients undergoing craniotomy under general anesthesia and 20 patients undergoing awake function-controlled craniotomy were included in this prospective, observational, two-armed study. Circulating levels of IL-6, IL-8, and IL-10 were determined pre-, peri-, and postoperatively in both patient groups. VAS scores for pain, anxiety, and stress were taken at four moments pre- and postoperatively to evaluate physical pain and mental duress.

Results. Plasma IL-6 level significantly increased with time similarly in both groups. No significant plasma IL-8 and IL-10 change was observed in both experimental groups. The VAS pain score was significantly lower in the awake group compared to the anesthesia group at 12 hours postoperative. Postoperative anxiety and stress declined similarly in both groups.

Conclusion. This study suggests that awake function-controlled craniotomy does not cause a significantly different inflammatory response than craniotomy performed under general anesthesia. It is also likely that function-controlled craniotomy does not cause a greater emotional challenge than tumor resection under general anesthesia.

INTRODUCTION

General anesthesia using endotracheal intubation is the standard procedure during brain tumor resection. Vital parameters are monitored and intubation provides a safe airway; drugs ensure analgesia and suppress vegetative reactions. Immobilization is relatively simple, even for patients in an atypical position. However, the use of general anesthesia precludes intraoperative monitoring of higher brain functions, and lesions made to the central nervous system being detected when reversibility of damage control might still be possible. Therefore, awake function-controlled neurosurgery may be beneficial in that respect. During awake craniotomy, the cerebral cortex of the patient is electrically stimulated. This allows the surgeon to properly identify and spare functionally relevant areas of the brain. Awake craniotomy has been shown to be a well-tolerated procedure with minimal side effects. Nevertheless, it is considered to be more challenging for the patient. By allowing for maximal tumor excision while keeping healthy tissue intact, awake craniotomy has the potential for better patient outcomes [1]. In such a procedure, the need to provide sufficient analgesia and sedation without interfering with electrophysiological monitoring is essential [2].

Before, during, and after craniotomy all patients are confronted with anxiety, stress, and pain. These factors can all negatively influence the perioperative experience. Patients undergoing craniotomy using general anesthesia, however, have to endure additional physical stress factors like intubation, longer hospital stays, and mechanical ventilation [3].

Patient perspectives regarding awake brain surgery have been investigated and adequate preoperative consultation has been found to be essential for patient confidence. In addition, scalp incisions and fixation of pin-holding sites were regarded as major sources of pain and discomfort. Still, the benefits far outweigh those of general anesthesia because awake craniotomy patients report less pain, anxiety, and fear [4, 5]. Even though there are drawbacks, the majority of patients tolerate awake craniotomy very well.

No study has attempted to compare the inflammatory impact of awake craniotomy versus general anesthesia procedures. Pathological inflammatory states can have far ranging clinical effects and negatively influence a patient's neurological outcome [6–8]. Recent research has demonstrated that cytokine levels can be correlated to the degree of brain tissue manipulation [9]. Plasma cytokine levels could reflect stressrelated biochemical pathways after surgery [10–12].

Cytokines orchestrate the complex network of cellular interaction that regulate both cell-mediated and humoral immunity, as well as the acute phase response [13]. Cytokines are glycopeptide signaling molecules that act at extremely low concentrations, mediating key immune responses. Several cytokines are released during periods of stress, including interleukin-6 (IL-6), IL-8, and IL-10 [14]. IL-6 is a proinflammatory cytokine secreted by T-cells, macrophages, and other cells. IL-6 is involved in both the immune response to trauma and the acute phase response; its targets being T- and B-cells. IL-8 is a chemokine produced mainly by macrophages and epithelial cells and functions to attract neutrophils towards inflammation sites. These proinflammatory cytokines play a key role in the physiological response to trauma and surgery, whereas IL-10 is an anti-inflammatory cytokine produced by Th2-cells that cause a reduction in proinflammatory cytokine synthesis [15].

Our aim was to investigate whether awake function-controlled craniotomy causes a significantly different inflammatory response than craniotomy performed under general anesthesia. We thought both procedures would create similar inflammatory profiles despite differing anesthesia techniques used. In order to test our hypothesis, plasma levels of IL-6, IL-8, and IL-10 were measured during the pre-, peri-, and postoperative periods in both patient groups. We also noted corresponding subjective outcome parameters for pain, anxiety, and stress to investigate whether performing an awake procedure causes more physical pain and mental duress.

PATIENTS AND METHODS

Study Design and Inclusion Criteria.
This was a prospective, single centre, two-armed observational study with 40 patients (20 men and 20 women). The protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. All procedures were performed in accordance with the Helsinki declaration. Written informed consent was obtained from all patients.

Plasma cytokine determinations were performed blinded, but randomization was limited. The decision to perform either function-controlled awake craniotomy or craniotomy under general anesthesia was determined by the neurosurgeon who based his decision on the intracerebral location of the tumor. The type or size (WHO classification of brain tumors) had no influence on whether or not awake craniotomy was chosen. By proxy, patients were allocated to the general anesthesia group unless the location of the tumor warranted the benefits of an awake procedure. Patients with tumors close to functional relevant areas like the motor cortex or areas related to speech require the

awake monitoring made possible by the awake craniotomy procedure. By allocating these patients to the awake craniotomy group maximal tumor resection is made possible with a minimal risk of functional neurological damage.

Eligible patients were >18 years of age and were undergoing craniotomy for an intracerebral tumor. Patients were excluded if they were (1) ASA-classification IV-V, (2) did not provide written informed consent, (3) had a tumor location other than intracerebral, (4) had surgery beginning later than 11:00 a.m., (5) had a disease of the endocrine system or (6) were taking drugs that alter endocrine metabolism (like thyroxine). Noncooperative or noncompliant patients could be withdrawn from the study, as could patients who developed serious adverse effects.

Anesthesia Procedure.

Patients in both groups received 1.5 mg lorazepam on the evening before the surgery. All patients were on a regimen of dexamethasone 4×4 mg/day with the first dose given at least one day prior to surgery; regular personal drug regimens were continued during the study. In the awake function-controlled group, 7.5 mg piritramide and 25 mg promethazine were given 30 minutes prior to induction. In the general anesthesia group, premedication consisted of 50 mg promethazine. In both groups propofol was administered for sedation and remifentanil for analgesia. The general anesthesia group received an additional 0.25mg fentanyl before intubation and placement of the Mayfield clamp. Cis-atracurium was used for muscle relaxation prior to intubation. In order to provide adequate pain control during awake craniotomy patients were infiltrated with bupivacaine 0.375% with adrenaline 1:200.000 at the site of scalp incision. Postoperatively all patients were offered 4 times one gram paracetamol per day, and if required, supplemental morphine.

Outcome Measures.

Patient characteristics, medications used during and after surgery, fluid balance, and duration of surgery were documented. Pain, anxiety, and stress were measured at 12 and 24 hours pre- and postoperatively, using visual analogue scale (VAS) scores (0 = none, 10 = extreme).

EDTA blood samples (7mL) for cytokine level determinations were collected preoperatively, during the opening and closing of the dura, and 12 and 24 hours postoperatively. Plasma was isolated by centrifugation at 2650 g_{max} for 10 minutes at 20 $^{\circ}$ C; samples were stored at -80 $^{\circ}$ C until assay.

Enzyme immunoassays for the quantitative determination of human IL-6, IL-8, and IL-10 were performed with a sandwich ELISA (Pelikine Compact and additional Pelikine

Toolset, Sanquin, Amsterdam, The Netherlands) as described previously [16]. Data were calculated as pg/mL plasma and presented in Figures 1, 2, and 3 as (log) pg/mL.
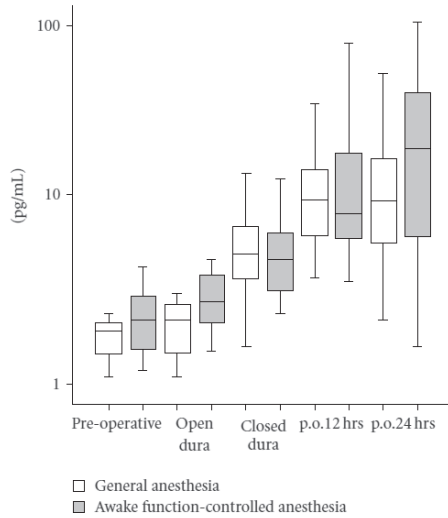
FIGURE 1: *Box plots of plasma IL-6 levels.* A significant IL-6 level increase is found in both experimental groups $F(1.336, 49.416) = 24.148$, $P < .001$. No significant plasma IL-6 level difference is found between groups.
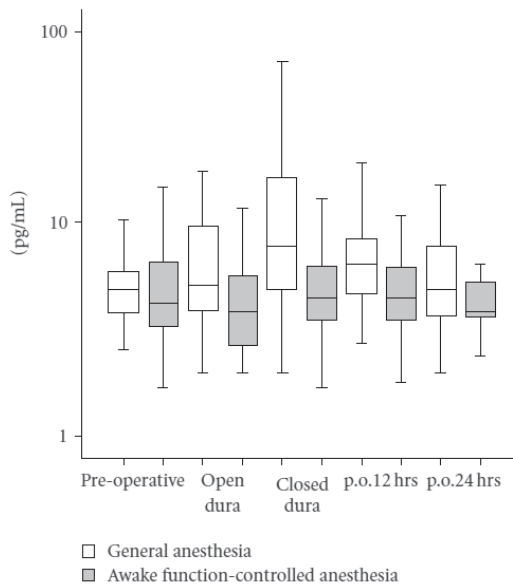
FIGURE 2: *Box plots of plasma IL-8 levels.* IL-8 levels do not significantly change throughout time for both experimental groups. No significant difference in plasma IL-8 levels is found between groups.
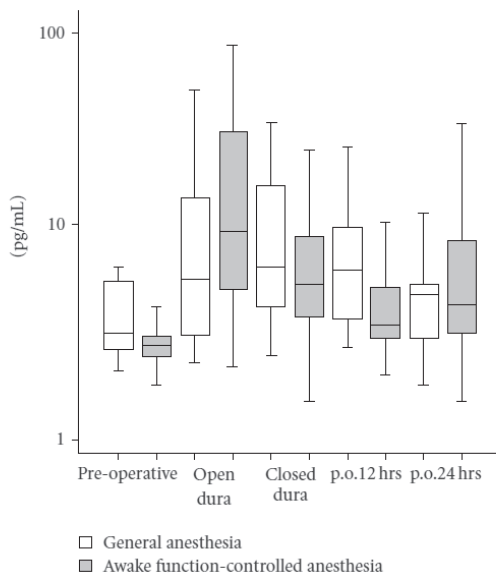
FIGURE 3: *Box plots of plasma IL-10 levels*. IL-10 levels do not significantly change throughout time for both experimental groups. No significant difference in plasma IL-10 levels is found between groups.

Statistical Analysis.

Data were analyzed using SPSS for Windows, version 16.0.1. The independent sample *t*-test was used to compare means for patient demographics (excluding ASA classification) and perioperative characteristics. The Pearson Chi-square test was used to evaluate differences in ASA classification. All data were reported as the mean (SD), counts, or median (25%–75%).

Sample size was calculated using the O'brien-Shieh Algorithm for the MANOVA repeated measures test. Assuming a medium effect, an effect size of 0.6 was used and a power of 0.8. There were two experimental groups and 5 repetitions. The required a priori sample size computed by this method was 39.

For the VAS scores and cytokine data the MANOVA test was used. Differences in VAS score or cytokine values between the experimental groups across all time points and interaction between experimental groups and time were analyzed using multivariate repeated measures. Experimental group and time were the independent variables. When Mauchly's Test of Sphericity was significant, the Greenhouse-Geisser test of within-subjects-effects was used. When a significant difference was found between experimental groups a one-way ANOVA test with posthoc multiple comparisons

(Bonferroni correction) was used to analyze the relationship between the cytokines or VAS scores from the first preoperative measurement until 24 hours postoperative. The same Bonferroni correction was employed to analyze differences between experimental groups and time. A *P*-value < .05 was considered statistically significant.

RESULTS

Forty patients were included in the study. The awake function-controlled and general anesthesia groups contained 20 patients each, stratified for gender (10 males and 10 females). No significant intergroup differences were observed for age, height, weight, ASA classification, or Hb concentration (Table 1).

Perioperative characteristics are described in Table 2. As expected, the total amount of propofol administered throughout the operation was significantly less in the awake group than in the general anesthesia group. The general anesthesia group also received

Table 1: Patient demographics

	General anesthesia	Function-controlled
Age (years)	48 ± 15.4	44 ± 13.2
Gender m/f	10/10	10/10
Height (cm)	174 ± 11.3	176 ± 9.6
Weight (kg)	74 ± 16.5	81 ± 14.7
ASA classification 1/2/3 (number of patients)	9/10/1	5/15/0
Hb concentration (mmol/L)	9.3 ± 1	9.0 ± 0.6

Data presented as mean ± SD

Table 2: Perioperative Characteristics

	General anesthesia	Function-controlled
Propofol during operation (mg)	3277 ± 1632	673 ± 313[a]
Operation time (min)	327 ± 104	275 ± 56
Blood loss during operation (ml)	400 (300–500)	450 (300–600)
Colloids during operation (ml)	500 (500–500)	500 (0–500)
Colloids after operation (mL)	50 ± 200	100 ± 400
Crystalloids during operation (L)	3.7 ± 2.0	1.6 ± 0.7[a]
Crystalloids after operation (L)	2.0 ± 1.0	2.0 ± 0.9
Urine during operation (mL)	1620 (1043–2050)	1042 (480–1483)[b]
Urine after operation (mL)	1759 ± 836	1668 ± 620
Remifentanil	8.4 ± 5.4 mg	200 μg*
Postoperative paracetamol (mg)	2100 ± 1483	1900 ± 1477
Postoperative morphine (mg)	1.60 ± 4.72	2.00 ± 5.48

Function-controlled versus general anesthesia significantly different: [a] *P* < .001 and [b] *P* = .004.
Data presented as mean ± SD and median (25%–75%). *Maximum total amount of boluses given.

more crystalloids during the operation. The total amount of remifentanil used in the general anesthesia group was 8.4 ± 5.4mg. No more than 200 μg of remifentanil was given to the awake craniotomy group.

Plasma concentrations of IL-6, IL-8, and IL-10 during all time points are displayed in Figures 1 through 3.

IL-6 level significantly increased with time in both experimental groups (main effect of time: $F(1, 49) = 24.1$, $P < .001$, observed power = 1.00).

However, there were no differences between groups (group-time interaction: $F(1, 37) = 1.3$, $P = .3$, observed power = 0.20). Furthermore, IL-8 levels did not significantly change with time in both experimental groups (main effect of time: $F(1, 48) = 2.2$, $P = .1$, observed power = 0.35) and no significant IL-8 differences between groups (group-time interaction: $F(1, 37) = 2.8$, $P = .1$, observed power = 0.37).

The same applied for IL-10 levels, there were no significant change with time in both experimental groups (main effect of time: $F(1, 39) = 2.6$, $P = .1$, observed power = 0.36) and no significant differences between groups (grouptime interaction: $F(1, 37) = 0.6$, $P = .4$, observed power = 0.12).

There were no significant differences between groups in the amount of postoperative morphine and paracetamol used. The mean subcutaneous postoperative morphine administered in the general anesthesia group was 1.60 (±4.72 mg), while the mean given to the awake group was 2.00 (±5.48 mg). The mean postoperative paracetamol administered to the general anesthesia group was 2100 (±1483 mg), while the mean given to the awake group was 1900 (±1477 mg).

Pain increased significantly with time in both experimental groups (main effect of time: $F(2, 80) = 24.6$, $P < .001$). However, a significant difference between groups ($F(1, 35) = 7.6$, $P = .009$) was noted with the awake group having less pain at the 12 hours postoperative time point (Figure 4).

   Anxiety significantly decreased with time in both experimental groups (main effect of time: $F(2, 69) = 4.6$, $P = .013$) and there was a significant stress decrease with time in both experimental groups (main effect of time: $F(2, 85) = 7.9$, $P < .001$).
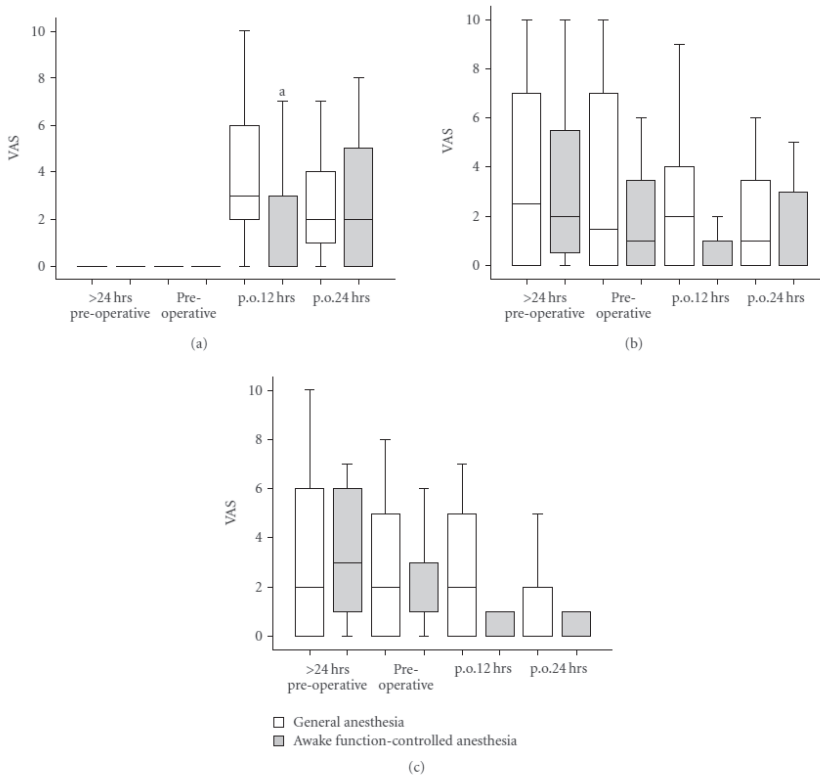
FIGURE 4: *Box plots of pain, anxiety, and stress.* (a) *Pain.* A significant increase in pain is experienced in both experimental groups $F_{(2.290, 80.165)} = 24.642$, $P < .001$. A significant difference $F_{(1, 35)} = 7.632$, $P = .009$ was observed in the awake group compared to the general anesthesia group at "p.o.12 hours" [a]. (b) *Anxiety.* A significant decrease in anxiety is experienced in both experimental groups $F_{(1.982, 69.362)} = 4.637$, $P = 0.013$. (c) *Stress.* A significant decrease in stress is experienced in both experimental groups $F_{(2.426, 84.911)} = 7.920$, $P < .001$.

DISCUSSION

We believe we are the first to compare the cytokine profiles of awake and general anesthesia craniotomy groups. Cytokine release is also a known physical reaction to tissue damage. The influence of surgery on cytokine plasma levels has been addressed during several studies. There is a great amount of evidence linking IL-6 to the degree of surgical trauma [17–22]. In addition, there are also studies that establish a clear relationship between dynamic IL-6 changes and cortisol plasma levels during the perioperative period [11,23]. The nonsignificant differences in IL-6 levels between groups found during this experiment suggest from an immunological perspective that both procedures are likely to be similarly stressful for the body. However, the low and medium observed power of our negative findings requires a larger patient group to provide more certainty.

It is interesting to note the significant plasma IL-6 increase despite the exact dexamethasone 4×4mg/day regime given to both experimental groups. Another study investigat-

ing the effects of dexamethasone produced different results. Morariu et al. found that after receiving dexamethasone (1 mg/kg) before anesthesia induction, plasma levels of both IL-6 and IL-8 were significantly reduced, while levels of IL-10 increased perioperatively [24].

Our finding that there was a significant plasma IL-6 increase throughout time for both experimental groups and a significant increase in reported pain can be partially explained by the expected increase in pain after tissue damage. It is noteworthy that an increasing pain trend matches the increasing IL-6 tendency observed. The important role interleukin-6 plays in nociception and the pathophysiology of pain during a variety of different conditions might explain this trend [25]. A study done with rat models observed that higher IL-6 concentrations were linked to more intense hyperalgesia [26].

Recently, plasma IL-8 has been measured as a key mediator for neuroinflammation in patients with severe traumatic brain injuries [27]. Central venous plasma IL-8 levels were significantly lower in survivors than in nonsurvivors. In our study, the insignificant in-between- and within-subject plasma IL-8 change in both experimental groups was unexpected. Due to IL-8's presence in neutrophils, microglia, astrocytes and endothelial cells of the brain [28–31] we expected damaged brain tissue to cause an increased release of IL-8 over time from these sources. However, the studies involving traumatic brain injury patients contain a different patient population then ours and different confounders. The additional hypoxia and ischemia experienced in these severely injured traumatic brain injury patients can be attributed to shock and resulting hypoperfusion and might account for increased plasma IL-8 levels [32].

Awake craniotomy is considered a stressful procedure. It seems logical that being awake while a neurosurgeon removes pathological brain tissue would lead to a more intense emotional response than undergoing the same procedure under general anesthesia. However, perhaps good psychological support and active coping mechanisms may actually make awake craniotomy less stressful for the patient. This might be due to the awake group having decreased feelings of dependency and loss of control than those in the general anesthesia group.

Our results show that patients undergoing awake function-controlled craniotomy experience less 12 hours postoperative pain than their general anesthesia counterparts. The intensive preoperative consultation patients received might have influenced results due to the subjective nature of the VAS scoring system [33]. It could be argued that perioperative medication may also have influenced VAS score results. Patients who underwent awake function-controlled craniotomy received 25 mg of promethazine and 7.5 mg

of piritramide 30 minutes before surgery. In comparison, general anesthesia patients received 50mg of promethazine and two boluses of fentanyl, one prior to induction and another prior to placement of the Mayfield clamp. Piritramide and fentanyl are both opiates with additive sedative and euphoric properties. They are also accepted drugs for surgical procedures like craniotomy [34]. Additionally, the seven and six hours half life of piritramide and fentanyl make them unlikely to affect the first postoperative VAS score measurement taken at 12 hours postoperative [35, 36]. We think that the local anesthesia provided by bupivacaine infiltration at the site of scalp incision was the primary reason why VAS scores were significantly lower in the awake group.

The differing nature of awake craniotomy and general anesthesia techniques requires a larger amount opiates to be given to the general anesthesia group. There is some evidence that opiates can modulate the immune system [37–39]. However, our results reveal similar pro- and anti-inflammatory profiles for both groups with no significant difference having been found between groups. It is still important to consider that the larger opiate amount given to the general anesthesia group could have altered its immunological profile. However, the aim of this study is to compare the inflammatory profile of two different anesthesia techniques. General anesthesia cannot be performed without a greater amount of opiates being used by the anesthesiologist.

The smaller amount of propofol administered to the awake group is due to the reduced need for sedation during the awake craniotomy procedure. On the other hand, the larger amount of crystalloids given to the general anesthesia group can be explained by the need to counteract the vasodepressive properties of propofol (Table 2).

A limitation of our study is that for ethical reasons allocation of patients to one group or another could not be randomized. This restriction could bias our results. However, keeping the previously mentioned limitations in mind, the plasma levels of pro- and anti-inflammatory cytokines measured during this study suggests that awake function-controlled craniotomy does not cause a significantly different inflammatory response than craniotomy performed under general anesthesia. Furthermore, the nonsignificant difference in subjective outcome parameters for pain (with exception 12 hours postoperative), anxiety, and stress insinuates that both procedures are equally mentally challenging. Therefore, it is likely that function-controlled craniotomy does not cause a greater inflammatory insult or emotional challenge than patients undergoing tumor resection using general anesthesia.

ACKNOWLEDGMENTS

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Chapter 4

Awake craniotomy induces fewer changes in the plasma amino acid profile than craniotomy under general anesthesia.

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AWAKE CRANIOTOMY INDUCES FEWER CHANGES IN THE PLASMA AMINO ACID PROFILE THAN CRANIOTOMY UNDER GENERAL ANESTHESIA.

ABSTRACT

In this prospective, observational, 2-armed study, we compared the plasma amino acid profiles of patients undergoing awake craniotomy to those undergoing craniotomy under general anesthesia.

Both experimental groups were also compared with a healthy, age-matched, and sex-matched reference group not undergoing surgery. It is our intention to investigate whether plasma amino acid levels provide information about physical and emotional stress, as well as pain during awake craniotomy versus craniotomy under general anesthesia. Both experimental groups received preoperative, perioperative, and postoperative dexamethasone. The plasma levels of 20 amino acids were determined preoperatively, perioperatively, and postoperatively in all groups and were correlated with subjective markers for pain, stress, and anxiety.

In both craniotomy groups, preoperative levels of tryptophan and valine were significantly decreased whereas glutamate, alanine, and arginine were significantly increased relative to the reference group. Throughout time, tryptophan levels were significantly lower in the general anesthesia group versus the awake craniotomy group. The general anesthesia group had a significantly higher phenylalanine/tyrosine ratio, which may suggest higher oxidative stress, than the awake group throughout time. Between experimental groups, a significant increase in large neutral amino acids was found postoperatively in awake craniotomy patients, pain was also less and recovery was faster. A significant difference in mean hospitalization time was also found, with awake craniotomy patients leaving after 4.53±2.12 days and general anesthesia patients after 6.17±1.62 days; P=0.012.

This study demonstrates that awake craniotomy is likely to be physically and emotionally less stressful than general anesthesia and that amino acid profiling holds promise for monitoring postoperative pain and recovery.

INTRODUCTION

General anesthesia using endotracheal intubation is the standard procedure during brain tumor resection; however, it does limit intraoperative monitoring of functional lesions made to the central nervous system. The anesthetic drugs used suppress neuronal activity making it impossible to monitor certain higher cortical brain functions unless the patient regains consciousness during the operation. Examples of higher cortical brain functions that can only be checked during awake craniotomy are speech, sensibility, and complex motor functions like drawing. Therefore, awake craniotomy is the ideal anesthetic approach for when function-controlled neurosurgery is necessary. During this procedure, the cerebral cortex of the awake patient is electrically stimulated identifying and thus sparing functionally relevant areas of the brain. Details of our technique have been described previously.[1]

Public perception is that awake craniotomy is physically and emotionally more stressful than brain tumor resection under general anesthesia. However, with adequate local anesthesia and proper preoperative consultation patients undergoing awake craniotomy report less pain, discomfort and fear.[2,3] When proper steps are taken, the majority of patients tolerate awake craniotomy very well. In comparison, patients undergoing craniotomy using general anesthesia have to endure more physical stress factors like intubation, longer hospital stays, and artificial ventilation.[4]

Biochemical factors relating to stress and anxiety, the perception of pain, and the rate of postoperative recovery in neurosurgical patients have not been investigated. Cortisol levels have traditionally been used to indicate physical stress [5]; however, our standard operating procedure mandates the administration of dexamethasone, which influences cortisol levels. It was therefore decided to investigate whether or not plasma amino acids have potential to be used as biomarkers for pain and physical stress.

A number of amino acids play an important role in pain pathways. The neuropeptide bradykinin is known to increase sensitization of pain via the N-methyl-D-aspartate (NMDA) receptor in the central nervous system, which is turn, is stimulated by the amino acid glutamate.[6] The amino acid glutamine also plays a role in this pathway because it is the precursor for glutamate.[7,8] Glutamine, on the other hand, may inhibit the generation of the amino acid arginine, a precursor for nitric oxide (NO) and citrulline. [9] Interestingly, the amino acid ratio of citrulline/arginine is used and accepted as an index of NO synthesis.[7] It is known that NO is a potent vasodilator. Less NO production causes vasoconstriction resulting in diminished tissue blood perfusion and increased pain intensity.[10]

Glycine is an amino acid that acts as a coagonist with glutamate on the NMDA receptor. [11] Both amino acids are thought to be mainly responsible for neuropathic pain and mood disorders.[12,13]

Taurine is an amino acid known to play a significant role in neuromodulation.[14] Animal studies have shown that physical stress is associated with a sharp rise in plasma taurine levels.[15] It has also been demonstrated that taurine diminishes neuropathic nociception.[16]

Current data about the effects of physical stress on large neutral amino acids (LNAAs), that is valine, leucine, isoleucine, tryptophan (trp), tyrosine (tyr), and phenylalanine (phe) are somewhat contradictory. A study performed with rats found that although rested rats had decreased plasma levels of valine and tryptophan, tyrosine levels increased.[15] Yet, patients undergoing cardiac surgery using general anesthesia had decreased levels of valine, leucine, isoleucine, and tyrosine, whereas tryptophan and phenylalanine levels increased.[17]

This is the first study to compare absolute plasma values of amino acids over time during surgery between patient groups who received general anesthesia and patients who underwent an awake craniotomy procedure. Our aim was to determine whether or not the changes in plasma amino acid levels can be correlated to the type of anesthesia administered.

We also compared these plasma amino acid values to an age-matched and sex-matched reference group that did not undergo surgery. Furthermore, plasma amino acids were correlated with quality of life factors such as stress, anxiety, and pain.

When we compare the general anesthesia and awake craniotomy groups, we hypothesize that awake craniotomy patients will have fewer changes in their amino acid profiles while having a faster recovery and resulting shorter hospitalization time.

PATIENTS, MATERIALS, AND METHODS

Study Set-up and Inclusion Criteria
This study was a prospective, single center, 2-armed observational study with 40 patients, stratified for sex. Sex stratification is necessary because there are known intersex differences in amino acid and hormone profiles.[18] The protocol was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. All procedures

were performed in accordance with the Helsinki declaration. Written informed consent was obtained from all patients.

The patients were not randomized because allocation to an awake craniotomy procedure or a general anesthesia group had to do with location of the tumour. The type or size (World Health Organization classification of brain tumours) had no influence on whether or not awake craniotomy was chosen. By proxy, patients were allocated to the general anesthesia group unless the location of the tumor warranted an awake procedure. Patients with tumors close to functional relevant areas like the motor cortex or areas related to speech require the awake monitoring made possible by the awake craniotomy procedure. By allocating these patients to the awake craniotomy group, maximal tumor resection is made possible with a minimal risk of functional neurological damage.[19]

Sex stratification was achieved by including consecutive patients to all groups until the maximum for a certain group (eg, women, awake) was achieved. Once a maximum number of patients for a particular group was attained, only patients belonging to one of the other still open groups (eg. man, general anesthesia) were included in the study.

Inclusion criteria were (1) undergoing craniotomy for a cerebral neoplasm situated in close proximity to an eloquent area, (2) age >18 years, (3) American Society of Anesthologists (ASA) classification I-III, and (4) written informed consent. Exclusion criteria were (1) ASA classification IV-V, (2) informed written consent missing, (3) tumor other than intracerebral, (4) surgery beginning later than 11:00 AM. (5) endocrine problems, or (6) taking drugs that influence endocrine metabolism. Operations starting after 11:00 AM were excluded because Eriksson et al[20] found that essential amino acids are affected by the circadian rhythm. Patients had the right to withdraw from the study at any time. Patients who developed serious adverse effects were to be withdrawn from the study. Examples of serious adverse effects include prolonged unconsciousness, severe bleeding requiring a blood transfusion, or any other event likely to strongly interfere with our protocol.

A healthy age-matched and sex-matched reference group was used to compare results obtained from the experimental groups. Blood plasma donors in this reference group donated blood after having had a light breakfast low in fat and protein.

Food Intake

All patients were hospitalized the day before surgery. They were allowed to eat and drink until midnight. Afterward, only apple juice or tea with sugar were permitted until 06:00 AM on the morning of surgery. Anesthesia was induced between 8:00 and 8:15 AM. After surgery, all the patients were transferred to the postanesthesia care unit (PACU) and monitored for 14 hours. During this time, morphine was available and if necessary titrated intravenously until acceptable pain levels were achieved. While in the PACU, patients were told that food could be requested and delivered at any time during their stay.

Anesthesia Procedure

Patients in both the groups received 1.5 mg lorazepam on the evening before surgery. Otherwise, all patients were on a regimen of dexamethasone 4x4 mg/d while regular personal drug regimens were continued. In the awake craniotomy group, 7.5 mg piritramide and 25 mg promethazine was given 30 minutes before induction. Piritramide was used to reduce pain perception during skull infiltration with 40 mL bupivacaine 0.375%+adrenaline 1:200,000. Benzodiazepines were not an option due to the paradoxical reactions that are sometimes associated with its use. In addition, benzodiazepines would reduce the responsiveness of propofol, making it less effective for sedation. In the group undergoing general anesthesia, the premedication consisted of 50 mg promethazine. In both groups, propofol was used for sedation and remifentanil for analgesia. In the general anesthesia group, cis-atracurium was used for muscle relaxation.

Postoperative Pain Control

After surgery, patients were transferred to the PACU where they were monitored and primarily treated with paracetamol for pain. If pain control was not adequate, morphine was administrated until adequate pain control was achieved. Postoperative pain medication administered was documented.

General Outcome Measures

Patient demographics (Table 1) as well as perioperative characteristics were noted (Table 2). Quality of life was measured using the visual analog scale (VAS) for stress, pain, and anxiety preoperatively and at 12 and 24 hours postoperative (Table 3). Although there are overlapping elements relating to the concepts of stress and anxiety, VAS scores for each was obtained separately.

TABLE 1. Patient Demographics

	General Anesthesia	Awake
Age (y)	48 ± 15.4	44 ± 13.2
Sex (M/F)	10/10	10/10
Length (cm)	174 ± 11.3	176 ± 9.6
Weight (kg)	74 ± 16.5	81 ± 14.7
ASA classification 1/2/3 (no. patients)	9/10/1	5/15/0
Hb concentration (mmol/L)	9.3 ± 1	9.0 ± 0.6

Data are mean ± SD except for sex and ASA classification.
ASA indicates American Society of Anesthesiologists; Hb, hemoglobin.

TABLE 2. Perioperative Characteristics

	General Anesthesia	Awake
Propofol during operation (mg)	3277 ± 1632	673 ± 313*
Operation time (min)	327 ± 104	275 ± 56
Blood loss during operation (L)	0.8 ± 1.7	0.4 ± 0.2
Colloids during operation (L)	0.6 ± 0.5	0.4 ± 0.3
Colloids postoperative (L)	0.05 ± 0.2	0.1 ± 0.4
Crystalloids during operation (L)	3.7 ± 2.0	1.6 ± 0.7*
Crystalloids postoperative (L)	2.0 ± 1.0	2.0 ± 0.9
Urine during operation (mL)	1857 ± 1583	1007 ± 469†
Urine postoperative (mL)	1759 ± 836	1668 ± 620

Data are mean ± SD. Awake versus general anesthesia.
*$P < 0.001$.
†$P < 0.03$.

TABLE 3. Preoperative and Postoperative Stress, Anxiety, and Pain as Determined by Visual Analog Score

	Preoperative		12h Postoperative		24h Postoperative	
	General Anesthesia	Awake	General Anesthesia	Awake	General Anesthesia	Awake
Stress (0-10)	3.15 ± 3.2	2.4 ± 2.1	2.3 ± 2.7	0.90 ± 1.9	1.4 ± 2.1	0.90 ± 1.9
Anxiety (0-10)	3.5 ± 3.6	1.6 ± 2.1†	2.1 ± 2.7	0.80 ± 2.0†	1.8 ± 2.0	1.1 ± 1.8
Pain (0-10)	0.1 ± 0.3	0.3 ± 0.7	3.8 ± 2.8	1.5 ± 2.4*	2.6 ± 2.3	2.7 ± 2.6

Data are mean ± SD. Awake versus general anesthesia.
*$P < 0.01$.
†$P < 0.05$.

Blood Sampling

Ethylene diamine tetra-acetate blood samples (7mL) for amino acid level determinations were collected preoperatively (t1), during opening (t2) and closing of the dura (t3), and 12 (t4) and 24 (t5) hours postoperative. Plasma was isolated by centrifugation at 2650 g_{max} for 20 minutes at 20 º C; samples were stored at -80º C until assay.

Plasma Amino Acid Level Determination

Blinded plasma amino acid determinations were performed. Each plasma sample was deproteinized with 5-sulphosalicylic acid (6%, wt/vol) containing norvaline and ho-moserine as internal standards. Amino acids were assayed by high performance liquid chromatography using automated precolumn derivatization with o-phthaldialdehyde and fluorescence detection.[21] The amino acids measured were: the essential amino acids including the LNAAs tryptophan, valine, leucine, isoleucine, tyrosine, and phe-nylalanine; as well as lysine, histidine, threonine, and methionine; and the nonessential amino acids (NEAAs) glutamate, glutamine, glycine, serine, taurine, asparagine, alanine, ornithine, arginine, and citrulline. The trp/LNAA ratio was calculated by dividing 100 times the plasma concentration of trp by the sum of all other LNAAs. The phe/tyr ratio was calculated to estimate the functional availability of the cofactor tetrahydrobiopterin (BH4). Hydroxylation of phe to tyr is highly dependent on this cofactor.

The limits of detection depended on the amino acid because of the different fluores-cence responses and differing peak shapes of the derivatives. Typical values were 54 fmol for glutamate and 167 fmol for serine. Concentrations of amino acids as low as 0.5 mmol/L in plasma can be measured accurately with our method. The interassay coef-ficient of variation was for all amino acids below 4%.

Statistical Analysis

Data were analyzed using SPSS for Windows, version 12.0.1. The Kolmogorov-Smirnov test was used to analyze whether or not amino acids values were normally distributed. All amino acid values except glutamic acid measured at time points 1, 3, 5, and taurine 4 were normally distributed.

For the non-normal distributed values, we still decided to use multivariate analysis of variance (MANOVA) test. Although MANOVA test requires that each dependent variable entered into the analysis be normally distributed it was still used because the Monte Carlo experiments have shown that for sample sizes of 3 or 5 it is still possible to analyze leptokurtic, rectangular, J-shaped, moderately, and markedly skewed distributions. These experiments demonstrated that the empirically determined rejection region of the F-distribution would be no larger than a=0.08 when the usual 5% rejection is used. [22] The results are therefore presented as mean±standard deviation (SD).

Differences in plasma amino acid levels between experimental groups across all time points (5 moments of time) and interaction between experimental group and time were analyzed using multivariate repeated measures. Experimental group and time were the independent variables.

When a significant difference was found between experimental groups, a 1-way ANOVA test with post hoc multiple comparisons (Bonferroni correction) was used to analyze the relationship between plasma amino acids and time from the moment of plasma donation until 24 hours after donation. The same statistical method was employed to analyze differences between preoperative and 24-hour postoperative plasma amino acid levels in the 2 experimental groups.

Differences relating to patient demographics (excluding ASA classification), perioperative characteristics and preoperative plasma amino acid levels between experimental groups were tested using the t test for independent samples. This same test was used to compare the mean amount of postoperative analgesia given as well as the mean number of days until discharge for both experimental groups. Pearson χ2 test was used to evaluate differences in ASA classification.

Correlations between patient characteristics, amino acids, and the quality of life measures were evaluated using Pearson correlation test. Sample size was calculated using the MANOVA repeated measures test. An effect size of 0.6 was used and a power of 0.8. There were 2 experimental groups and 5 repetitions. The required a priori sample size computed by this method was 39. For all statistics, α was set at the traditional 0.05 level.

RESULTS

Demographics
A total of 40 patients were included in the study with 20 being allocated to both groups. The 2 groups of 20 were stratified for sex (10 males and 10 females). No intergroup differences were observed for age, length, weight, ASA classification, or hemoglobin concentration (Table 1).

Perioperative Characteristics
Perioperative characteristics are shown in Table 2. The total amount of propofol administered throughout the operation was significantly less in the awake craniotomy group. Total operating time in the awake craniotomy group was also less. The general anesthe-

sia group had more blood loss, higher urine output, and as a result received significantly more crystalloids during the operation. The average total amount of remifentanil used in the general anesthesia group was 8.4 mg whereas an average total bolus of 200 µg was given to the awake group.

Quality of Life Indicators

The awake craniotomy group reported significantly less preoperative and postoperative VAS scores for anxiety than the general anesthesia group. The awake craniotomy group also disclosed having less pain postoperatively (Table 3).

Recovery, Food Intake, and Hospitalization

Both the patient groups were offered food postoperatively during recovery in the PACU. All awake craniotomy patients requested and received their first meals within 12 hours of surgery. As a result, the awake craniotomy patients had blood taken (t3) after their first meal. All the patients in the general anesthesia group, however, requested and had their first meal after the12 hours postoperative blood sample (t3) was taken. Consequently, the general anesthesia group had blood taken before their first meal.

From the moment of arrival in the intensive care until 24 hours postoperative, all the patients were offered 4 times 1 gram paracetamol, and if required, nurses titrated IV morphine until acceptable pain levels were achieved. There was no significant difference found between both groups in postoperative morphine and paracetamol use. The mean postoperative morphine administrated in the general anesthesia group was 1.60±4.72 mg, whereas the mean given to the awake group was 2.00±5.48 mg; P=0.806. The mean postoperative paracetamol administered to the general anesthesia group was 2100±1483 mg, whereas the mean given to the awake group was 1900±1477 mg; P=0.668.

A significant difference in mean hospitalization time was also found. Awake craniotomy patients left the hospital after an average of 4.53±2.12 days. Patients in the general anesthesia group left on average after 6.17±1.62 days; P=0.012.

Preoperative Plasma Amino Acid Levels

We detected no differences in the preoperative plasma amino acid levels between craniotomy groups (Tables 4 and 5); therefore, anesthesia procedure assignment did not affect preoperative amino acid levels. However, significant preoperative sex differences were observed for glutamate (males, 104±47 mmol/L; females, 73±44 mmol/L; P=0.040) and tryptophan levels (males, 36±8.1 mmol/L; females, 30±9.1 mmol/L; P=0.037).

TABLE 4. Preoperative and Postoperative Plasma Levels of Essential Amino Acids Craniotomy Patients

Amino Acid (µmol/L)	General Anesthesia		Awake		
	Preoperative	Postoperative 24 h	Preoperative	Postoperative 24 h	Reference
Tryptophan	30 ± 8*	43 ± 12*	36 ± 9*	48 ± 11	50 ± 8
Valine	236 ± 76*	262 ± 54	232 ± 54*	269 ± 67	285 ± 58
Leucine	132 ± 37	164 ± 50	134 ± 28	168 ± 44	147 ± 31
Isoleucine	69 ± 21	91 ± 26	67 ± 14*	85 ± 23	82 ± 23
Tyrosine	58 ± 12*	80 ± 25	61 ± 10	81 ± 17	70 ± 16
Phenylalanine	62 ± 10	79 ± 17*	63 ± 10	76 ± 13*	62 ± 10
Lysine	201 ± 29	216 ± 63*	214 ± 54*	220 ± 59*	185 ± 35
Histidine	81 ± 11	80 ± 18	85 ± 16	78 ± 15	84 ± 11
Threonine	117 ± 29*	139 ± 43	124 ± 32	140 ± 50	144 ± 33
Methionine	29 ± 5	38 ± 12	32 ± 7	38 ± 12	31 ± 6

Data are mean ± SD.
*$P < 0.05$ versus reference group T.
No significant differences between craniotomy groups, preoperative and postoperative.
BAAs indicates basic amino acids; BCAAs, branched chain amino acids; LNAAs, large neutral amino acids.

TABLE 5. Preoperative and Postoperative Plasma Levels of Nonessential Amino Acids

Craniotomy Patients

Amino Acid (µmol/L)	General Anesthesia		Awake		
	Preoperative	Postoperative 24 h	Preoperative	Postoperative 24 h	Reference
Glutamate	99 ± 67*	85 ± 63*	84 ± 29*	66 ± 24*	47 ± 20
Glutamine	587 ± 131	531 ± 135	616 ± 126	520 ± 108	559 ± 85
Glycine	224 ± 50	220 ± 68	226 ± 72	216 ± 86	216 ± 40
Serine	104 ± 22	108 ± 23	110 ± 20*	112 ± 30	111 ± 20
Taurine	50 ± 12	46 ± 30	53 ± 20	38 ± 9	42 ± 8
Asparagine	51 ± 9*	59 ± 14	51 ± 11	57 ± 18	58 ± 11
Alanine	503 ± 171*	487 ± 184*	480 ± 167*	439 ± 189	396 ± 85
Ornithine	59 ± 9*	66 ± 25*	61 ± 14*	60 ± 16*	86 ± 23
Arginine	109 ± 24*	93 ± 36*	108 ± 18*	90 ± 22*	71 ± 22
Citrulline	33 ± 9	23 ± 7*	30 ± 7	22 ± 6*	35 ± 8

Data are mean ± SD.
*$P < 0.05$ versus reference group.
BAAs indicates basic amino acids; NMDA, N-methyl-D-aspartate–related amino acids. No significant differences between craniotomy groups, preoperative and postoperative.

There are significant differences in the preoperative and postoperative levels of a number of amino acids when comparing the experimental groups with the reference group (Tables 4 and 5). Preoperative fasting could have influenced these levels. However, when comparing the plasma amino acid levels of experimental groups to the reference group at the 24-hour postoperative time point when fasting is not a problem, it was found that the general anesthesia group still had decreased levels of tryptophan and ornithine. In addition, postoperative levels of lysine, arginine, glutamate, and alanine were still increased in both experimental groups.

At t5, citrulline and phenylalanine are worth noting. Citrulline is decreased in both experimental groups in comparison to the reference group, whereas the inverse was true for phenylalanine.

Time-related Effects of Anesthesia and Surgery

We analyzed the time-related effects of anesthesia and surgery on the plasma levels of amino acids. Figure 1 shows the plasma levels of tryptophan and the other essential LNAAs. During anesthesia/surgery, both experimental groups demonstrate a similar

decline in plasma tryptophan levels. However, worth noting is that tryptophan levels were significantly lower in the general anesthesia group when compared with the awake craniotomy group both during anesthesia/surgery and 12 hours postoperatively.

Figure 1 also shows a plot of the phenylalanine/tyrosine ratio. The ratios before and at the start of surgery are remarkably elevated for both groups when compared with our healthy nonsurgical reference group. The ratio then peaks at the end of surgery.
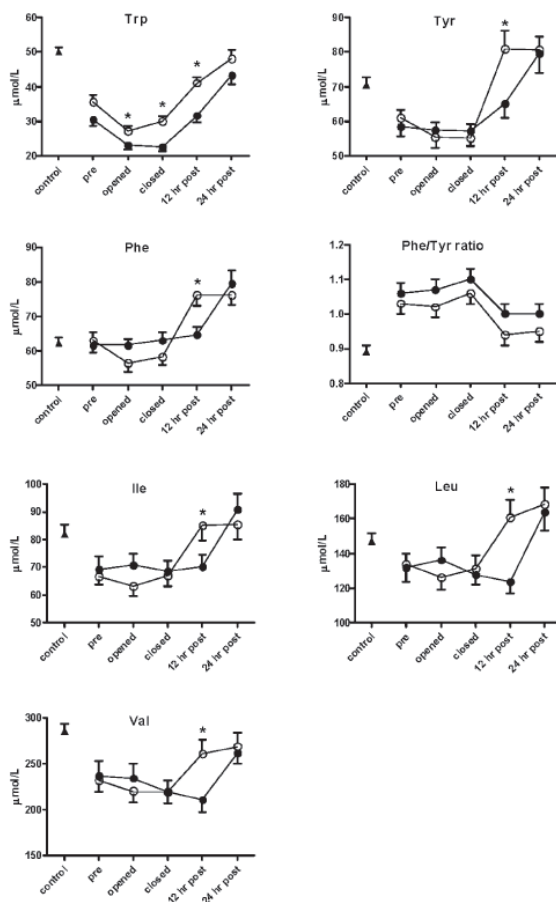
FIGURE 1. Time course of plasma levels (μmol/L) of large neutral amino acids (LNAAs) tryptophan (Trp), tyrosine (Tyr), phenylalanine (Phe), phenylalanine/ tyrosine ratio (Phe/Tyr), valine (Val), isoleucine (Ile), and leucine (Leu) in awake and general anesthesia craniotomy patients versus reference group. Reference group, sex-matched, and age-matched healthy person without anesthesia or surgery; pre, preoperative; opened, opened dura; closed, closed dura; 12-hour post, 12-hour postoperative; 24-hour post, 24-hour postoperative. *$P<0.05$ awake craniotomy versus general anesthesia. ($\circ$ indicates awake; $\bullet$, general; $\blacktriangle$, healthy reference group).

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However, postoperatively both experimental groups experience a considerable drop to levels similar to the healthy reference group. It is worth noting that throughout time, the general anesthesia group has a significantly higher ratio then the awake group (P=0.016).

The rest of the LNAAs show a general trend with a major increase occurring postoperatively, except, a faster increase with significantly higher LNAA levels is noted in the awake craniotomy patients. This reflects the faster recovery awake craniotomy patients experience during their first 12 hours in the PACU.

The levels of NMDA receptor-related NEAAs glutamate, glutamine, and glycine are presented in Figure 2. Glutamate and glutamine exhibited time dependent level changes, although no group differences were found. On the contrary, glycine showed no significant time dependent or group differences.

Plasma levels of endothelium-related NEAAs arginineand citrulline demonstrated a time-dependent decline but there were no intergroup differences (Fig. 3).
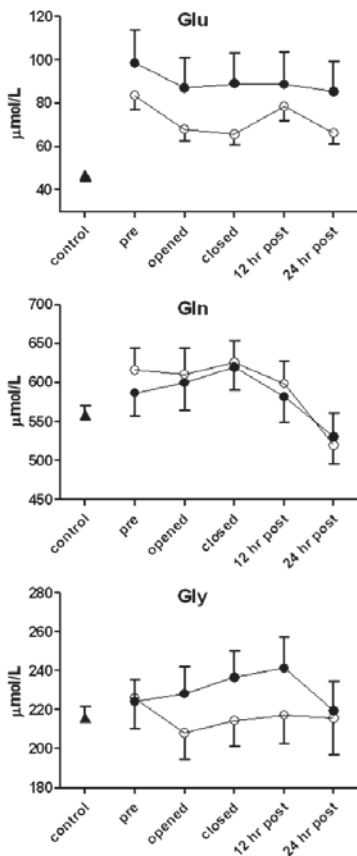
FIGURE. 2 Time course of plasma levels (μmol/L) of NMDA receptor-related and nonessential amino acids (NEAAs) glutamate (Glu), glutamine (Gln), and glycine (Gly) in awake and general anesthesia craniotomy patients versus reference group. Reference group, sex-matched, and age-matched healthy person without anesthesia or surgery; pre, preoperative; opened, opened dura; closed, closed dura; 12-hour post, 12-hour postoperative; 24-hour post, 24-hour post-operative. (○ indicates awake; ●, general; ▲, healthy reference group). NMDA indicates N-methyl-D-aspartate.
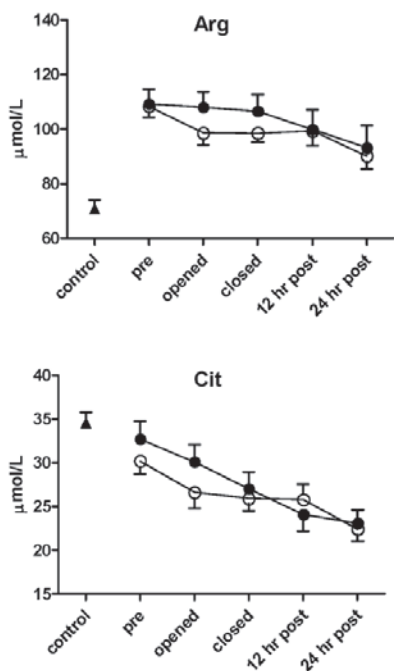
FIGURE 3. Time course of plasma levels (μmol/L) of endothelium-related and nonessential amino acids (NEAAs) arginine (Arg) and citrulline (Cit) in awake and general anesthesia craniotomy patients versus reference group. Reference group, sex-matched, and age-matched healthy person without anesthesia or surgery; pre, preoperative; opened, opened dura; closed, closed dura; 12-hour post, 12-hour postoperative; 24-hour post, 24-hour postoperative. (○ indicates awake; ●, general; ▲, healthy reference group).

Correlations Between Patient Characteristics, Amino Acid Levels, and Quality of Life

Preoperative stress and anxiety were correlated to each other (r=0.77, P<0.001). However, none of the quality of life factors like stress, anxiety, and pain related to amino acid levels. Additionally, levels of citrulline (r=0.40, P=0.011), serine (r=-0.53, P=0.001), and methionine (r=-0.38, P<0.001) were found to be related to patient age.

DISCUSSION

Pain and Amino Acids

As is expected after surgery, pain is significantly increased 12 hours postoperatively in both groups. However, this increase was significantly greater in the general anesthesia group. Anxiety and stress, however, declined similarly for both groups (Table 3).

The subjective nature of pain could explain why the awake craniotomy group reports feeling less postoperative pain than the general anesthesia group. Administration of postoperative pain medication cannot be a factor because in both groups no significant difference in the amount of pain medication given was found. Intensive preoperative consultation might have helped reduce fear in the awake group by giving patients the opportunity to know what to expect during and after the operation.[23] It is also possible

that postoperative pain might have been lessened by the 7.5 mg of piritramide given to the awake craniotomy group, although the 7-hour half life of piritramide and relatively low dosage makes this less likely.[24] A synergistic effect with remifentanil given during surgery is also not very likely considering the remifentanil half life of 3 minutes.[25] In retrospect, although selectively giving piritramide to the awake craniotomy group inorder to make scalp infiltration more bearable might be a confounder, we think the confounding influence is limited considering that around the same time a much more than equivalent dose of opioids is given for the purpose of anesthesia induction in the general anesthesia group.

In both craniotomy patient groups, plasma glutamine levels decreased 24 hours postoperatively (Fig. 2). Despite the administration of analgesics, patients reported mild pain. Reduced levels of plasma glutamine have also been found in burn patients, for whom immunologic function and wound healing are the most prominent issues, in addition to pain.[26] Preoperative levels of plasma glutamate were significantly elevated in both patient groups as compared with our healthy reference group (Fig. 2). Pain perception was not determined at that time, but patients with brain tumours generally have little or no preoperative pain. Preoperative stress and anxiety were mild to moderate in the general anesthesia groups and were lower in the awake group (Table 3). Although not significant, plasma glutamate was 15% lower in the awake craniotomy group, suggesting that physical stress and anxiety might influence levels of the NMDA receptor-related glutamate. Lastly, glutamate levels in the general anesthesia group are noteworthy because it has previously been reported that propofol causes a reversible increase in plasma glutamate.[27] We were not able to confirm this trend.

Sex, Age, and Amino Acids

As Table 1 shows, observed differences between groups cannot be accounted for by sex, however, glutamate and tryptophan were an exception. They were found to be greater in males then in females. Age was positively correlated with preoperative levels of citrulline, suggesting that more NO formed in older individuals. Nonetheless, serine and methionine were negatively correlated with age. These findings agree with data from aging studies[18,28,29] and suggest altered uptake and/or production with advancing age. However, the levels of these amino acids did not undergo significant changes during surgery or anesthesia.

Effects of Premedication, Fasting, Stress, and Anxiety

Dexamethasone, a selective glucocorticoid-receptor antagonist, has been found to increase plasma levels of glutamate, glutamine, and alanine.[30] On the contrary, both tryptophan and tryrosine are diminished after administration of dexamethasone.[31] In

this study when comparing to the reference group, preoperative levels of glutamate and alanine are indeed increased, although glutamine showed no significant changes. Preoperative fasting probably affects plasma amino acid levels. A limitation of our study is that our reference group was not fasted. This influenced the level of essential amino acid levels as illustrated in Figure 1. Preoperatively, levels of essential amino acids in both experimental groups were in all cases, with exception of phenylalanine, lower than in our reference group.

In rats, fasting plus physical stress reduces the plasma levels of the NEAAs alanine and arginine whereas increasing glutamate and glutamine.[32] However in our patients, plasma levels of alanine, arginine, and glutamate were increased.

Time-related Effects of Surgery and Anesthesia

It is known that surgery can cause a decline in fasting plasma levels of alanine, arginine, glutamate, glutamine, and glycine relative to fasting control groups not undergoing surgery.[33] In another study involving patients undergoing thoracic surgery, perioperative plasma levels of tryptophan, glutamine, glycine, and arginine declined rapidly, whereas the levels of valine, leucine, and phenylalanine were slightly or not affected.[34] A study with patients experiencing abdominal aortic aneurysm surgery had glutamine levels decline and remain below preoperative levels for at least 7 days.[35]

Results from this study reveal that only levels of tryptophan are lower during surgery. An additional anesthesia-dependent effect was demonstrated by tryptophan levels being significantly lower in the general anesthesia group. This observation agrees with those of Nunn et al[36] who found a 15% reduction in plasma tryptophan after short-term routine surgery (mean duration 88 min).

Recent research has revealed a remarkable stress mechanism likely to explain the levels tryptophan and phe/tyr ratios found in Figure 1. Stress induces the enzyme indole amine dioxygenase responsible for metabolizing the amino acid tryptophan via the kynurenine pathway.[37] This causes a decrease of available tryptophan in blood plasma. Our results confirm this with the general anesthesia group having a more significant reduction in tryptophan than the awake craniotomy group. Furthermore, it is known that oxidative stress causes a decrease in the cofactor BH4. This cofactor is necessary for the production of serotonine, dopamine, NO, and the conversion of phenylalanine (phe) into tyrosine (tyr).[38]

Therefore, the phe/tyr ratio serves as a reflection of the cofactor BH4 concentration.

The phe/tyr ratio shown in Figure 1 nicely symbolizes expectations before, during and after surgery. In comparison with our healthy reference group the ratio for both experimental groups is increased pre-operatively. At the end of surgery the ratios peak, a time when the body has experienced the maximum amount of physical stress. Twelve hours post-operatively, levels are drastically reduced being lower than pre-operative levels and close to levels found in our healthy reference group. Throughout time, the general anesthesia group has significantly higher ratios than the awake group suggesting that this group experienced higher levels of oxidative stress.

NO

The results show a marked preoperative increase in arginine levels in the two experimental groups with a decrease after surgery but still being increased 24 hours postoperatively relative to our reference group. Considering that citrulline is a marker of NO synthesis, the continuous decline of this amino acid could indicate diminished postoperative c-GMP-dependent vasodilatation. If so, this would result in diminished tissue blood distribution and the spread of pain.[10]

CONCLUSIONS

Preoperative plasma levels of all LNAAs, with the exception of phenylalanine, were decreased in craniotomy patients when compared to levels in our reference group. On the contrary, the NEAAs glutamate, alanine and arginine were markedly increased prior to surgery. Only tryptophan, the precursor of serotonin, decreased significantly during general anesthesia and surgery.

The phe/tyr ratio needs additional study in order to establish whether it can be used as a molecular marker for emotional and/or physical stress. Furthermore, patients undergoing awake craniotomy showed rapid postoperative improvement, as displayed by a faster and significant increase in plasma LNAA levels and shorter hospital discharge times. This fits with our clinical impression that these patients experience less perioperative physical stress than patients undergoing general anesthesia.

This study indicates that amino acid profiling holds promise as an extra physiological tool that could potentially help monitor postoperative recovery. Therefore its value for monitoring surgery-induced stress and pain should be investigated further. In future studies, levels of kynurenine will also be determined along with tryptophan to unravel more direct changes in the activity of indoleamine dioxygenase during surgical stress.

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Chapter 5

Awake craniotomy: improving the patient's experience. (invited review)

Potters JW, Klimek M.

AWAKE CRANIOTOMY: IMPROVING THE PATIENT'S EXPERIENCE.

ABSTRACT

Purpose of review

Awake craniotomy patients are exposed to various stressful stimuli while their attention and vigilance is important for the success of the surgery. We describe several recent findings on the perception of awake craniotomy patients and address nonpharmacological perioperative factors that enhance the experience of awake craniotomy patients. These factors could also be applicable to other surgical patients.

Recent findings

Proper preoperative counseling gives higher patient satisfaction and should be individually tailored to the patient. Furthermore, there is a substantial proportion of patients who have significant pain or fear during an awake craniotomy procedure. There is a possibility that this could induce post-traumatic stress disorder or related symptoms.

Summary

Preoperative preparation is of utmost importance in awake craniotomy patients, and a solid doctor–patient relationship is an important condition. Nonpharmacological intraoperative management should focus on reduction of fear and pain by adaptation of the environment and careful and well considered communication.

Keywords

awake craniotomy, communication, patient management, patient satisfaction

INTRODUCTION

An awake craniotomy remains an intriguing procedure for the anaesthesiologist, as the need for prolonged active cooperation of the patient during a surgical intervention is quite unique. Thereby awake craniotomy stands in stark contrast to other regional anaesthetic techniques in which the patient (or the procedure) profits from a passive cooperation or reduced consciousness of the patient. The need of prolonged vigilance of the patient comes at a price because the patient is exposed to a range of stress factors on different domains and with various intensities. These stress factors range from the diagnosis of a malignant brain tumor and hospital admittance up to the experience of fear, pain and the discomfort of the positioning on the OR-table [1]. Pain during the procedure ranges from mild pain in 14–56% of the patients to severe pain in 5–20% [2,3]. Incidence of anxiety and fear during the procedure also has been assessed in several studies, and ranges from 5 to 50% of the patients [2,4,5]. The overall experience of patients during the procedure has recently been extensively reviewed elsewhere [6]. Although the short-term response of patients who underwent an awake craniotomy is largely very positive, it comes as no surprise that patients can even exhibit post-traumatic stress disorder symptoms directly attributable to the procedure itself [7].

In the recent literature that evaluates the patient's perception of the awake craniotomy, only a few articles explicitly mention the role of the anaesthesiologist during the preoperative phase [4,8,9]. This may reflect local practice or the relationship between anaesthesiologists and neurosurgeons. However, we believe that the success of this procedure is made as a team effort. Therefore, we see a crucial role for the anaesthesiologist, being responsible for the vital functions of the patient and creating conditions that enable the neurosurgeon to perform a smooth tumor resection with a cooperative and unstressed patient. Previous reviews on awake craniotomy in this journal focused on the feasibility and safety of the procedure and medical and pharmacological aspects [10–13]. In this review, we want to highlight techniques and measures that the anaesthesiologist can apply to optimize the patient's experience. The studies we refer to were not exclusively performed in patients undergoing awake craniotomies, but also in other clinical settings. However, we are convinced that many of these findings can be transferred to the awake craniotomy patient as well.

PREOPERATIVE COUNSELING AND PREMEDICATION

The psychological effect of preoperative counseling by the anaesthesiologist has been proven for decades [14]. Although straightforward at first sight, counseling can bring along several possible conflicting interests [15]. General aspects that are important dur-

ing the preoperative counseling are listed in Table 1. Here, we emphasize certain aspects in this process that are important during the counseling of awake craniotomy patients.

Table 1. Do's and don'ts during the preoperative consultation

Do's	Don'ts
Give honest information about the procedure(s)	Give too much or too little information
Discuss risks and complications	Take away opportunities for questions
Be straightforward about options and outcomes	Use technical terms or jargon
Tailor information need to the individiual patient	Take too little time or try to rush
Avoid negative suggestions, assure positive suggestions	Be misinformed about the patient

Adapted with permission from [15].

More than for any other procedure, a trustful, solid doctor–patient relationship between the anaesthesiologist who carries out the procedure and the patient is mandatory for a successful awake craniotomy. A personal relationship is in the patient's perspective one of the most essential aspects of the premedication visit as found in a general preoperative population [16]. The authors emphasize the anxiolytic aspect of the premedication visit and the desire for patients to build a personal doctor–patient relationship. This is understandable because patients experience the perioperative process as a loss of control and 'giving up' to strangers. Aust et al. [16] describe that patients cope with this process by focusing their own fear and uncertainty onto the person(ality) of the physician, giving the patient a strategy to direct his emotions. Keeping emotions under control has been described as an important psychological factor in awake craniotomy patients [1]. This is supported by other studies, which found that 'the key element of patient satisfaction' is 'spending time establishing a trusting alliance' [17].

There is a controversy going on to what extent and what level of detail the patient has to be preoperatively counseled in preparation for the surgical procedure. There are suggestions that proper counseling before the procedure alleviates anxiety before and during the operation [18], especially with other forms of information provision such as short films [19]. In a large interview study, the need for information was assessed in patients planned for noncardiac surgery. Generally, patients were satisfied with the information from the anaesthesiologist, but there is a relatively large proportion of patients that either have more or less need of preoperative information. ASA-score, education and quality of life were independent predictors for the need of information. This underlines the amount and kind of information needs to be tailored to the individual patient [20]. It is unknown whether the extent of the surgical procedure plays a role in the information needs; one could argue that the need for information in patients undergoing an awake craniotomy is considerably larger, given the invasiveness and the character of the procedure. Shaping perceptions, managing expectations and preventing surprises by

detailed descriptions seem important to prevent an acute psychological stress reaction or the acute withdrawal of the consent of the patient before or during the procedure.

It is important to be aware of possible 'side-effects' of a too detailed preoperative information, leading to a nocebo effect: the expectation of a negative outcome that could precipitate or exacerbate the corresponding symptom [21]. Nonetheless, besides psychological preparation, there is a legal obligation to inform patients about risks and complications because the preoperative consult has to end with the informed consent of the patient. Seemann et al. [22] describe several strategies that could be used to prevent a nocebo effect. The first one is 'linking', which is the strategy to describe risks with possible benefits. An example of linking could be the description of the placement of an arterial line. Pain and a hematoma are possible side-effects, but these are rare and well justified against the fact that it helps to keep the patient safely and closely monitored during the procedure. The second strategy could be the explanation of measures that are taken to prevent complications and the treatment options in case of a complication.

In general, it is important to empower the own responsibility and the autonomy of the patient with the aim to improve active cooperation and to reduce complications. However, personal experience shows that a significant number of patients – despite all active engagement during the neuromonitoring – feels fine with being directed through the procedure by the anaesthesiologist. This will work out much smoother if patient and anaesthetist do not meet for the first time on the OR table.

Brain tumors can affect different brain functions, both simple and complex. Quality (e.g. executive functions, emotion and cognition) and quantity of the disruptions depend on the localization and the histology of the tumor. Recent work shows that patients suffering from temporal lobe gliomas have impaired neurocognitive functions. It is important to realize that these patients have difficulties or disruption of learning and memory, attention and executive functions [23]. More subtle changes such as changes of personality or disruption of social interaction and social cognition have also been described. These changes can be caused not only by the tumor, but also by the surgical intervention [24]. In the perioperative process, the anaesthesiologist needs to be aware of these possible alterations of the higher brain functions because they can interfere with the patient's cooperation during the procedure. Furthermore, the patient and family members should be informed about the possible effects of surgery, like the previously described personality changes. Data on postoperative quality of life is growing, and this enables better patient education and management of expectations after surgery. Recent studies addressed not only fatigue, mood and cognitive dysfunction [25] but also sexual dysfunction [26].

Besides nonpharmacological interventions mentioned above, pharmacological interventions could be of use to reduce anxiety and fear and optimize the patient's vigilance during the procedure. Benzodiazepines and especially midazolam are the most used group of drugs in awake craniotomy patients, but there are many studies that do not use any premedication at all (e.g. [3,27]). There is accumulating evidence that the use of benzodiazepines is not necessarily beneficial in awake craniotomy procedures. Drawbacks are respiratory depression (especially in combination with opioids given during the procedure), paradoxical agitation and interference with electro cortical recordings [28]. It was recently shown in general surgery patients that sedative premedication did not improve patient satisfaction or preoperative anxiety [29]. The use of benzodiazepines is also associated with a higher occurrence of postoperative delirium [30]. The use of other agents like clonidine, promethazine and dexmedetomidine as preoperative sedatives is also common and at least partially understandable considering the pharmacological profiles. Nevertheless, higher evidence supporting the use of these drugs is lacking.

INTRAOPERATIVE MANAGEMENT

Intraoperative awareness is indispensable in patients undergoing an awake craniotomy procedure. Phases of the operation that leaves the most significant memory are the positioning, the fixation in the Mayfield clamp and the craniotomy itself [1]. Given the results from research on perioperative pain, comfort, anxiety and the postoperative satisfaction, there is still ample room for improvement during the procedure.

Karlsson et al. [31] systematically interviewed patients under spinal anaesthesia. Patients experience a feeling of being left out and feel that they have no control, which they counterbalance by communication either way by eye contact or verbal communication. To improve eye contact and communication, we recommend that the drapes are placed carefully so that the patient can keep a certain field of vision and eye contact with at least the anaesthesia team and the neuropsychologist. If transparent drapes and blankets are used, even eye contact with the surgeon can easily be established and the patient might feel less claustrophobic. Although described first almost 40 years ago as an improvement for the anaesthesiologist and the surgeon [32], the idea is still not widespread.

In general, VAS scores during the awake craniotomy procedure are below the acceptable range of 4 of 10 (see [3,5]). However, there are significant numbers of patients who experience discomfort because of pain during the procedure [7]. This pain is not only because of the surgical intervention but also the continuous pressure on the lower parts of the body due to the positioning on the table. A simple measure that could improve the tolerance of patients is to do a preoperative 'practice run' [33]. Patients should also

be encouraged to practice this at home (e.g. lying on the floor, not moving, letting others scratch on their itching nose) to identify possible pressure points, to cope with unpleasant sensations and to get better used to lying on the OR-table without too much spontaneous movements.

Preoperative fasting could also lead to perioperative discomfort. In concordance with European guidelines [34] it is well tolerated to drink clear fluids 2h before surgery. In our practice, we reduced the fasting period to 1h without any perioperative complications. Because caffeine withdrawal has been identified as a major cause of postoperative headache in fasted patients undergoing general anaesthesia, especially in awake craniotomypatients who are used to a morning cup of coffee, patients should drink it on the day of the procedure as well, to prevent this withdrawal headache [35]. To prevent a dry mouth, we use lemon glycerin swabs, although they have not been investigated in patients undergoing regional anaesthesia. In tobacco-addicted patients, we do not restrict smoking prior to the surgery. Although tobacco use is associated with various perioperative complications [36], acute nicotine withdrawal could lead to undesired side-effects like coughing or stress during the procedure. The question whether nicotine affects gastric emptying is also under debate [37].

It is at least questionable whether patients with an extremely high level of preoperative anxiety (panic) should undergo an awake craniotomy. In any case, perioperative psychological decompensation must be prevented. Continuous eye and verbal contact ('vocal anaesthesia') during the procedure could reduce feelings of helplessness [31,38], and some patients could benefit from physical contact with one of the members of the treating team, for example by holding the patient's hand [33]. Physical contact serves two ways: on one hand it can give guidance to patients, on the other hand it can serve as a monitor that helps to detect stress quite early [22]. Inviting family members to support their relatives during the procedure on the OR table could also be considered, naturally in children [39] but under some circumstances also in adults. Whittle and Lim [40] described three patients in whom their relatives provided crucial support during the procedure; however, all family members had nursing qualifications.

Patients describe noise as one of the most disturbing factors during the procedure [1,9,15]. Noise could arise from different sources, ranging from OR personnel to the surgical drill, and has an intensity of up to 120 dBA [41]. In non-neurosurgical patients, noise was experienced as annoying, disruptive and stressful. There was no correlation between the actual sound level and the perception of noise, which leaves the recommendation to keep noise levels as low as possible [42]. A strategy to prevent the impact of ambient noise is 'reframing' disturbing noises such as reframing the noise of a surgical drill to that of the motorcycle [9].

Another intervention is the application of music. In patients under loco regional anaesthesia, music led to lower anxiety scores, higher postoperative patient satisfaction and better sedation of patients [43–45]. Recently, the effect of music was also assessed in awake craniotomy patients in which the same results have been found [46&]. Interestingly, patients reported here that music acted as a distraction from the actual surgical procedure.

To conclude, the anaesthesiologist can exert great influence by means of communication. There are two important aspects of communication. First, it is important to avoid negative suggestions. Although much used in the perioperative process and used with a good intention, these suggestions can lead to a higher experience of anxiety and pain [47] and lead to a nocebo effect [48]. As patients have a higher level of attention, it is not only important for the anaesthesiologist to refrain from negative suggestions like misinformation, denial or suggestive questions, but for the whole team to be attentive of their verbal and nonverbal communication.

Reframing negative suggestions into positive suggestions is therefore an important other aspect. Positive suggestions have been shown to decrease pain, anxiety and the use of analgesics [49]. Positive suggestions show overlap with hypnotic techniques and can help patients to regain their own responsibility and use their own resources to reduce stress and anxiety [47,50].

The domain of positive suggestions can be extended to hypnotherapeutic techniques. These techniques are an example of a coping strategy for patients and have been successfully used in awake craniotomy patients [9]. In short, patients are invited to imagine another place and situation, and the anaesthesiologist can encourage and invite patients to explore and revive these thoughts, resulting in a form of dissociation. Seemann et al. refer to this as a 'safe place' in which the patient can retreat, which is left to the patient's imagination. An example could be a beach or a forest. Hypnotherapeutic techniques can help patients to explore and experience this well tolerated place [22]. There is no question that a strong doctor-patient relationship and a thorough preparation are essential for successful application of this technique. Hypnosis and hypnotic techniques have been extensively studied in surgical patients (for a meta-analysis, see [51]). To assist patients in adopting a successful coping strategy, either aware or unaware, communication with the patient and the team is of utmost importance. The importance of 'vocal anaesthesia' cannot be overestimated.

CONCLUSION

In summary, next to all pharmacological developments of the last decades, there is growing evidence supporting the application of psychological techniques and simple interventions to improve the patient's experience of an awake craniotomy. These techniques should be used well tailored to the patients' needs and personality and should be used by an anaesthesiologist who feels comfortable with applying them. Further research is necessary to assess the additional value of these techniques. Furthermore, the publication of new techniques, both pharmacological and nonpharmacological, and experiences in awake craniotomy procedures by anaesthesiologists should be encouraged. The patient's experience during an awake craniotomy is largely depending on the anaesthesiologist's careful preoperative preparation and professional intraoperative performance. It is beyond dispute that a professional patient–doctor relationship based on mutual trust and respect is an essential condition for the success of this life-changing procedure.

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IV

How awake is awake? - Psychological effects of an awake craniotomy

Chapter 6

Quality and quantity of memories in patients ondergoing awake brain tumor resection.

Klimek M, van der Horst PH, Hoeks SE, Stolker RJ.

QUALITY AND QUANTITY OF MEMORIES IN PATIENTS ONDERGOING AWAKE BRAIN TUMOR RESECTION.

ABSTRACT

Objective: Awake craniotomy is performed with increasing frequency for brain tumor surgery in eloquent areas. However, little is known about patient's memories of this procedure. Therefore, we retrospectively analyzed quality and quantity of memories, in our patients, treated following a standardized protocol.

Methods: We treated 61 consecutive patients within 3 years. 48 of them were alive, when the study was performed. These patients received a questionnaire about their peri-operative memories and perceptions. The perioperative process was cut down to several steps, and for each step the patients had to judge quantity (nothing – everything) and quality (very negative – very positive) of their memories.

Results: 36 patients responded (75%). Quantity of memory was quite incomplete, even for intraoperative moments when patients were awake and cooperative. In average, quality of memories was neutral or positive. A higher quantity of memories was associated with a higher quality of memories. Most important sources of discomfort were the placement of the Mayfield clamp, followed by laying on the OR-table with movement restriction, and irritation by the urinary catheter in situ.

Conclusions: Awake craniotomy can be performed with our protocol in such a way that it is experienced as (very) comfortable. However, there are moments of discomfort, which can be managed by the team. Extensive preoperative preparation may be considered as a crucial part of the procedure. Less amnesia seems to improve patient satisfaction. The results of this study can be used for protocol optimization, expectation management and information of future patients.

INTRODUCTION

Evidence that extensive resection of brain tumors can improve length of survival has contributed to a renaissance of awake brain surgery in case of tumors in eloquent areas.[1-3] This technique allows instantaneous control of higher brain functions and enables the neurosurgeon to perform a maximum of brain tumor resection with a minimal risk of functional damage for the patient. Despite multiple positive studies showing a high acceptance by patients, being awake during brain tumor removal is still considered as difficult to tolerate by some anesthesiologists and neurosurgeons.[4] However, we demonstrated that even a nine-year old child was able to tolerate this procedure by good psychological preparation and support.[5] After years of studies only addressing safety and feasibility of awake craniotomies, just recently a rising number of studies addresses the perspective of the patient undergoing awake brain tumor resection. These have been mostly performed in small groups (<30 patients) and focus mostly on "satisfaction" in a general way.[4,6-10]

However, we are not aware of any other study trying to quantify the amount and the quality of memories of the perioperative period in patients undergoing awake brain tumor resection. Preoperative preparation plays a key role in alleviating the understandable anxiety of patients undergoing an awake craniotomy. Providing data about the quantity and quality of memories around this procedure must be considered useful for preoperative patient information to decrease anxiety and to improve appropriate expectation management. We therefore performed this retrospective observational study.

METHODS

This voluntary, retrospective short questionnaire study was performed in accordance with the guidelines of our local ethical committee. Sixty-one consecutive patients were operated within a 3-year period for different types (including grade IV glioblastoma multiforme) of malignant brain tumors following a standard protocol for preoperative preparation, intraoperative sedation and postoperative care as published earlier.[5,11]

The cornerstone of our protocol is an intensive preoperative preparation of the patients using a digital presentation (slides and short movies) of the whole procedure provided by the anesthesiologist scheduled. Intraoperatively we use a light propofol sedation with spontaneous respiration in combination with local infiltration of the surgical field and the insertion points of the Mayfield clamp during the craniotomy period and for wound closure. We do not use any invasive airway management or continuous remifentanil infusion. However, we give boluses (50-75 mcg) of remifentanil just before local infiltration anesthesia. After opening of the dura all patients stay completely unsedated until

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the end of tumor resection, so that not only a cortical mapping can be performed, but also intraoperative deeper stimulation and mapping of the resection field is possible. A neuropsychologist/linguist is available for neuropsychological testing and distracting chat during this period.

When we started this study, in our hospital database 13 of the 61 patients were documented to be deceased. The remaining 48 patients received by "snail"-mail a paper questionnaire (Appendix 1) about the quality and quantity of their memories of the perioperative period and the sources of possible discomfort they experienced through-out the procedure. We mailed the questionnaire once; no reminder was sent; patients received a free and addressed envelope to return their answers. In an accompanying letter the goal of the study was explained and a contact address was given in case of any questions or distress caused by the questionnaire.

The perioperative process was depicted into 11 consecutive steps according to our local protocol. Table 1 shows these steps and the sedative drugs given during the respective step.

Table 1. Steps and Use of Sedative Drugs According to Our Awake Craniotomy Protocol

Step	Sedative Drugs Used
1. Preparation on the ward	No
2. Arrival in the operating room	Promethazine 25 mg i.m., piritramid 7.5 mg i.m.
3. Placement of the lines/catheters	Propofol (1—2 mg/kg bolus, 4—6 mg/kg/hour continuing)
4. Placement of the Mayfield clamp	Remifentanil 50—75 µg i.v.
5. Local anesthesia of the surgical field	Remifentanil 50—75 µg i.v.
6. Craniotomy	Propofol (1—2 mg/kg bolus, 4—6 mg/kg/hour continuing)
7. Neuropsychological monitoring	No
8. Resection of the tumor	No
9. Closure of the craniotomy	Propofol (1 mg/kg bolus, 3—4 mg/kg/hour continuing)
10. Transport to the PACU	No
11. First night on the PACU	No

PACU, postanesthesia care unit.

The quantity of the memories the patients could rate from 0 = remember nothing, 1= remember a little, 2 = remember partially, 3 = remember quite a lot, 4 = remember (almost) everything; for the quality of the memories they could rate from 0 = absolutely negative, 1 = more negative than positive, 2 = neutral, 3 = more positive than negative, 4 = absolutely positive. Patients reporting no memories for a certain step of the procedure (quantity = 0) were excluded from analysis of the quality of the memories for the respective step.

Furthermore, patients were asked specifically whether they experienced any discomfort by the possible causes of discomfort (Mayfield clamp, position on the table, restricted movement, shaving of the hair, lying under the drapes, iv / arterial catheters, urinary catheter, dry mouth, local anesthesia of the surgical field, body temperature). Multiple answers were possible for that question.

The time-interval between the surgical procedure and answering the questionnaire varied between the patients from 0-37 months. Because this variation might have an effect on the quantity of memories, we analyzed, whether there was a correlation between the average amount of memories of all 11 steps and the time between the procedure and the questionnaire.

Statistical analyses were performed using SPSS software version 22.0.0 (SPSS Inc., Chicago, IL) and figures were plotted using R version 3.1.3. Categorical variables are presented as numbers and percentages. Continuous data are presented as mean ± standard deviation (SD) when normally distributed or as median values and corresponding 25th and 75th percentiles when data was skewed. Quantity and quality of memories of each of the 11 steps up were summed to quantity and quality sum-scores, respectively (possible range 0-44 for both scores). Differences in sum-scores between subgroups of patients were analyzed using the non-parametric Mann-Whitney test or Kruskal Wallis test, when appropriate. Correlations were assessed using Spearman's correlation coefficient. Significance was set at a two-sided P-value < 0.05.

RESULTS

The procedure could be performed in all patients as planned. In no patient we had to perform invasive airway measures (intubation, laryngeal mask airway, mechanical ventilation), no patient was converted to general anesthesia.

Of the total 48 patients who received a questionnaire, 36 patients responded (75%, 19 women, 17 men). Their basic characteristics are shown in **Table 2**. The excluded 13 patients who died, all but one suffered from a high-grade brain tumor compared to half (18/36) of the responding patients. Of the remaining 12 non-responding patients, 10

Table 2. Baseline Characteristics of the 36 Responding Patients	
Characteristic	**Value**
Male sex, number (%)	17 (47.2)
Age (years), mean ± SD	43.0 ± 12.4
Weight (kg), mean ± SD	73.3 ± 13.8
American Society of Anesthesiologists class, number (%)	
1	13 (36.1)
2	21 (58.3)
3	2 (5.6)
Tumor side, number (%)	
Left	22 (61.1)
Right	14 (38.9)
Tumor localization, number (%)	
Frontal	16 (44.4)
Insula	5 (13.9)
Parietal	11 (30.6)
Temporal	4 (11.1)
Pathohistological diagnosis, number (%)	
High grade	18 (50.0)
Low grade	12 (33.3)
Other	6 (16.7)
Antiepileptic drug use, number (%)	29 (80.6)
None	7 (19.4)
1	21 (58.3)
≥2	8 (22.2)
Type of antiepileptic drugs used, number (%)	
Benzodiazepine	5 (3.9)
Valproate	12 (33.3)
Carbamazepine/fenytoin	12 (33.3)
Other	7 (19.4)
Complete resection*, number (%)	18 (50.0)
Surgical time†, minutes, mean ± SD	293.3 ± 65.7
Time awake on the OR, minutes, median (IQR)	138 (114—164)
Propofol dose during sedation, mg/kg/hour, median (IQR)	4.1 (3.3—5.2)

OR, operating room; IQR, interquartile range.
*According to postoperative magnetic resonance imaging.
†Time from incision to suturing.

were documented as alive when the study was performed, two had their follow-up in another hospital and could not be tracked any further despite our efforts.

Patients who responded were more often ASA class 1 (36%) compared to non-responders (0%). All patients undergoing awake craniotomy have been conscious and cooperative during the preoperative evaluation. The medical conditions making patients ASA class >I were not neurological, but mostly for cardiovascular and respiratory reasons.

No significant differences between responders and non-responders were observed in age, side of the tumor, pathological diagnosis, or complete resection. All patients re-ported to have filled in the questionnaire on their own.

The results on the quantity of the memories can be found in **Figure 1**. Obviously, the majority of patients has only partial memories of the whole perioperative period, despite the fact that they were completely conscious and cooperative at least during the preparation on the ward, the intraoperative neuropsychological testing and the first night on the PACU, where they underwent hourly neurological controls.

Figure 2 shows the quality of the memories. The absolute majority of the memories are neutral or even more positive than negative. The craniotomy itself has the most memories with a negative score (2/6, 33%); however, only 6 patients had any memories. The most positive memories can be found during the period of neuropsychological monitoring. A positive correlation was observed between the quantity sum-score and quality sum-score (r=.636, p<.001).

Among the possible causes of discomfort, 50% of the patients choose the application of the Mayfield clamp as the most important item. Lying on the OR-table with movement restrictions is the second most important cause, mentioned by 28% of the patients. Details can be found in **Table 3**.

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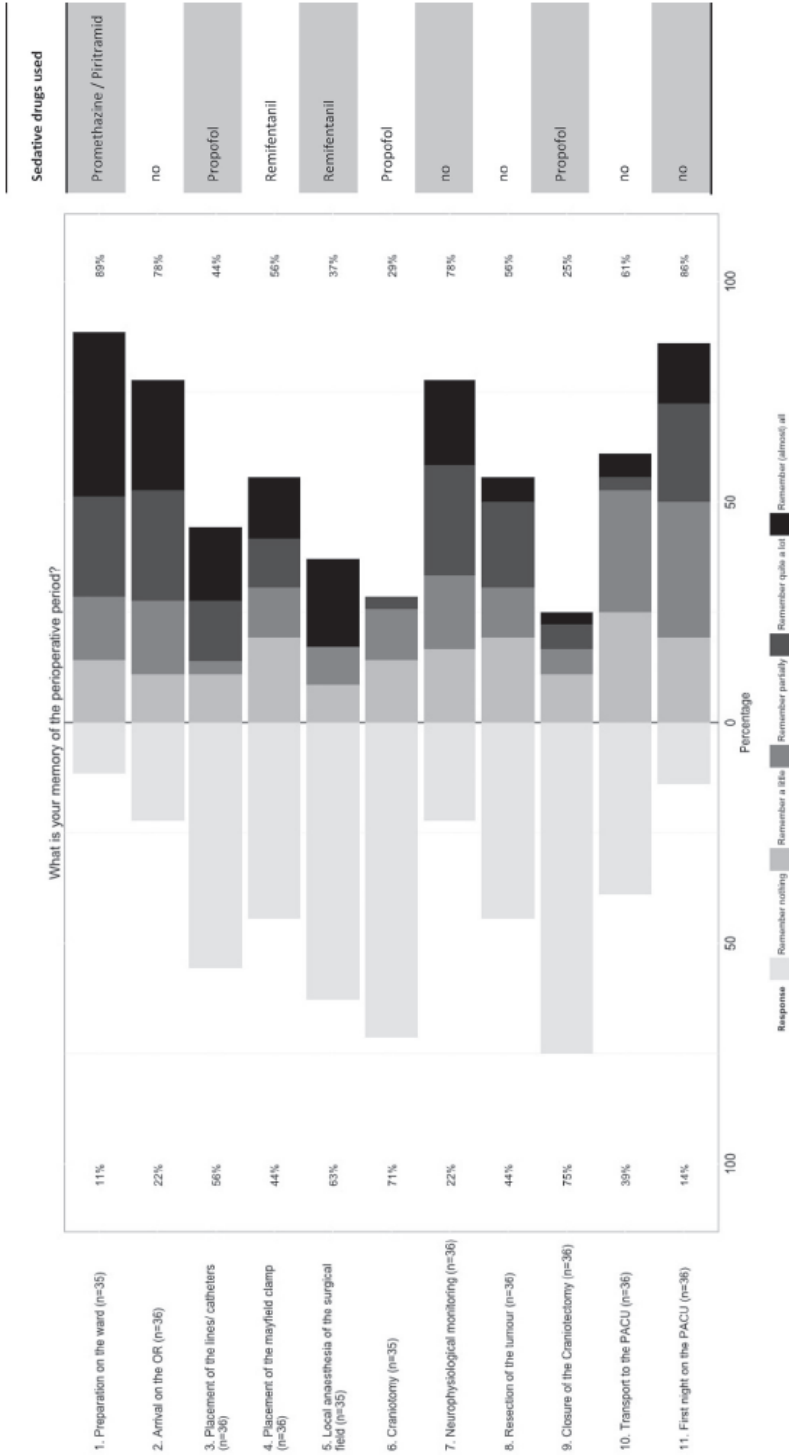
Figure 1. Quantity of memory: responses to the 5-point Likert scale questionnaire, represented as a net-stacked distribution. The scale represents the percentage of answers for each question, with no memory at the left side and any memory (ranging from 'a little' until '(almost) all') at the right side.
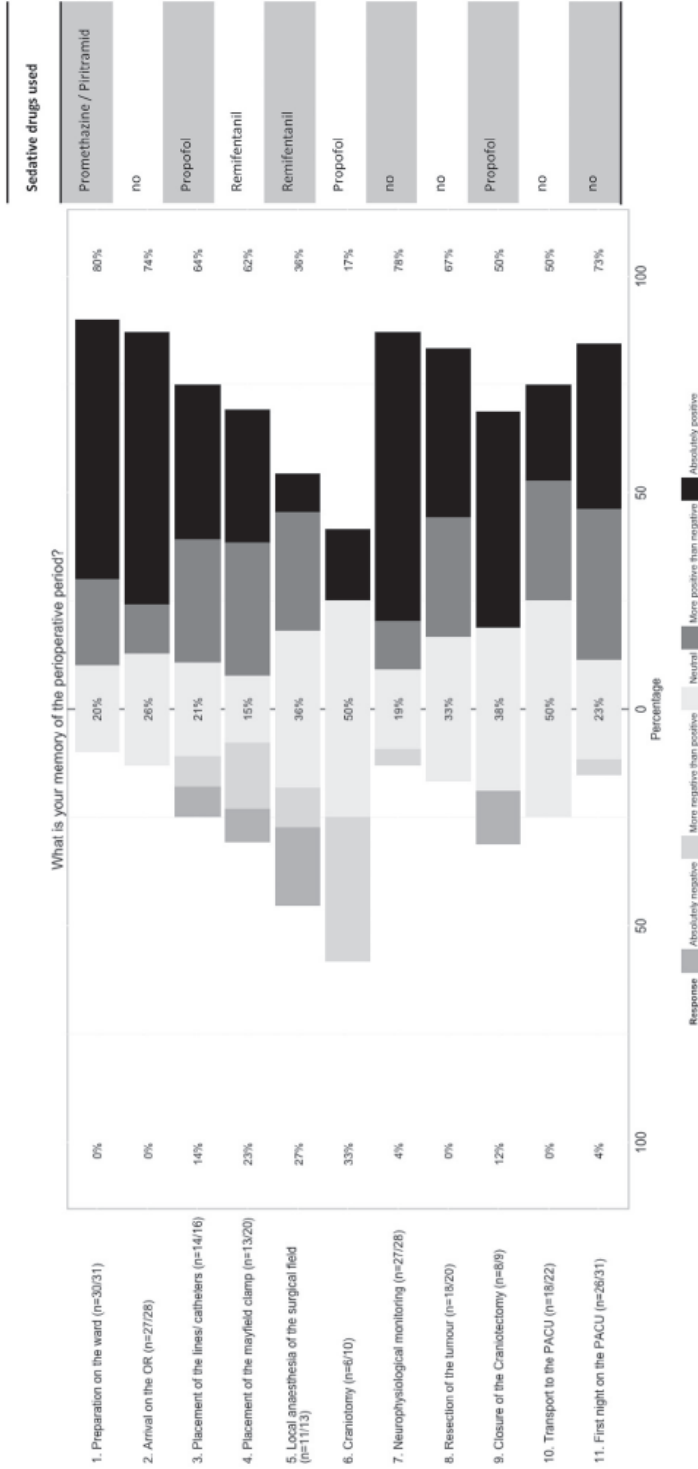
Figure 2. Quality of memories: responses to the 5-point Likert scale questionnaire, represented as a net-stacked distribution. The scale represents the percentage of answers for each question, with negative memory at the left side, neutral in the middle and positive memory at the right side.

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Table 3. Sources of Experienced Discomfort During the Perioperative Period

Possible Source of Discomfort	Reported Rate, %
Mayfield clamp	50
Restricted movement	28
Position on the operating room table	17
Dry mouth	17
Urinary catheter	14
Local anesthesia of the surgical field	11
Body temperature	3
Shaving	3
Laying under drapes and blankets	3
Inserted arterial and intravenous lines	0

Multiple answers are possible.

We could not find any correlation between the average amount of memories and the time passed since the procedure. We also were unable to detect a correlation between the quantity of memories and the dose of propofol given or the completeness of the resection. However, we found a significant higher quantity of memories in patients treated with enzyme inducing anti-epileptic drugs (Carbamazepine, Phenytoin) compared with those using other drugs or without anti-epileptic treatment (sum-scores 22 (IQR 11-28) vs. 11 (IQR 4-18) vs. 13 (IQR 11-28) (p=.043). The use of anti-epileptic drugs did not lead to significant differences in the dosages of propofol used for sedation. We also found a higher quantity sum-score in patients with a tumor located in the left hemisphere compared with a right-sided tumor (sum-scores 18 (IQR 11-25) vs. 11 (IQR 4-13) (p=.030)).

DISCUSSION

Our patients have limited, but mostly positive memories of the perioperative period, even of the relatively long periods of tumor resection when they were fully awake and cooperative. 22% of our patients had absolutely no memories of being neuropsychologically tested, a number in line with previous published data by Whittle et al.[6] who state that 8-37% of the patients won't remember of being awake intraoperatively. In another study, where the procedure was also analysed in several steps, only 33% of the patients remembered the stimulation of the cerebral cortex to map language and motor centres.[12] However, in a large recent study 17% of the patients had no recollections at all

about their awake operation.[13] So, the quantity and the quality of memories in patients undergoing awake craniotomy is varying. The mean age of our patients is 43 ± 12.4 years, memory loss due to physiological aging is improbable.

It should be noticed, that - despite the fact that the most memories are positive - we found a positive correlation between the quality and the quantity of memories, which can be summarized as: the more the patient remembers, the more positive the memories are. This finding deserves further study, because many recent articles about the management of awake craniotomies promote the use of dexmedetomedine, which induces less amnesia and thus more awareness than the use of propofol.[14-18] However, in our own practice (after this study) we had two patients undergoing a re-craniotomy, who received propofol during the first and dexmedetomidine during the second procedure. Both complained over the fact that they were more aware than during their first procedure and felt less comfortable. Furthermore, the risk of intraoperative epileptic seizures should be considered.[15.19]

Recently published articles address the impact of different tumor grades and locations on the neuropsychological performance of patients undergoing brain tumor resection (awake and under general anesthesia).[20,21] However, we were not able to find a convincing explanation for the right-left-differences in the quantity of memories we observed in our patients. Frontal tumors might interfere with memory formation more than other locations. However, we did not have many frontal tumors in our patient group, because most frontal tumors safely can be resected under general anesthesia as they don't affect eloquent areas.

It is surprising, that the average quality of the recollections of our patients is neutral or positive, even of the situations that are linked to some painful interventions. This can be explained at least partially by the high level of intrinsic motivation and the positive attitude, which is typical for patients undergoing awake procedures.[12] This might be a kind of "selection bias" compared with patient satisfaction-scores in other surgical procedures.

All patients also received perioperatively (starting in general some days before the procedure) dexamethasone, which is known to mediate an acute energizing effect, but induces dysphoria in case of prolonged administration.[22] Therefore we think that a "euphoric bias" by dexamethasone is quite improbable. However, for the use of propofol such an "euphoric bias" cannot be excluded.[23,24]

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Furthermore, intense management of patients' expectations as recently recommended by others[25] has been for years a crucial part of our protocol. Preoperative information in our institution is always done by the responsible anesthetist and includes a 90-120 minutes talk with the patient a relative including a slide-show with photographs and some videos from the whole perioperative course. Positive effects of this extra attention to the patient are suggested by literature, but not yet quantified.[26]

Despite a bolus of remifentanil and efficient local anesthesia, 50% of our patients experienced the application of the Mayfield clamp as the most relevant source of discomfort, followed by lying for a long time with restricted movement on the OR-table. These results confirm previous data.[4,9,13] However, the detailed data on the quality of memories in figure 2 clearly show, that the average memories of this step of the procedure still are much more positive than negative. In our protocol, the Mayfield clamp is placed with the patient awake. Our idea behind this regimen is, that if we keep the patient sedated throughout positioning, placement of the clamp and preparation of the surgical field with all drapes and blankets, they will wake up in a completely different situation than they were, when sedation was started, which might cause agitation and irritation. The Mayfield clamp does not only prevent accidental head-movements of the patient under the surgeon's microscope, but also enables the reliable use of neuro-navigation techniques. Therefore, we feel no need to change our protocol based on these findings.

The 75% response rate of the patients still alive in a once mailed questionnaire without a second reminder is very high and might reflect the loyalty and thankfulness of the responding patients. Furthermore, the positive results of the questionnaire match with the verbal feedback we receive from the patients during the routine postoperative visits on the ward.

Nevertheless, a small number of patients with significant fear or even Post-Traumatic-Stress-Disorder-like symptoms after awake craniotomy have been published by other groups.[10,27,28] However, we think that this should not be used as a general argument to withhold the awake procedure when indicated, because awake resection enables a maximum of tumor resection with a minimal risk of functional damage, which in conclusion means: a longer survival without disability for the majority of the patients.[1-3]

Limitations of the study

The retrospective design might be a limitation of our study, especially due to the broad variation of time interval between the procedure and answering the questionnaire. As we know from pain studies, recall of acute events is more accurate than recall of chronic events.[29] However, by addressing not only the quality, but also the quantity of

the memories, we tried to deal with the known phenomenon of fading recall. Finally, we could not find any influence of the time interval between the procedure and answering the questionnaire and the quantity of memories. Nevertheless, a selection bias in patients choosing to respond is possible.

Another limitation might be, that this is a single-center study, where a strict protocol for preoperative information of and perioperative sedation was used. Extrapolation of our results to other settings and other protocols might be difficult. However, our sedation regimen is based on propofol only with a spontaneously breathing patient without any invasive airway management. The chance of recall in our population should be much higher than in other settings, where an asleep-awake-asleep-technique including the continuous application of opioids, the use of a laryngeal mask airway or even endotracheal intubation is used.

We have chosen for a not validated method to grade patients' memories because there are no comparable studies in patients undergoing awake craniotomy. Splitting the procedure in separate steps and describing them might promote recall compared with an open question like "tell me all you remember…". However, the relatively low quantity of memories makes a strong recall-promoting effect quite unlikely.

It must be expected, that awake craniotomies will be performed more frequently in the next years, and maybe even as a day-care procedure.[30] However, the patients must be selected carefully, to avoid a failing procedure.[31,32] Not all recent studies reported a better outcome of awake patients compared to patients operated under general anesthesia.[33]

CONCLUSIONS

In conclusion, our results support that patients are operated awake for brain tumor resection. Despite being awake for a major part of the perioperative period the quantity of explicit memories of awake operated patients is limited. The quality of the memories in our patients is neutral to positive. We found no patient with signs of traumatic psychologic experiences due to the awake technique. The key to successful awake neurosurgery is ensuring a well-informed patient who is calm, comfortable and co-operative throughout the procedure.[8] This can be achieved reliably by propofol-sedation and local anesthesia. The finding that propofol provides a pleasant, quite strong amnesia even for the longer periods when the patient is fully awake is notable. Our results can be used, to inform the patients preoperatively about the possible recall of (parts of) the procedure and to manage their expectations. This will hopefully further improve patients' satisfaction.[34]

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Chapter 7

Anxiety, memories and coping in patients undergoing intracranial tumor surgery.

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ANXIETY, MEMORIES AND COPING IN PATIENTS UNDERGOING INTRACRANIAL TUMOR SURGERY.

ABSTRACT

Objectives: The diagnosis and the surgical removal of a brain tumor can have serious impact on the quality of life of a patient. The question rises, whether having more or just less memories of the procedure is better for coping with such an event. Furthermore, for preoperative information of future patients it is important to know how patients process their emotions and memories. The primary objective of this study was to investigate the link between preoperative anxiety, the perioperative experience and the quantity and quality of postoperative memories in patients who underwent intracranial tumor surgery.

Patients and Methods: This study was a retrospective observational study; all patients who underwent intracranial tumor surgery at the Erasmus Medical Centre Rotterdam between January 1st 2014 and December 31st 2015 were identified. In May 2016, all patients who were not registered as deceased were sent a questionnaire about their anxieties, perceptions and memories of the perioperative period.

Results: In total 476 patients were included. 272 patients responded, which resulted in a response rate of 57.14%. In the general anesthesia (GA) group there was a significant negative correlation between anxiety in the perioperative period and the quantity and quality of memories. In the awake craniotomy group, there was a significant negative correlation between anxiety after the operation and the quantity of memories.

Conclusion: Patients in the GA group who experienced anxiety in the perioperative period had less quantity and quality of memories and less patient satisfaction. Patients in the AC group who experienced anxiety after the operation had only a lower quantity of the memory; there was no correlation with patient satisfaction.

Key words: Anesthesia; anxiety; awake craniotomy; brain tumor; coping; memory; neurosurgery; patient satisfaction.

INTRODUCTION

The diagnosis of a brain tumor and the surgical removal of this tumor can have serious impact on the quality of life of the patient. As patient centered care and value-based health care have become increasingly important, information about the quality of postoperative recovery and management of patient expectations are especially relevant [1,2]. Patients may undergo this procedure awake or under general anesthesia (GA), which has impact on the quantity, but possibly also on the quality of the memories about the perioperative period. It may be questioned, whether more or less memories about the procedure are an advantage for coping with such a major life event?

Only a few earlier studies investigated patient experience of patients who underwent an awake craniotomy (AC) [3-5]. These studies showed that according to the patients' memories this anesthesia technique is well tolerated by the patients, but nevertheless still can have considerable impact. This impact did not only reflect on the direct perioperative period, but also on the period of recovery and rehabilitation after the procedure.

Therefore, we strived to learn more about how patients process and cope with their emotions and memories of the perioperative period in order to better inform future patients and manage their expectations about the operation.

Recently, we published data of a different, previous, small patient population on the quality and quantity of memories in patients who all underwent an awake craniotomy [6]. These data showed, that patients did not remember a lot of the procedure despite being awake during the whole period of resection, but also that the majority of these memories were very positive.

Inspired by these findings, this study is the first one to compare the correlation between anxiety and the quantity and quality of memories of the perioperative period, in patients who underwent brain tumor resection awake or under general anesthesia. The primary objective of this study was to investigate the link between preoperative anxiety, the perioperative experience and the quantity and quality of postoperative memories. Our hypothesis was, that preoperative anxiety will result in more negative memories and less patient satisfaction.

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MATERIALS AND METHODS

The institutional medical ethics committee of the Erasmus University Medical Centre approved this study (MEC-2016-125). Written informed consent was obtained from all patients who participated in this study.

Study design

For this study, all consecutive adult patients who underwent neurosurgery at the Erasmus Medical Centre Rotterdam between January 1st 2014 and December 31st 2015 were identified. Based on surgery coding, 739 patients with an intracranial tumor resection were found.

Participants

In May 2016, after excluding patients registered as deceased in our hospitals patient registry, 503 of these 739 patients received a questionnaire about their perception of the perioperative period. Patients who did not reply, were sent a reminder in August 2016. Non-responders were included in the final analysis to check for structural factors differing significantly between responders and non-responders.

Setting

In case of general anesthesia, the technique was chosen by the responsible anesthetist (Total Intra-Venous Anesthesia or balanced anesthesia). Our standardized technique of awake craniotomy has been described previously and has not been changed for the patients included in this study [6]. In summary, we rely on a detailed, personal preoperative patient information and psychological preparation. Intraoperatively we use a combination of local anesthesia with propofol sedation during craniotomy and closure in spontaneous breathing patients with a nasal oxygen probe (non-invasive asleep-awake-asleep technique).

Study size

In this study, all adult patients who underwent (stereotactical) biopsies, intra-cranial tumor surgery and pituitary adenoma surgery were included. After removing double cases (of patients who had multiple operations in this period only the first procedure was included), a total number of 739 cases remained (see figure 1).

Patients undergoing a supratentorial tumor resection were mostly extubated on the OR, patients with infratentorial tumors were frequently transferred intubated to the Intensive Care Unit / Post Anesthesia Care Unit (ICU/PACU), where extubation was performed on a later moment. For uniformity reasons in our questionnaire extubation was put after the transport to the PACU / ICU. It is worth mentioning, that in our hospital the PACU is a
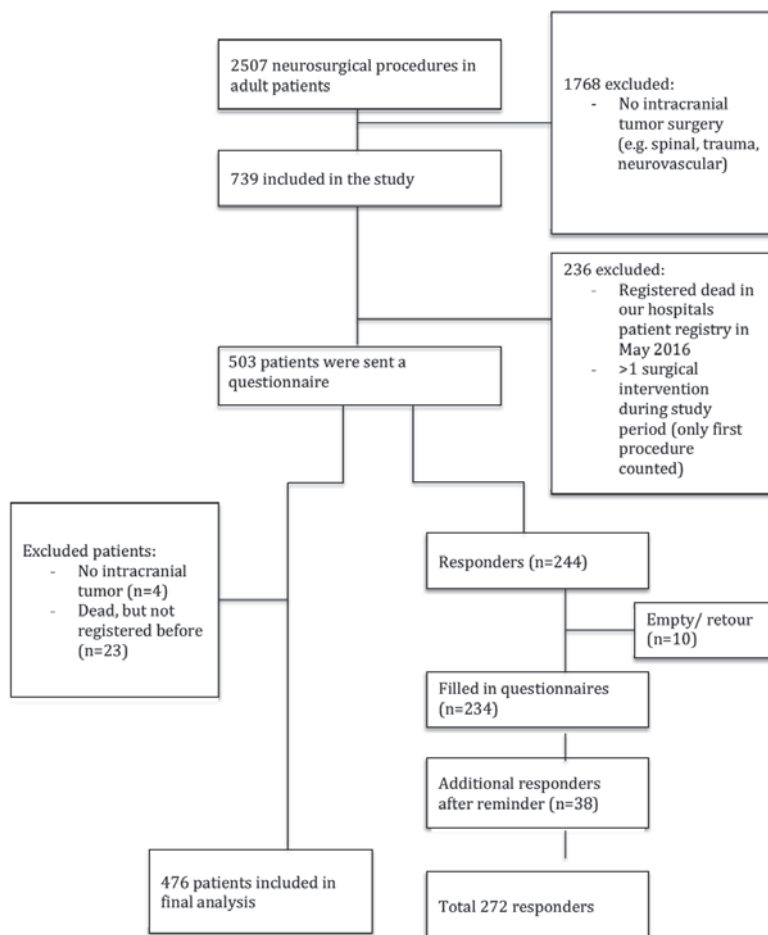
Figure 1: Flowchart of the study-inclusion

high dependency unit with the option for mechanical ventilation, which is independent from the recovery room and dedicated to postoperative care for up to the first 24 hours.

Variables

Our questionnaire focused on anxiety and memories. Questions addressing anxiety referred to different time-points of the perioperative process and to the patients and their relatives. The measured anxiety in the relatives of patients was reported by the patients. These questions could be answered on a 10-point scale (0= no anxiety, 10 = maximum anxiety). The questions addressing the quality and quantity of memories were divided in 13 sub-questions, referring to the consecutive events during the perioperative period, e.g. preoperative night on the ward, arrival on the OR etc. (see table 1). The questionnaire is added (appendix).

Table 1: Sub-questions about the consecutive events in time of the perioperative period and the analyzed questions in each group.

Sub-questions of question 1 and 2	Analyzed in the awake craniotomy group	Analyzed in the general anesthesia group
Preoperative night on the ward	✓	✓
Arrival on the OR	✓	✓
Inserting the i.v.-lines	✓	✓
Intubation	✗	✓
Fixing the head in the Mayfield clamp	✓	✓
Local anesthesia of surgical field	✓	✓
Craniotomy	✓	✓
Testing brain function	✓	✗
Tumor resection	✓	✓
Closure of surgical field	✓	✓
Transport to the ICU/ PACU	✓	✓
Extubation	✗	✓
First night on the ICU/ PACU	✓	✓

All 13 sub-questions could be answered on a 5-point scale. For the sub-questions in question 1 the scale ranged from no memory at all (1) to a full and complete memory (5) and in question 2 the scale ranged from totally negative (1) to totally positive (5). To analyze the quantity and quality of memories the authors computed a sum score per patient of all given answers. If the patient underwent an awake craniotomy the answers to the questions about in- and extubation were not taken into account for the sum scores concerning the quantity and quality of the memories. So, the maximum sum scores of questions 1 and 2 were 11 x 5 (=55) (table 1). Furthermore, if the patient received general anesthesia, the answers to the question about testing of the brain function were not taken into account for the sum scores of the quantity and quality of the memories. So the maximum sum scores of question 1 and 2 in the general anesthesia group was 12 x 5 (=60) (table 1).

If the respondent did report to have no memories of the specific sub-question of the perioperative period when asked about the quantity, any quality score on that specific sub-question was considered invalid and not taken into account.

If the respondent did report to have any memory of the specific sub-question of the perioperative period, answered "no memories" when asked about the quality, the quality score was counted as "neutral" for that specific sub-question. Furthermore, if a respondent did not completely answer a question, then for the respective sub-question(s) the responder was counted as a non-responder.

Data sources

The following data were collected from the electronic patient record system of the Erasmus MC: age, gender and ASA (American Society of Anesthesiologists)-class of the patient - a rough indicator of the general state of health [1= healthy to 4 = seriously reduced vital functions], type and side of the tumor, pathological determination of the tumor and degree of resection of the tumor. The degree of resection of the tumor was extracted from postoperative MRI scans and was categorized as complete resection or a resection with remnant of tumor. If the first postoperative MRI scan was inconclusive due to edema or residual blood, findings from later scans were analyzed.

Our primary outcome was the correlation between the quantity and quality of memories of patients and the experienced anxiety. We also analyzed the following possible influencing factors on the quantity and quality of the memories: the amount of time elapsed between answering the questionnaire and date of surgery (time-q) and the technique of anesthesia (awake craniotomy or general anesthesia). Furthermore, we analyzed the correlation between the overall satisfaction score and the quantity and quality of the memories, the correlation between anxiety prior and anxiety after the surgical procedure with the quantity and quality of memories and the correlation between anxiety prior and after the operation procedure and the overall satisfaction score. In addition, we analyzed which parts of the procedure were seen as discomforting by patients.

Because we had a quite large group of patients (91/476) who underwent surgery for pituitary adenoma or craniopharyngeoma, we also analyzed whether there was a difference between those operated via a transphenoidal approach and those via a frontal craniotomy.

Statistical methods

All data were gathered by two of the authors (TvA, PdS) and any inconsistencies and controversies were discussed with a third author (MK), until consensus was reached. Processing of data and statistical analysis was done using IBM SPSS Statistics, version 23, (Armonk, NY: IBM Corp.) Differences in mean scores for quality and quantity of memories between the awake craniotomy and general anesthesia group were calculated using Mann-Whitney U tests. Differences in mean scores for anxiety prior to surgery and looking back to surgery were calculated using the paired T-test. Correlations were analyzed using Spearmen's correlation coefficient. The threshold for significance was set on a two-sided P value <0.05.

RESULTS

Figure 1 shows a flowchart of the included and excluded patients.

In total, 476 patients were included. 272 patients responded, which resulted in a response rate of 57.14%. There were no differences found in baseline characteristics between responders and non-responders (table 2).

Table 2: Baseline characteristics of responders versus not responders.
This means tumors in both hemispheres and midline tumors like pituitary adenomas that were transphenoidally resected.
****Time-q: time between questionnaire and surgery date in years.**

	Responders (N=272)	Non-responders (N=204)
Male N (%)	131 (48.2)	99 (48.5)
Mean age (Years)	53.58	53.26
Body mass index (BMI, kg/m²)	26.89	26.92
ASA class N (%)		
I	52 (19.1)	44 (21.6)
II	176 (64.7)	118 (57.8)
III	43 (15.8)	39 (19.1)
IV	1 (0.4)	2 (1.0)
V	0 (0.0)	1 (0.5)
Complete resection N (%)	80 (29.5)	59 (28.9)
Awake craniotomy (%)	27 (9.9)	8 (3,9)
Side of tumor (%)		
Left	108 (39.7)	69 (33.8)
Right	92 (33.8)	77 (37.7)
Bilateral / midline*	72 (26.5)	58 (28.4)
Outcome pathology N (%)		
Glioblastoma	33 (12.1)	31 (15.2)
Astrocytoma	47 (17.3)	35 (17.2)
Schwannoma	6 (2.2)	1 (0.5)
Metastasis	19 (7.0)	14 (6,9)
Adenoma/craniopharyngeoma	52 (19.1)	39 (19.1)
Meningioma GR I	61 (22.4)	35 (17.2)
Meningioma GRII	23 (8.5)	10 (4.9)
Other	31 (11.4)	39 (19.1)
Time-q** (year)	1.30	1.38

Primary outcome

In the general anesthesia group there is, as expected, a relative large percentage of patients who do not know anything about the operation. However, in the awake craniotomy group there is also a relatively high percentage of patients who do not recall anything from the intraoperative events.

Whilst almost no patients in the awake craniotomy group report 'completely negative memories' at any moment of the perioperative period (only 2 patients reported completely negative memories about their first night on the ICU/PACU), one patient in the general anesthesia group has 'completely negative memories' about the intra-operative period. In 3 other patients of the general anesthesia group some intraoperative memories were reported as "neutral".

The mean scores for quantity of the memories of each sub-question of question 1 are shown in table 3. The quantity of memory in the patients who underwent an awake craniotomy was significantly higher for fixing the head in the Mayfield clamp (P<0.001), local anesthesia of surgical field (P=0.001), tumor resection (P<0.001), closure of surgical field (P=0.001), transport to the ICU/ PACU (P<0.001) and first night on the ICU/ PACU (P=0.008). Despite these significant differences, the mean scores of the patients who underwent an awake craniotomy still show a very low total quantity of memory in the period after the iv-lines were placed until the first night on the ICU/PACU.

Table 3: Mean scores for quantity of the memories in patients who underwent an awake craniotomy vs. patients who received general anesthesia. A Mann-Whitney U-test was performed to test for differences between groups.

Sub questions in question 1 and 2	N	Mean score for quantity of memory in awake craniotomy (95% CI)	N	Mean score for quantity of memory in general anesthesia (95% CI)	P value
Preoperative night on the ward	27	3.11 (2.65-3.57)	242	2.90 (2.73-3.07)	0.586
Arrival on the OR	27	2.63 (2.01-3.25)	243	2.63 (2.44-2.83)	0.903
Inserting the i.v. lines	27	1.15 (0.55-1.75)	243	1.37 (1.17-1.58)	0.532
Intubation	-	-	244	0.23 (0.14-0.33)	-
Fixing the head in the Mayfield clamp	27	0.74 (0.27-1.21)	244	0.18 (0.09-0.27)	<0.001
Local anesthesia of surgical field	27	0.67 (0.18-1.16)	244	0.19 (0.10-0.28)	0.001
Craniotomy	27	0.15 (0.00-0.36)	240	0.02 (0.00-0.04)	0.053
Testing brain function	27	2.44 (1.94-2.95)	-	-	-
Tumor resection	27	1.93 (1.36-2.50)	244	0.03 (0.00-0.06)	<0.001
Closure of surgical field	27	0.07 (0.00-0.18)	239	0.00 (0.00-0.01)	0.001
Transport to the ICU/ PACU	27	1.37 (0.80-1.94)	243	0.27 (0.16-0.37)	<0.001
Extubation	-	-	242	0.18 (0.10-0.26)	-
First night on the ICU/ PACU	27	2.48 (1.99-2.98)	241	1.72 (1.54-1.90)	0.008

The mean score for quality of the memories of each sub-question of question 1 and of each sub-question of question 2 are shown in table 4. The only significant difference between both groups was that patients after an awake craniotomy experience the transport to PACU/ICU with more positive memories than those after a general anesthesia (P=0.032).

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Table 4: Mean scores for quality of the memories in patients who underwent an awake craniotomy vs. patients who received general anesthesia. A Mann-Whitney U-test was performed to test for differences between groups.

Sub questions in question 1 and 2	N	Mean score for quality of memory when awake craniotomy (95% CI)	N	Mean score for quality of memory when general anesthesia (95% CI)	P value
Preoperative night on the ward	25	4.48 (3.19-3.77)	217	4.12 (3.99-4.26)	0.144
Arrival on the OR	21	4.29 (3.88-4.70)	197	4.27 (4.14-4.40)	0.937
Inserting the i.v. lines	11	3.55 (2.85-4.24)	119	3.59 (3.40-3.77)	0.833
Intubation	-	-	29	3.34 (3.09-3.60)	-
Fixing the head in the Mayfield clamp	7	3.43 (2.70-4.16)	21	3.43 (3.01-3.85)	0.832
Local anesthesia of surgical field	7	2.86 (2.22-3.50)	20	3.55 (3.04-4.06)	0.097
Craniotomy	2	2.50 (0.00-5.00)	4	2.50 (0.91-4.09)	0.784
Testing brain function	22	4.14 (3.72-4.55)	-	-	-
Tumor resection	18	3.94 (3.48-4.41)	4	3.00 (0.40-5.60)	0.213
Closure of surgical field	1	-	1	-	-
Transport to the ICU/ PACU	15	4.27 (3.82-4.71)	30	3.57 (3.17-3.97)	0.032
Extubation	-	-	25	3.32 (2.83-3.81)	-
First night on the ICU/ PACU	24	3.54 (3.97-4.11)	172	3.76 (3.60-3.92)	0.541

We found no significant differences in quantity and quality of the memories in the general anesthesia group between patients who had a pituitary adenoma, which was transspheniodally resected, and patients who underwent a standard craniotomy.

Four patients in the GA group reported at least some intraoperative memories of their craniotomy. Those patients were not positive about their memories. In all four patients, we reviewed the files carefully, but could not find any other indicators (e.g. hemodynamic changes, postoperative complaints) of unwanted intraoperative awareness.

The mean scores for anxiety of patients and their relatives in the perioperative period for both the GA and AC group are shown in table 5a. Patients undergoing an awake craniotomy experienced less pre-operative anxiety than patients who received general anesthesia (P=0.020).

Table 5a: Differences between awake craniotomy and general anesthesia in sum score of quantity and quality of memory, overall satisfaction and anxiety. A Mann-Whitney U test was performed to test for differences between groups.

	N	Awake craniotomy	N	General anesthesia	P value
Mean sum score of quantity of memory (95% CI)	27	16,74 (13.54-19.94)	245	9.63 (8.93-10.34)	<0.001
Mean sum score of quality of memory (95% CI)	25	24.16 (20.79-27.53)	233	14.01 (13.19-14.84)	<0.001
Mean overall satisfaction score	27	8.04 (7.28-8.79)	242	8.01 (7.78-8.23)	0.823
Anxiety in patients prior to procedure	27	4.59 (3.39-5.79)	243	6.16 (5.77-6.54)	0.020
Anxiety in patients after procedure	27	4.26 (3.17-5.35)	237	4.70 (4.33-5.08)	0.564
Anxiety in relatives prior to procedure	27	7.48 (6.59-8.38)	238	7.92 (7.64-8.21)	0.225
Anxiety in relatives after procedure	27	6.30 (5.23-7.36)	229	6.16 (5.81-6.50)	0.785

Table 5 b: Differences between benign and malignant tumors in sum score of quantity and quality of memory, overall satisfaction and preoperative anxiety. A Mann-Whitney U- test was performed to test for differences between groups.

	AC malignant	GA malignant	P value*	GA benign	P value**
Mean sum score for quantity of memory	16.04 (n=25)	10.31 (n=72)	0.001	9.41 (n=132)	0.194
Mean sum score for quality of memory	23.57 (n=23)	14.68 (n=69)	<0.001	13.62 (n=125)	0.214
Mean score for pre-operative anxiety	4.84 (n=25)	6.09 (n=70)	0.096	6.20 (n=132)	0.655
Mean satisfaction score	8.00 (n=25)	8.27 (n=70)	0.774	7.82 (n=131)	0.237

* P value for difference between AC malignant vs GA malignant
** P value for difference between the GA malignant group vs the GA benign group

In both groups we performed a paired t-test to investigate the change of the mean scores of anxiety during the perioperative period. We found a significant decrease in mean anxiety score after the operation procedure in the GA group (6.16 vs 4.70; P<0.001). There was only an insignificant decrease of the quite low mean anxiety score in the AC group (4.59 vs 4.26; P=0.612). However, there was a significant decrease in anxiety experienced by the relatives, after the operation procedure for both GA (7.48 vs 6.30; P< 0.001) and AC (7.92 vs 6.16; P=0.006).

There was a significant difference between men (N=131) and women (N=139) in mean scores for anxiety prior to surgery, (5.62 vs 6.36; P=0.032). There was no significant differ-

ence between men (N=127) and women (N=137) in mean scores for anxiety postoperatively (4.33 vs 4.96; P=0.087).

The degree of malignancy of a tumor might add an extra impact to the patients' coping with the diagnosis and the surgical removal. Therefore, we performed a sub-group-analysis, pairing the malignant tumors glioblastoma, astrocytoma and metastasis (97 patients in total) on the one side and the benign tumors meningioma, adenoma and schwannoma (132 patients) on the other side. The only significant differences between the groups we found were a higher quality (16.9 vs. 13.62, P=0.002) and quantity (11.78 vs. 9.42, P=0.005) of memories for malignant tumors. However, when splitting the malignant group between those operated as an awake craniotomy and those operated under general anesthesia, it became evident, that not the malignancy of the tumor, but the anesthesia technique has the highest impact on this difference (table 5b).

Correlation analysis

There was a significant positive correlation between the sum scores of the answers related to the quantity of memories and the sum scores of the answers related to quality of memories (P<0,001, table 6). So, patients who remembered more, experienced the perioperative period in a more positive way than patients who remembered less. There was a significant positive correlation between the sum scores of the answers related to the quality of memories and the overall satisfaction score regarding the perioperative period, independent of the anesthesia technique used.

Table 6: Correlation analysis

Correlation	Spearman's rho	P value
Sum score quantity of memory with sum score quality of memory	0.801	<0.001
Time-q with sum score quantity of memory	-0.019	0.760
Time-q with sum score quality of memory	0.023	0.708
Sum score of quantity of memory with overall satisfaction score	0.066	0.281
Sum score of quality of memory with overall satisfaction score	0.186	0.003
Sum score quantity of memory with age	-0.352	<0.001
Sum score quality of memory with age	-0.273	<0.001
Sum score quantity of memory with duration of anesthesia	-0.143	0.018
Sum score quality of memory with duration of anesthesia	-0.197	0.001
Anxiety prior to surgery with age	0.050	0.417
Anxiety looking back at surgery with age	0.022	0.725

We performed a correlation analysis between the duration of anesthesia and the quality and quantity of memories and found for both a significant but small negative correlation, meaning that patients undergoing longer procedures have a lower quality and quantity of memories (table 6).

There was a significant negative correlation between age and quantity and quality of the memory (P=0.013 vs P<0.001). Older patients experienced the procedure in a less positive way than patients who were younger. There was no significant correlation between age and anxiety prior to and after surgery (P=0.417 vs P=0.725). There was no significant correlation between the time passed since the procedure (time-q) and the sum score of the answers related to the quality and quantity of memories. A longer interval did not influence the memories in a more positive or more negative way.

To investigate the influence of anxiety on the quantity and quality of the memories, we performed a subgroup analysis for both general anesthesia and awake craniotomy. The sub-group analysis showed significant negative correlations between anxiety prior to the operation procedure and the quantity and quality of the memories in the GA group (P=0.012 for quantity and P=0.003 for quality, table 7). There were also significant negative correlations between anxiety after the operation procedure and the quantity and quality of the memories in the GA group (P=0.005 for quantity and P=0.001 for quality). In the AC group we found only a significant negative correlation between anxiety after the operation procedure and the quantity of the memories, there was not a significant negative correlation for quality of the memory (P=0.018 for quantity and P=0.581 for quality). There were no significant correlations between anxiety prior to the operation procedure and the quality and quantity of the memories in the AC group.

In both groups (GA and AC) we found a significant positive correlation between anxiety experienced by the relatives and anxiety experienced by the patient prior and after surgery (table 7).

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Table 7: Correlation analysis of anxiety with quantity and quality of memories is general anesthesia and awake craniotomy

Correlation	General anesthesia (Spearman's rho)	P value	N	Awake craniotomy (spearman's rho)	P value	N
Sum score quantity of memory with anxiety prior to operation procedure	-0.161	0.012	243	-0.116	0.564	27
Sum score quantity of memory with anxiety looking back at operation procedure	-0.181	0.005	237	-0.415	0.018	27
Sum score quality of memory with anxiety prior to operation procedure	-0.193	0.003	243	-0.007	0.974	25
Sum score quality of memory with anxiety looking back at operation procedure	-0.217	0.001	237	-0.116	0.581	25
Sum score quantity of memory with anxiety in relatives prior to operation procedure	-0.022	0.736	238	-0.417	0.030	27
Sum score quantity of memory with anxiety in relatives looking back at operation procedure	-0.112	0.092	229	-0.419	0.029	27
Sum score quality of memory with anxiety in relatives prior to operation procedure	0.103	0.122	226	-0.243	0.242	25
Sum score quality of memory with anxiety in relatives looking back at operation procedure	-0.124	0.066	219	-0.226	0.277	25
Anxiety in patients prior to surgery with anxiety in relatives prior to surgery	0.377	<0.001	238	0.600	0.001	27
Anxiety in patients after surgery with anxiety in relatives after surgery	0.424	<0.001	229	0.708	<0.001	27
Anxiety in patients prior to surgery with the overall satisfaction score	-0.128	0.048	243	0.210	0.292	27
Anxiety in patients after surgery with the overall satisfaction score.	-0.217	0.001	235	-0.430	0.832	27

The mean overall satisfaction score in the studied patient group was 8.01 (S.E. mean 0.110). There were no significant differences in overall satisfaction score between men (N=131) and women (N=138) (8.00 vs 8.02; P=0.545), and patients with complete resection and remnant of tumor (8.06 vs 8.00; P=0.336). The mean overall satisfaction score per diagnosis is shown in table 8. Three patients did not fill in an overall satisfaction score.

Table 8: Mean overall satisfaction score per diagnosis

Diagnosis	N	Mean score (95% CI)
Glioblastoma	32	8.31 (7.78-8.84)
Astrocytoma	32	8.09 (7.56-8.63)
Oligodendroglioma	13	8.15 (6.64-9.67)
Ependymoma	2	8.50 (0.00-10.00)
Schwannoma	6	7.83 (6.04-9.64)
Lymphoma	7	8.14 (5.91- 10.00)
Metastasis	18	8.22 (7.59-8.85)
Craniopharyngioma	4	8.00 (5.40-10.00)
Cyst	7	8.42 (6.51-10.00)
Adenoma	48	7.75 (7.20-8.29)
Meningioma WHO GR I	61	7.98 (7.53-8.43)
Meningioma WHO GR II-III	22	7.54 (6.32-8.77)
Hemangioblastoma	7	8.57 (7.84-9.30)
Other	9	7.88 (6.91-8.86)

When asked to recall specific events, men (N=70) and women (N=70) experienced different events as most discomforting. Men experienced the urinary catheterization the most discomforting (42.9% N=30), followed by pain after surgery (17.1% N=12). Women found the pain after surgery the most discomforting (24.3% (N=17), followed by the insertion of the intravenous cannula (14.3% N=10).

Anesthesia technique

There was a significant difference in the sum scores of the quantity and quality of the memory between patients who underwent an awake craniotomy and patients who received general anesthesia (P<0.001 and P<0.001, table 6). The mean of the overall satisfaction score, computed from the satisfaction scores given by the patients, was not different between patients who underwent an awake craniotomy and patients who received general anesthesia (8.04 vs 8.01; P=0.823).

DISCUSSION

The primary goal of this study was to investigate the link between preoperative anxiety, the perioperative experience and the quantity and quality of postoperative memories in patients who underwent intracranial tumor surgery.

The results show that patients who remembered more, experienced the perioperative period in a more positive way than patients who remembered less. This suggests that more (positive) memories are better for coping with such a major life event. Further research is necessary to confirm this correlation and to identify possible mechanisms. Future research should focus on psychological outcomes in relation to the memory about the event to identify the role of memory on coping with a major life event.

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29 of the GA-patients indicated that they remembered at least something from the moment of intubation. We did not ask for further specification of these memories, but considering the reported quality of the memories it can be supposed, that these patients remember (parts of) anesthesia induction, but not really the performance of the endotracheal intubation. Due to our study design this was not further explored.

The contrast in our study between patients who received GA who stated to remember at least something from moments they were (supposed to be) under anesthesia and patients who underwent an awake-craniotomy but stated to remember nothing from moments they were obviously awake and cooperative is noteworthy. We were not able to find an appropriate explanation for this contrast except some memory blockade due to the initial sedation with propofol in the AC group.

For the patients who underwent an awake craniotomy, our results confirm the findings of our previous study in a different population of patients [6]. In the current study an even larger group of patients in the awake craniotomy group answered that they had no memories at all of the consecutive perioperative steps. The quality of the memories was in both studies mostly positive.

These findings also confirm earlier studies by other authors, showing that patient's acceptance and satisfaction for awake craniotomies is relatively high [7-11] and that an awake craniotomy is absolutely not more (and maybe even less) stressful than general anesthesia [12]. Our findings when comparing malignant and benign tumors (table 5b) support this hypothesis: even patients undergoing an awake craniotomy for a malignant tumor have a higher quality of memories and a tendency to less anxiety and more satisfaction than patients undergoing resection of a (benign) tumor under general anesthesia.

Our findings about anxiety in the patients and their relatives and the negative correlation between anxiety and the memories especially in the GA group raises the question, what role the experienced anxiety (by the relatives) plays in coping with such a major life event for the patient? Interestingly, the mean scores for the experienced anxiety in the relatives were higher than the mean scores for anxiety in the patient preoperatively and remain higher postoperatively. A possible explanation for this finding could be the experienced inability to help the patient for the relatives. The relatives of the patient have to watch how the patient is dealing with his disease, with only limited options to provide help. This can be very stressful for the relatives of the patient, whilst the patient can sense this stress. Our findings concerning anxiety are in line with an earlier study of Petruzzi et al. [13], who showed that caregivers of patients diagnosed with a brain

tumor experience more symptoms of anxiety, than the patient himself. Therefore, it is important to pay attention to the anxiety in the relatives of the patient, and how they are coping with the situation, too.

As far as we could find in the available literature, our findings of a decreased quality and quantity of memories in case of longer lasting procedures have not yet been described before. In opposite, for colonoscopies evidence was found that lengthy procedures were not remembered as particularly aversive [14].

Our results concerning the correlation between age and anxiety and differences in experienced anxiety between men and women are in line with Ruis et al [15]. However, we found a lower pre-operative mean anxiety score, which might be due to the difference in the used questionnaires. The questions in our questionnaire were about the general experience of anxiety and inconveniences, whilst Ruis et al. asked about specific anxieties patients may have about the procedure. This could be helpful in expectation management in patients undergoing brain tumor surgery, too.

In contrast, a study of Milian et al. [16] showed that 44% of the patients who underwent an awake craniotomy had either repetitive recollections or dreams who were related to the surgery, and 2 out of 16 patients were diagnosed to have PTSD. In our center, patients who are planned for an awake craniotomy receive an intensive information and preparation interview, which is done with video and slides by the responsible anesthesiologist who also will provide the care for the patient during the operation. We consider this preparation and the quite active role for the patient during the surgery as crucial factors for the positive results in our population. From our point of view, it would be unethical to proof this by a prospective interventional trial.

Santini et al. identified psychological warning signs like fear of pain, anxiety and the incapability of self-control as predictive for intraoperative monitoring failures [17]. These criteria might be helpful in patient selection.

This links also to the recent findings of Jenkins et al. [18], who showed that patients with brain tumors have more emotional changes, such as depression, and personality disturbances after surgery than a control group that had undergone spinal surgery. Another study by Richter et al. [19] suggests that white matter damage could be a cause for these psychological symptoms.

In the assessment of factors that might have influenced the appreciation of the patient perception about the perioperative period, the quantity and quality of memories should

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be taken into consideration. Patients who remember more about the perioperative period may be able to process such a major life event in a better way than patients who remember less.

We studied a relative large group of patients and had a relative large group of responders (> 57%). This provided the opportunity to examine the differences between responders and non-responders. However, we could not identify any structural differences between these groups. In our study population no generalized seizures occurred during AC, local seizures due to stimulation were treated with local ice water application at the surgical field only.

Our data do not confirm previously published evidence [20], that men are more satisfied with the care provided. Almost every patient in our study went to the PACU (Post Anesthesia Care Unit) or ICU after the operation. On the PACU and ICU there is a lower patients/nurse-ratio and therefore a higher and more personal level of care provided to all patients than on a recovery room followed by care on a normal ward.

In contrast to the earlier mentioned study [20], our patients who were older remembered less and gave a lower score for their experience of the perioperative period. We were not able to reveal a convincing cause for this phenomenon; however, with an aging population it deserves special attention in future research.

The sum score for the quantity of memories was surprisingly low in our awake craniotomy group. This was mainly caused by the low score for quantity of memory about the local anesthesia of the operation area and the placement of the head of the patient in the Mayfield clamp whilst both are performed according to our protocol with an awake and cooperative patient. However, we routinely give a bolus of about 50 mcg remifentanil before the local infiltration, which might influence the memories. We were not able to identify other possible factors that could explain this relative low score for these items.

Limitations

There are some limitations to this study. This was a retrospective study and although an intracranial surgery is a major life event, this could lead to recall bias in memories about the surgery. "Memory" as a neuropsychological correlate is a multi-location phenomenon. Memory formation might be influenced by location, grade and size of the tumor, too. However, these aspects cannot be clearly attributed to memory formation and therefore, we decided not to perform additional sub-group analyses.

The questionnaire used in this study was based on validated questionnaires, but was by itself not validated before this study. The authors did not find an applicable validated questionnaire for the central question of this study, therefore a new approach had to be

chosen. Furthermore, there could be a positive effect on patient satisfaction simply by showing interest in how the patient experienced the perioperative period.

Our questions about the psychological aspects in the used questionnaire are much more general as the often-used Hospital Anxiety and Depression Scale (HADS), however, we studied a relative large patient group and our findings are largely in line with studies which used the HADS in patients with a brain tumor.

The anxiety scores for the relatives of the patients were reported by the patient self. This could lead to bias. However, the relationship between brain tumor patients and their family caregivers is an upcoming research topic [21], and our data only show, how intense the patients experienced the anxiety of their relatives. This might be influenced by concerns about an actual or anticipated change in physical and/or cognitive performance of the patients due to the tumor and/or the surgery.

In our study there was a varying time interval between the operation and the moment the patients received our questionnaire. This might influence the results; however, we did not find any significant correlation between the time interval (time-q) and the quantity nor the quality of the memories.

Another limitation of this study is the fact, that we do not have any information about the ethnic-cultural background and educational level of the patients, whilst coping mechanisms most probably will be influenced by these factors. Interestingly, literature for brain tumor patients on this aspect is lacking.

This is a mono-center study, which might make it difficult to extrapolate our results to other centers working in a different way. Nevertheless, many aspects of brain tumor surgery show a world-wide uniformity which makes this limitation less relevant.

Our study interval is too short to come to a conclusion whether the quality and quantity of memories have any link with patients' outcome. Future studies will address this question.

CONCLUSIONS

The quantity of memories of the perioperative period in patients undergoing brain tumor surgery is low and the quality of these memories is quite positive. Patients who underwent an awake craniotomy had a higher quantity and quality of memory about the procedure than patients undergoing general anesthesia.

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We found selective aspects of unpleasant memories like the urinary catheter especially in men and pain in both sexes, which should be addressed better in pre-operative consulting and postoperative management to further increase patient satisfaction.

However, the total quantity of memories after an awake craniotomy is much lower than one would expect considering the fact that the patients are literally awake and fully cooperative for long parts of the procedure. Planned intraoperative awareness does not seem to be traumatizing for the patients.

Patients who remembered more about the perioperative period, experienced the perioperative period in a more positive way than patients who remembered less. This is independent of the anesthesia technique used. A possible explanation of these findings is that patients who remember more are better able to cope with their perioperative experiences.

Patients in the GA group, who experienced more anxiety prior to and looking back at the operation procedure had a lower quantity and quality of their memories. Furthermore, patients in this group who experienced more anxiety prior to and when looking back at the operation procedure had less patient satisfaction.

In the AC group only, patients who experienced more anxiety in the days after the operation procedure had a lower quantity of their memories. Patients in this group who experienced more anxiety had not less patient satisfaction.

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APPENDIX

Questionnaire with the questions used in this study.

The patients received the questionnaire with the questions in Dutch language.

1) How much do you remember of the surgery (Please tick an answer):

Phase of surgery	Nothing	Few	Partially	A lot	Everything
Preoperative night on the ward					
Arrival on the OR					
Inserting the i.v. lines					
Insertion of breathing tube (intubation)					
Fixing the head in the Mayfield clamp					
Local anesthesia of the surgical field					
Craniotomy					
Testing brain function					
Tumor resection					
Closure of surgical field					
Transport to intensive care unit/ PACU					
Removal of the breathing tube (extubation)					
First night on the intensive care unit/ PACU					

2) How are these memories for you? (Please tick an answer):

Phase of surgery	Totally negative	More negative than positive	Not positive, nor negative	More positive than negative	Totally positive	No memory
Preoperative night on the ward						
Arrival on the OR						
Inserting the i.v. lines						
Insertion of breathing tube (intubation)						
Fixing the head in the Mayfield clamp						
Local anesthesia of the surgical field						
Craniotomy						
Testing brain function						
Tumor resection						
Closure of surgical field						
Transport to intensive care unit/ PACU						
Removal of the breathing tube (extubation)						
First night on the intensive care unit/ PACU						

3) What was a cause of discomfort around or during the procedure. (1 not at all, 5 very big discomfort, please mark). Give an answer for each cause mentioned:

Cause of discomfort	1	2	3	4	5
Premedication					
Nausea / Vomiting					
Postoperative pain					
Mayfield-Clamp					
Lying position					
Not being allowed to move					
Shaving of hair					
Being covered with blankets and drapes					
Inserted anesthesia cannules and tubes					
Urinary catheter					
Dry mouth					
Injections for local anesthesia					
Body temperature					
Others, please specify:					

4) Which of the causes mentioned at question 3) was the most discomforting at all?

....

5) To what extent were you anxious by the idea of undergoing a brain tumor operation (1 is no anxiety at all, 10 very anxious)?

In the days prior to the operation?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

Looking back in the days after the operation?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

6) To what extent were your relatives anxious by the idea that you were undergoing a brain tumor operation (1 is no anxiety at all, 10 very anxious)?

In the days prior to the operation?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

Looking back in the days after the operation?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

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7) If you reflect on the whole process around your operation and you need to give an overall satisfaction score: Were you satisfied with the state of affairs (1 is not satisfied, 10 completely satisfied)?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

V

Awake craniotomy in special populations

Chapter 8

Awake craniotomy for a glioblastoma in a nine-year-old boy.

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AWAKE CRANIOTOMY FOR A GLIOBLASTOMA IN A NINE-YEAR-OLD BOY.

SUMMARY

We report the pre-operative preparation and anaesthetic management for resection of an intracerebral tumour during awake craniotomy in a 9-year-old boy. We believe this is the youngest patient reported to have undergone this procedure. The challenges of sedation and psychological care throughout the procedure are discussed. We conclude that the procedure can be performed safely and that it seems unacceptable to uphold an age restriction. We believe that it is the individual level of development of the child that determines suitability for this type of surgery.

Keywords: Craniotomy: awake. Anaesthesia: paediatric. Conscious sedation

During brain tumour resection with intra-operative neuropsychological monitoring in awake patients (awake craniotomy) the anaesthetist has an important role in providing optimal psychological care and ensuring minimal discomfort to the patient without using drugs or techniques which make functional monitoring impossible [1]. The procedure has been eloquently described by Pasquet as 'vocal anaesthesia' [2]. Awake craniotomy has been performed for resections of tumours and epileptic foci in adults and children down to the age of 11 years [3,4]. Psychological screening for suitability and extensive preparation for the procedure may be more important in children [5–7]. Specific problems may include agitation, restlessness, and lack of co-operation, which may become dangerous during open brain surgery. This paper describes the pre-operative preparation and anaesthetic management for the resection of an intracerebral tumour by awake craniotomy in a 9-year-old boy, which to our knowledge is the youngest patient to undergo brain tumour resection with intra-operative neuropsychological monitoring.

CASE REPORT

A 9-year-old, 32-kg boy with neurofibromatosis type I required resection of a recurrent high-grade glioblastoma in the left temporo-parietal region (**Fig. 1**) using intra-operative neuropsychological function monitoring (awake craniotomy). Six months previously, the same tumour had been partially removed under general anaesthesia. Postoperatively, the child had a mild disturbance of fine right-sided motor function. He had re-presented with headache, vomiting and photophobia.

The child was evaluated by a child psychologist and found to be eligible to undergo the procedure. He reported nightmares more appropriate for younger children demonstrating some psychological regression. He was, however, co-operative and showed a high level of endurance and was able to concentrate and perform specific frustrating tasks for more than 3 h. Because of his handicap, he had taught himself to become left-handed. He showed adequate emotional reactions with a low anxiety level and a panic attack during the operation was considered to be unlikely. He had a strong relationship with his father who was asked to accompany him throughout the operative procedure. As preparation for intra-operative brain mapping to identify language-controlling areas, he was extensively trained on a modification of the Aachen Aphasia Test in correctly recognizing and naming pictures [8, 9]. The child and his father received a detailed explanation including a video presentation of all aspects of the procedure. In particular the need to remain still was emphasised.

On the evening before surgery the child was given lorazepam 0.5 mg orally and he received piritramide 0.1 mg/kg and promethazine 0.3 mg/kg intramuscularly 0.5 h pre-
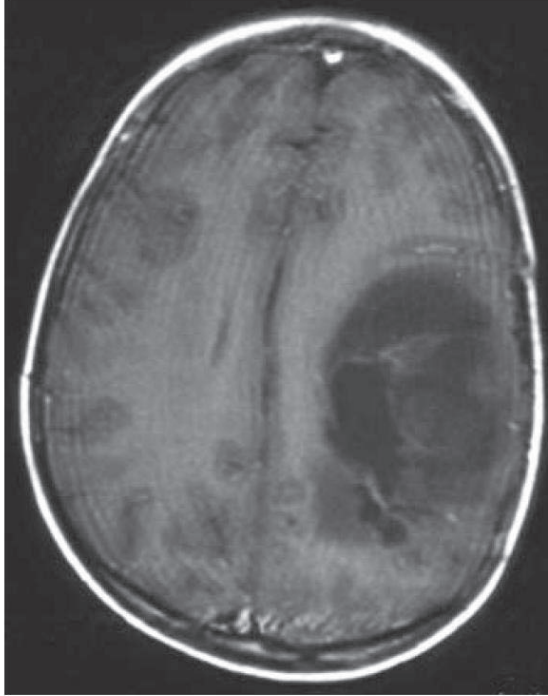
Figure 1 Pre-operative MRI scan showing a recurrent tumour in the left temporo-parietal lobe.

operatively. EMLA (Astra Zeneca, Zoetermeer, the Netherlands) cream was placed on the back of both hands. The pre-operative regimen of dexamethasone 2 mg four times daily and ranitidine 37.5 mg two times daily was continued right up to surgery. In theatre the boy was accompanied by his father and a child psychologist. Intravenous access was established and an infusion of Ringer's lactate solution (70 ml/kg) started. A nasal catheter was inserted and oxygen 2 l.min)1 started. He found this to be unpleasant.

Sedation with propofol (bolus 50 mg, continuous infusion 4.69 mg/kg/h) was started and the child became very agitated. Removal of the nasal catheter offered no relief. The sedation was stopped, the boy woken up and after discussion the procedure continued with a reduced level of sedation (propofol 2.5 mg/kg/h) which produced a calm and co-operative state. The child was positioned comfortably and covered in a warm air blanket [10]. Using local anaesthetic infiltration, an arterial cannula and a central venous catheter (via the antecubital fossa) were placed, and a urinary catheter inserted. To reduce peroperative blood loss and to decrease intracranial pressure the child was placed in a slight reverse Trendelenburg position [11, 12]. The scalp and periosteum were anaesthetised by local infiltration with bupivacaine 0.375% and epinephrine 1 : 200 000, 25 ml.

The craniotomy was started and the child's co-operation during the mapping procedure and subsequent tumour resection was excellent. During the mapping procedure the brain surface was electrically stimulated by the neurosurgeon to identify areas of functional relevance, whilst the child performed different tasks such as the Aachen Aphasia Test, moving his arm and his leg. This was the only period which he found stressful as judged from an increase in heart rate. The tumour was completely resected macroscopically after 3.5 h and the procedure finished. He felt a little pain during skin closure, which was managed with additional bupivacaine infiltration (5 ml).

Oxygenation was well maintained throughout the procedure and the child did not hyperventilate (P_aO_2 12.5 and 13.9 kPa without oxygen and P_aCO_2 5.3 and 5.0 kPa at the beginning and end of the procedure, respectively).

The total amount of propofol given throughout the procedure was 269 mg. Postoperatively, he received regular paracetamol and morphine 4 mg s.c. on demand, which was requested once. When visited 1 day after the operation the child could remember some specific details of the procedure, but had partial amnesia. He was discharged in good health without speech impairment or new motor disability on the fourth postoperative day.

DISCUSSION

Awake craniotomy allows maximal tumour resection with a reduced risk of functional deficits when used for brain tumours situated in functionally relevant areas [13]. In 1954, Pasquet noted that 'uncooperative adults and children under 10 years' will not tolerate the application of local anaesthesia, scalp incision and craniotomy [14]. This case demonstrates that an awake craniotomy is feasible and can be performed safely even in very young patients and it seems unacceptable to uphold an age restriction. The individual level of development of the child determines suitability.

Propofol sedation can lead to agitation and restlessness and it is advisable to use only mild levels of sedation to allow the patient to voluntarily suppress such restlessness. Soriano et al. stated that it is imperative that candidates for an awake craniotomy are mature and psychologically prepared to participate in the procedure [3]. They emphasised the importance of the cognitive level and motivation of the patient. Based on the nightmares the boy suffered, some psychological regression was evident. However, other psychological characteristics, considered to be better indicators of his ability to endure the procedure, showed that the child was mature for his age. When asked to draw a tree, he drew one bearing fruits and blossom, symbolic of the fact that he expected to survive

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the procedure, and a nest with two birds and a mother, symbolic of himself, his sister and his mother. When asked to repeat this while squeezing a ball in his impaired right hand, he was able to reproduce the same drawing even after 3 h of extensive concentration.

Other authors have used different techniques for sedation of older children undergoing awake craniotomy. Soriano et al. used a higher dose of propofol (1–2 mg/kg bolus, 9 mg/kg/h infusion) combined with fentanyl (0.5–2 µg/kg) [3], whilst Tobias and Jiminez combined midazolam (0.05 mg/kg), with fentanyl (1.2 µg/kg), and propofol (2 mg/kg bolus, 6–12 mg/kg/h infusion) [4]. Our decision to use propofol alone was based on our excellent experience with this agent in adults. The reliable pharmacodynamic and predictable pharmacokinetic properties of propofol make it very useful for this setting.

However, we found that with intensive psychological care throughout the procedure we were able to keep the child only lightly sedated (propofol 2.5 mg/kg/h) and he remained co-operative. The infiltration with local anaesthetic was sufficient to block pain from the surgical field and the use of opioids was unnecessary. There is very little published about operative procedures in awake children of a similar age using local or regional anaesthesia. However, even for simple procedures such as venepuncture, psychological preparation has been shown to reduce stress [15].

There is no guarantee that such a young child will understand the importance of this procedure, but the preoperative psychological evaluation gave strong support to our belief that our patient would fully co-operate. At this point, we believe that the more extensive tumour resection permitted by the technique of awake craniotomy with preservation of motor and speech function will outweigh the possible loss of quality of life due to the emotional distress of the procedure. To our knowledge, this is the youngest child to undergo a successful awake craniotomy. This case shows that such a procedure is feasible and safe in very young people with mild levels of sedation, provided they are appropriately evaluated pre-operatively and adequately guided throughout the per- and postoperative period.

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Chapter 9

Awake craniotomy versus craniotomy under general anesthesia for the surgical treatment of insular glioma: choices and outcomes.

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AWAKE CRANIOTOMY VERSUS CRANIOTOMY UNDER GENERAL ANESTHESIA FOR THE SURGICAL TREATMENT OF INSULAR GLIOMA: CHOICES AND OUTCOMES.

ABSTRACT

Objective: To investigate differences in outcomes in patients who underwent surgery for insular glioma using an awake craniotomy (AC) versus a craniotomy under general anesthesia (GA).

Methods: Data from patients treated at our hospital between 2005 and 2015 were analyzed retrospectively. The preoperative, intraoperative, postoperative, and longer-term follow-up characteristics and outcomes of patients who underwent surgery for primary insular glioma using either an AC or GA were compared.

Results: Of the 52 identified patients, 24 had surgery using an AC and 28 had surgery under GA. The extent of resection was similar for the two anesthesia techniques: the median extent of resection was 61.4% (IQR: 37.8%–74.3%) in the WHO grade <4 AC group versus 50.5% (IQR: 35.0%–71.2%) in the grade <4 GA group and 73.4% (IQR: 54.8%–87.2%) in the grade 4 AC group versus 88.6% (IQR: 61.2%–93.0%) in the grade 4 GA group. Consistent with literature, there were more early neurological deficits after an AC, while the GA group showed more new late neurological deficits; however, these trends were not significant. Survival was similar between the two groups, with 100% 1- and 2-year survival in the grade <4 groups.

Conclusion: Our results showed that the extent of resection, neurological outcomes, and survival were similar using the two anesthesia techniques. Since AC is more challenging for the patient and for his or her caregiver after surgery, this finding has implications for clinical decision making.

Keywords: Insula; Glioma; Awake craniotomy; General anesthesia; Retrospective

INTRODUCTION

The insular cortex of the brain plays roles in a variety of important neurological processes, including somatosensory processing, gustation, balance, control of cardiovascular tone and language [1,2]. Neoplasms, and especially gliomas, may cause dysfunction of these processes [1]. Insular gliomas represent a substantial portion of all central nervous system neoplasms, with 25% of all low-grade gliomas and 10% of all high-grade gliomas found in the insula [3]. The estimated incidence rates are 0.34 per 100,000 person-years for low-grade insular gliomas and 0.41 per 100,000 person-years for high-grade insular gliomas [4].

Surgical resection of insular gliomas is challenging due to their close proximity to several eloquent cortical areas and other critical areas. In addition, the presence of critical vascular structures, especially branches of the middle cerebral artery, can further complicate the procedure [5,6]. Case series of insular gliomal resections show similar results to other gliomal resection according to postoperative cognitive function[7].

Furthermore, these studies show that radical resection can improve progression-free survival and overall survival [8-11]. Traditionally, neurosurgeons have had the option to resect or debulk an insular glioma either by performing a craniotomy under general anesthesia (GA) or by using an awake craniotomy (AC), which allows cortical and/or subcortical mapping [12]. The AC procedure was developed to allow greater resection with less risk of damaging eloquent cognitive brain functions [1,13-15]. There is limited evidence regarding the best anesthesia technique for resecting these insular tumors, and the number of patients in published articles is relatively low. This is likely due to the technical challenges of the procedure and the low incidence of the disease.

Many patients with insular tumors have been treated at our hospital during the last decade. The data from these patients were analyzed to gain a better understanding of this specific patient population and the differences in outcomes between the two anesthesia techniques. Our aim was to investigate the differences in survival, extent of resection (EOR), and neurological outcomes in patients who underwent surgery using AC versus GA.

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METHODS

Patients

First, patients were identified who underwent a craniotomy under GA or using an AC for the resection or debulking of a primary insular glioma between 2005 and 2015. Patient information was retrieved from the electronic patient registry at our hospital. It is routine

practice to ask neurosurgical patients at intake whether they will allow their data to be used anonymously for research. Informed consent for the use of all data was provided by all of the patients in this retrospective analysis. This study protocol was approved by the ethics board at our hospital (MEC 2013-090). The neurosurgeon consulted with the neuro-anesthesiologist and then chose which anesthesia technique to use for each patient. This clinical choice was investigated in this case series in which patients were retrospectively categorized into two groups, an AC group and a GA group. All gliomas were resected using a transsylvian approach. Data were extracted for the entire peri-operative (pre-, intra-, and post-operative) period and for the follow-up period. All data were extracted by the first author, double-checked by the last author, and discussed with the co-authors. The use of the two anesthesia techniques over time was also analyzed.

Preoperative characteristics

The clinical characteristics at presentation and the tumor characteristics were de-termined in order to investigate the factors that may have influenced the choice of anesthesia technique. The following clinical characteristics were assessed: the presence of linguistic, motor, and sensory dysfunction; whether the patient had epilepsy; tumor size at MRI (calculated by volumetric analysis); dominant hemispheric localization; and glioma type. Although the tumor glioma type could only be confirmed histologically postoperatively, radiological presentation often clearly correlates with the pathological diagnosis, especially for glioblastoma multiforme (GBM) [16,17]. Therefore, the glioma type was used as a preoperative characteristic. The differences in these variables were analyzed between groups in order to assess which factors drove the clinical decision.

Intraoperative characteristics

The duration of the procedure, the amount of blood lost, and the EOR were compared between the two groups to investigate whether the anesthesia type influenced these factors. The duration of the procedure was determined according to the anesthesia time, which was defined as the time in hours between the time-out procedure (TOP) and signout/extubation/transport to the PACU and according to the surgical time, which was defined as the time in hours between the first incision and the last suture.

Volumetric analysis

Brainlab neuronavigation and planning software (version 3.0.0, BrainLAB, Feldkirchen, Germany) was used to define the borders of the tumor and to calculate its volume in order to assess the percentage of tumor that was removed. The volume was calculated both pre- and postoperatively using MRI scans that were performed as close to the surgical date as possible. In general, a T2-weighted or FLAIR MRI was used for lowgrade gliomas and a T1-weighted MRI with contrast was used for high-grade gliomas. The

radiology reports were used as a reference during each assessment to confirm the tumor location and borders. All tumor volumes were calculated in cubic centimeters. Cystic components were included in the total volume, but perifocal edema and intratumoral hemorrhages were not. Patients who did not have an MRI scan either pre- or postoperatively were excluded from the volume analysis.

Postoperative characteristics

The early postoperative characteristics were compared between the two groups by determining the mean lengths of hospital stay and the complications that occurred as a result of the procedure. The 1- and 2-year survival was determined for all patients, as was the 5-year survival for patients who were operated on before September 2012. Survival data for patients that were not followed-up at our hospital were obtained by calling each patient's general practitioner.

Neurological outcome

The scale used by De Witt Hamer et al. [18] was used to compare neurological outcomes in the two groups. Data were retrieved on new-onset postoperative neurological deficits that were categorized as early (up to 3 months after surgery) and late (3 months or longer after surgery), and data on severe and non-severe deficits were retrieved as well. Deficits were categorized as severe when the patient's muscle strength was grade 1, 2, or to 3 on the Medical Research Council scale or aphasia, severe dysphasia, hemianopsia or a vegetative state was present. All other deficits were considered non-severe. A deficit was scored when it persisted for more than one postoperative day and the patient needed an intervention for the deficit.

Statistical analysis

The clinical outcomes of WHO grade 4 gliomas are worse than for other gliomas that have similar effects on neurocognitive function at presentation [11,19]; accordingly, grade 4 gliomas were analyzed separately. After comparing patients with grade <4 and grade 4 gliomas, the GA and AC groups were compared within the grade <4 and grade 4 groups.

   Normally distributed continuous variables were compared using independent sample t-tests. Non-normally distributed non-nominal variables were compared using the Mann- Whitney U test and the exact significance was reported, while nominal variables were compared using Chi-squared ($\chi2$) and Fisher's exact test when any of the categories had an expected count less than 5. To assess neurological outcomes, the proportion of patients presenting with an early or late deficit and the proportion who suffered from a severe early or late deficit were calculated. Neurological outcomes were presented with 95% CIs. Because survival and EOR were not normally distributed, 95% CIs were

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not reported for these outcome measures. The EOR was calculated by subtracting the preoperative tumor volume by the postoperative volume and dividing the result by the preoperative tumor volume.

To deal with missing data, only available data were analyzed. However, the percentages are based on the whole group, including missing cases. Because multiple hypothesis testing was performed, an α-level of 0.01 was considered statistically significant; this was estimated by the Bonferroni correction technique [19]. Furthermore, a p-value below 0.05 was seen as a trend towards significance and is discussed as such. The statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corp., 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

RESULTS

Data were retrieved for 52 patients; of these, 24 patients were treated with an AC, and 28 patients were treated using a craniotomy under GA. Over time, there was a trend toward using AC less often and using GA more often in our hospital (**Figure 1**).
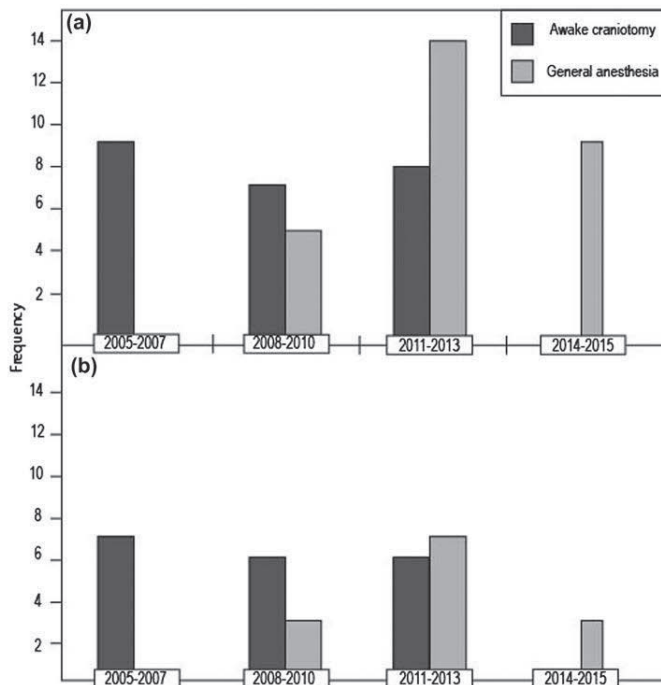
Figure 1. The frequency distribution of the performed techniques over time.
Notes: The bar graph shows the frequency of the procedures in the four indicated time periods. There was a decrease over time in the use of awake craniotomy, resulting in greater use of the general anesthesia procedure. Panel **a** shows the data for all surgeries, and panel **b** shows the data from surgeries for grade <4 gliomas.

Patient characteristics

The groups were similar for all descriptive variables except age (**Table 1**). The mean age was 55.2±16.0 years for patients in the grade 4 GA group versus 41.9±10.5 years for patients in the grade <4 GA group (p=0.017; 95% CI: 2.6–24.0 years). There were no significant differences in age between the patients in the two anesthesia groups. Variables that could influence the choice to use AC versus GA **Table 2** shows an overview of the variables that could influence the choice to use AC versus GA.

Table 1. Characteristics of the 52 patients who underwent primary resection for insular glioma at the Erasmus University Medical Center 2005–2015.

Variable	Awake craniotomy (AC)		General anesthesia (GA)	
	WHO grade <4 *n* = 19	WHO grade 4 *n* = 5	WHO grade <4 *n* = 13	WHO grade 4 *n* = 15
Age at surgery in years, mean±SD	41.1±11.8	41.5±6.3	41.9±10.5	55.2±16.0
Male, *n* (%)	16 (84.2%)	4 (80%)	8 (61.5%)	10 (66.7%)
Weight in kg, mean±SD	86.5±12.3	79.6±11.8	85.5±20.9	88.7±14.6
Height in m, mean±SD	1.80±0.08	1.83±0.05	1.80±0.12	1.80±0.12
BMI in kg/m², mean±SD	26.1±2.97	23.8±2.8	26.1±4.11	27.8±5.8
Right handed, *n* (%)	14 (73.7%)	5 (100%)	10 (76.9%)	11 (73.3%)

Notes: There was only one significant difference between any of the groups (grade 4 vs. grade <4 within the AC and GA groups or AC vs. GA within the grade 4 and grade <4 groups). That difference was for age, which was significantly different (*p* = 0.017) between the grade 4 GA group and the grade <4 GA group (95% CI: 2.6–24.0 years).

Clinical presentation

There were no significant differences in linguistic and motor dysfunction between the AC and GA groups. There was a trend towards statistical significance for differences in sensory dysfunction at presentation according to tumor grade in the GA group: 3 (23.1%) patients in the grade <4 GA group suffered from sensory dysfunction vs. 9 (60.0%) patients in the grade 4 GA group (p=0.049).

There was also a trend towards statistical significance for differences in epilepsy according to tumor grade in the GA group: 8 (53.3%) patients in the grade 4 GA group suffered from epilepsy vs. 12 (92.3%) patients in the grade <4 GA group (p=0.038). The tumor size was similar in the two groups for both grade <4 tumors and for grade 4 tumors. There

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Table 2. Preoperative clinical characteristics of the 52 patients who underwent primary resection for insular glioma at the Erasmus University Medical Center 2005–2015.

Variable	Awake craniotomy (AC)		General anesthesia (GA)		P-value for AC vs. GA		P-value for WHO grade <4 vs. grade 4	
	WHO grade <4 n=19	WHO grade 4 n=5	WHO grade <4 n=13	WHO grade 4 n=15	WHO grade <4	WHO grade 4	AC	GA
Clinical presentation								
Linguistic dysfunction, n (%)	11 (57.9%)	4 (80%)	3 (23.1%)	7 (46.7%)	n.s.	n.s.	n.s.	n.s.
Motor dysfunction, n (%)	6 (31.6%)	2 (40.0%)	5 (38.5%)	5 (33.3%)	n.s.	n.s.	n.s.	n.s.
Sensory dysfunction, n (%)	8 (42.1%)	3 (60.0%)	3 (23.1%)	9 (60.0%)	n.s.	n.s.	n.s.	0.049
Epilepsy, n (%)	11 (57.9%)	3 (60%)	12 (92.3%)	8 (53.3%)	n.s.	n.s.	n.s.	0.038
Tumor size at presentation in cm³, mean±SD	61.2±24.5	107.2±62.1	54.6±25.4	96.5±59	n.s.	n.s.	n.s.	0.02
Tumor in dominant hemisphere, n (%)	17 (89.5%)	4 (80%)	8 (61.5%)	5 (33.3%)	0.021	n.s.	n.s.	n.s.
Histological classification, n (%)								
Astrocytoma	6 (31.6%)	–	13 (100%)	–	0.001	–	<0.001	<0.001
Oligodendroglioma	10 (52.6%)	–	0 (0%)	–				
Mixed glioma	3 (15.8%)	–	0 (0%)	–				
Glioblastoma	–	5 (100%)	–	15 (100%)				

was a trend towards statistical significance for differences in tumor size according to tumor grade in the GA group: 54.6±25.4 cm^3 in the grade <4 GA group vs. 96.5±59 cm^3 in the grade 4 GA group (p=0.02); the difference was 41.9 cm^3; 95% CI: 7.0–76.8 cm^3. The tumors were more often localized in the dominant hemisphere in the grade <4 AC group than in the grade <4 GA group: 17 (89.5%) versus 8 (61.5%) (p=0.021). No such trend towards significance was found in the grade 4 groups in terms of localization in the dominant hemisphere. However, there was a significant difference in the glioma type in the GA group versus the AC group. Specifically, astrocytomas were mostly resected using GA, while oligodendrogliomas were all resected using an AC. GBM was more often treated under GA. The p-value was <0.001 for these differences.

Intraoperative and postoperative characteristics
Table 3 shows the intraoperative and postoperative characteristics of the patients in the GA and AC groups.

Surgical duration
There was a trend towards significance for differences in anesthesia time in the GA group according to tumor grade: the anesthesia time was 6.4±1.2 hours for the grade <4 GA group and 5.0±2.1 hours for the grade 4 GA group (p=0.036; mean difference, 1.4 hours; 95% CI: 0.10–2.8 hours). Post-hoc analysis showed a trend towards significance regarding the duration of anesthesia induction and preparation of the patient in the GA group: the time between the TOP and the incision was 1.2±0.13 hours for patients in the grade <4 GA group versus 0.99±0.24 hours for patients in the grade <4 GA group (p=0.02; mean difference, 0.19 hours; 95% CI: 0.032–0.34 hours).

Surgical characteristics
The intraoperative blood loss was higher in the grade <4 AC group, which showed a mean blood loss of 584±214 ml versus 307±188 ml in the grade <4 GA group (p=0.001; mean difference, 277 ml; 95% CI: 127–427 ml). There was no difference in blood loss between the grade 4 GA group vs. the grade 4 AC group or between the grade 4 and the grade <4 glioma groups within the two groups. Even though blood loss was greater in the grade <4 AC group, none of the patients received a blood transfusion. The EOR was similar in the grade <4 groups and in the grade 4 groups, but the EOR in the grade 4 GA group was significantly higher than in the grade <4 GA group: 82.4% (IQR: 60.1%– 92.8%) in the grade 4 group, and 50.5% (IQR: 35.0%–71.2%) in the grade <4 group (p=0.003) (**Figure 2**). One patient was excluded from the analysis because a postoperative MRI scan was not available, as the patient had pneumonia and was in the intensive care unit for 20 days. An MRI has not been performed in the ICU.

Table 3. Intraoperative and postoperative characteristics of the surgeries for primary insular glioma.

Variable	Awake craniotomy (AC)		General anesthesia (GA)		P-value for AC vs. GA		P-value for WHO grade <4 vs. grade 4	
	WHO grade <4 n=19	WHO grade 4 n=5	WHO grade <4 n=13	WHO grade 4 n=15	WHO grade <4	WHO grade 4	AC	GA
Anesthesia time in hours, mean±SD	5.6±1.2	5.0±0.8	6.4±1.2	5.0±2.1	n.s.	n.s.	n.s.	0.036
Surgical time in hours, mean±SD	4.2±1.1	3.6±0.6	5.0±1.1	3.8±1.9	n.s.	n.s.	n.s.	n.s.
Blood lost in ml, mean±SD	584±214	860±456	307±188	436±373	0.001	n.s.	n.s.	n.s.
Length of hospital stay in days, median (IQR)	7 (6–9)	9 (8–12)	9 (7–11)	7 (6–13)	n.s.	n.s.	n.s.	n.s.
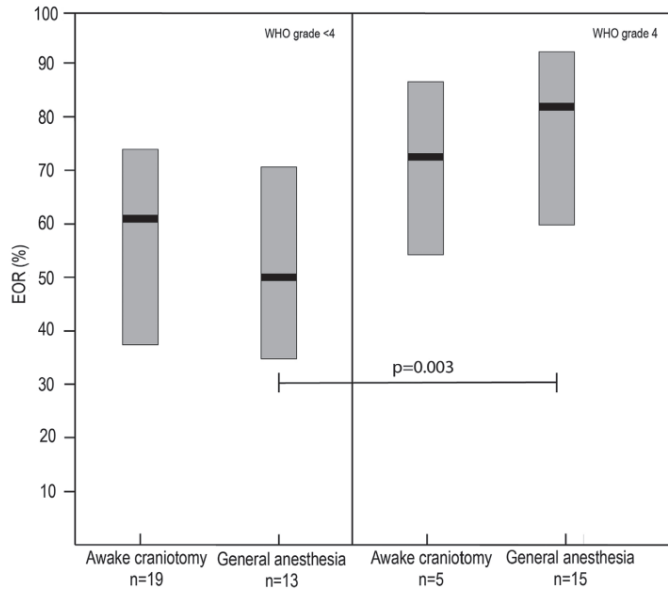
Figure 2. A box plot shows the median extent of resection (EOR) and the 1st and 3rd quartiles for each group of patients.
Note: The grade 4 patient groups had a larger extent of resection, and this difference was significant between the grade <4 and grade 4 GA groups ($p = 0.002$).

Postoperative characteristics

The length of hospital stay was similar in the AC and GA groups. **Table 4** shows the complications. The 1-, 2-, and 5-year survival rates were higher in the grade <4 groups than in the grade 4 groups. No difference between AC and GA was found according to 1-, 2-, and 5-year survival (**Figure 3**). The 5-year survival time could be determined for the AC group, but some information was missing for the GA group.

Neurological outcome

Early onset deficits developed in 67% (95% CI: 46%–88%) of the patients in the AC group and in 57% (95% CI: 37%–77%) of the patients in the GA group. Severe early onset deficits developed in 25% (95% CI: 6%–44%) of the patients in the AC group and in 11% (95% CI: 0%–24%) of the patients in the GA group. Late onset deficits developed in 48% (95% CI 26%–70%) of the patients in the GA group and in 33% (95% CI: 10%–56%) of the patients in the AC group. Severe late onset deficits developed in 12% (95% CI: 0%–27%) of patients in the GA group and in 5% (95% CI: 0%–17%) of the patients in the AC group. None of the differences between the groups were significant. The groups were too small to analyze differences between grade 4 and grade <4 groups (**Figure 4**).

Table 4. Summary of the surgical complications that occurred after surgical resection and before discharge in the 52 patients who underwent primary resection for insular glioma at the Erasmus University Medical Center 2005–2015.

	Awake craniot-omy (n=24)	General anesthe-sia (n=28)	Total n
Complication			
Postoperative insult	1	1	2
Periorbital edema	3	0	3
Atelectasis	0	1	1
Postoperative hemorrhage	2*	0	2
Headache	1	2	3
Hyperglycemia	1	1	1
Nausea	1	1	2
Pulmonary embo-lism	0	1	1
Urinary tract infection	1	0	1
Pneumonia	0	1	1

*1 patient underwent a recraniotomy.
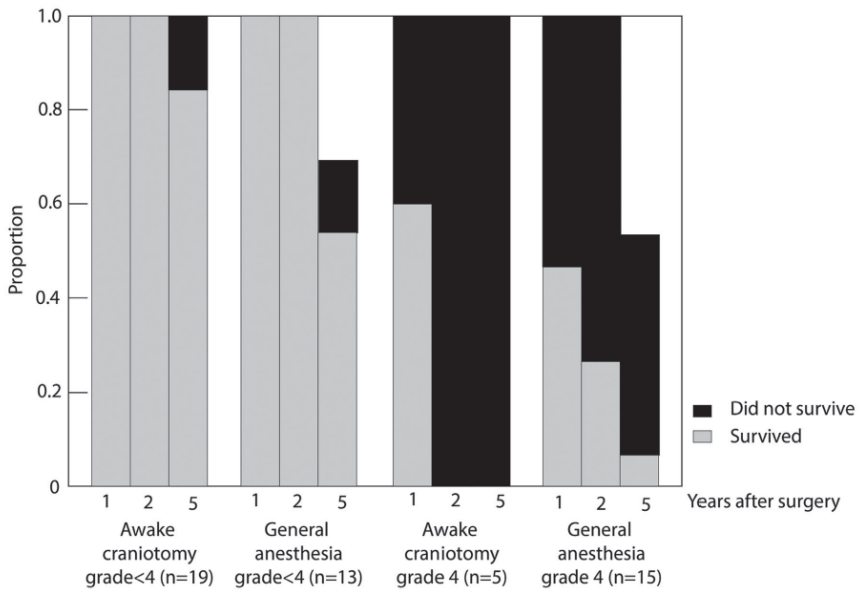
Figure 3. A bar graph shows the proportion of patients who were alive one, two, and five years after surgery.
Note: In the general anesthesia (GA) group, information on five-year survival was not available for 4 (30.8%) patients in the grade <4 GA group or for 7 (46.7 patients in the grade 4 GA group.

Summary of results:

To summarize, a total of 52 patients underwent primary insular glioma resection at our hospital. This retrospective case series analysis found that over the course of the study period, the GA procedure was used more often than the AC procedure. Astrocytomas and GBMs were more often treated under GA, while oligodendrogliomas were more often treated using AC. Intraoperative blood loss was greater in patients with grade <4 tumors in the AC group than in the GA group. The EOR was similar between the AC and GA groups, but the mean EOR was greater in the grade 4 GA group than in the grade <4 GA group. The 1-, 2-, and 5-year mortality was similar between the AC and GA groups, but patients with grade 4 gliomas had worse survival than those with grade <4 tumors. New early deficits were more prevalent in the AC group, and new late deficits were more prevalent in the GA group, but the differences were not significant.
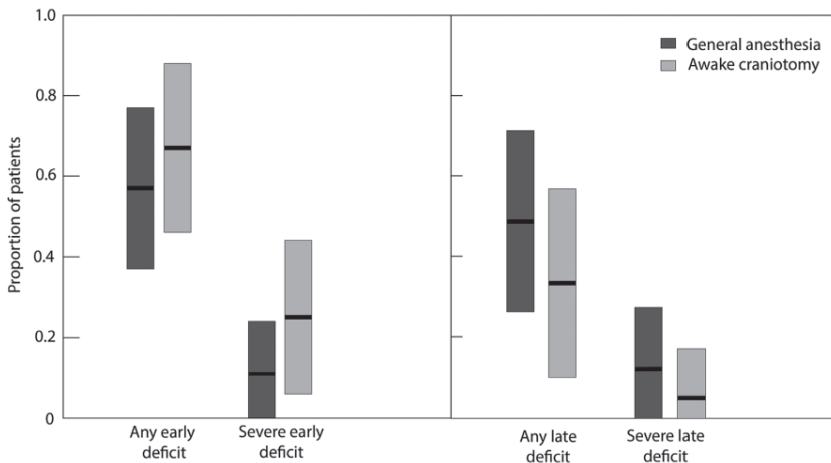
Figure 4. A box plot shows the proportions and 95% confidence intervals of patients with newly developed, any early, severe early, any late, or severe late neurological deficits.
Notes: More early neurological deficits were seen in the awake craniotomy group, while more late neurological deficits were seen in the general anesthesia group. This trend was seen for any deficits and for severe deficits, but none of the differences reached statistical significance.

DISCUSSION

This retrospective analysis of patients with insular gliomas who were treated by an AC or by a craniotomy under GA was performed to gain insights into the effects of these two techniques on the patients, especially on EOR, survival, and neurological outcome.

Choice of anesthesia technique

In the later part of the investigated period, the GA technique was preferred over the AC technique because the GA procedure is less challenging for the patient and has advantages for the doctors. GA was also preferred for grade 4 gliomas, which more often present perivascularly and with adhesions to the M2 and M3 branches of the

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middle cerebral artery [21]. Pressure on these branches is painful for AC patients, so GA is typically used for grade 4 gliomas. The neurosurgeons at our hospital found that surgeries performed using AC were often quite long; the patients became fatigued, reducing the advantages of performing an awake surgery. Since craniotomy under GA showed good results, neurosurgeons who became comfortable resecting these tumors more often opted to use GA. However, AC was still preferred for patients with frontal opercular extension, especially when the dominant frontal operculum was involved and the patients presented with speech problems following an epileptic insult. Indeed, patients were more often treated with an AC if they presented with a tumor localized in their dominant hemisphere. Note that linguistic dysfunction as a symptom did not differ significantly between the groups. Because linguistic function resides mostly in the dominant hemisphere [22], AC may have been chosen for these patients to allow resection while ensuring clear demarcation of the functional language area in order to preserve this function [23].

Oligodendrogliomas were more often operated on using AC, and astrocytomas more often resected under GA. This is most likely because oligodendrogliomas are more often located in the frontal operculum than astrocytomas; therefore, AC is more often used for these tumors. A study on the use of AC for the resection of tumors in eloquent areas showed that all tumors had an oligodendroglial component [24].

Outcomes

The EOR was similar using AC and GA, but the EOR was smaller within the GA group for grade <4 tumors than for grade 4 tumors. This group also had a larger preoperative tumor volume, and this might explain the higher EOR. Since the edges of the tumor are the most difficult to resect, a larger tumor with a smaller surface area-to-volume ratio, could result in a higher EOR. In addition, GBMs with central necrosis are easier to distinguish from normal brain tissue than are low grade gliomas, allowing easier resection without the need to map the region. In the literature, the median EOR for insular gliomas varies from 83.4% to 86.2% [7, 10, 23]. However, only Lang et al. reported the EOR for the non-glioblastoma group separately (median EOR, 86%) [5]. However, it seemed that in this study, the population that presented with grade <4 tumors mainly had small diffuse tumors that were hard to resect. Diffuseness was not measured, so it cannot be compared to reports in the literature, but tumor size was measured. The mean tumor size was 61.2 cm^3 in the AC group and 54.6 cm^3 in the GA group, which contrasts with, for example, the mean tumor size of 107.7cm^3 reported in the study by Alimohadi et al. [23].

The neurological outcomes observed in our population suggested that the AC results in fewer late neurological deficits than the GA technique, although the difference was not

significant. For a power of 80%, a sample size of 49 per group would be needed to find the same difference in the occurrence of early deficits, as in the study by De Witt Hamer et al. (α=0.01) [18]. For a power of 80%, a sample size of 1953 per group would be needed to detect the same difference in late deficits using the same assumptions. These larger sample sizes may not be attainable for this rare disease. Nevertheless, the trends of more early-onset neurological deficits after AC and more late-onset neurological deficits after GA are consistent with the literature [18]. De Witt Hamer et al. hypothesized that an AC enables more extended resection and more tumor control, resulting in the preservation of neurological functions that can be mapped at the cost of early transient neurological deficits.

Differences in 1- and 2-year mortality were not observed between the two anesthesia groups. GA was preferred for the treatment of astrocytomas, which have a worse survival prognosis than oligodendrogliomas [11,25]. This apparent contradiction is explained by the small sample size in this study. Furthermore, the literature suggests that survival curves start to diverge after more than two years. Since most GA procedures were performed in the second half of the study period, data were not available for some patients for the 5-year survival analysis, and conclusions regarding 5-year survival cannot be drawn. Our results indicated that 1 and 2 years after surgery for insular glioma, there were no differences in survival using AC versus GA.

Other findings

In the GA group, patients in the grade <4 group were younger than patients in the grade 4 group and more often presented with epilepsy. These findings can be explained by differences in the pathogenesis of primary and secondary GBM. Primary GBMs are most likely derived from neurological progenitor cells, while secondary GBMs are most likely derived from dedifferentiated glial cells [26]. Primary GBMs are more frequently diagnosed and often express wild type isocitrate dehydrogenase 1 or 2 (IDH1/2); in contrast, 73%–88% of the patients with secondary GBMs express mutated IDH1 or IDH2 [26]. The epidemiological distribution of IDH1/2 mutations, which are associated with epilepsy, in the types of GBMs could explain the lower frequency of epilepsy in the grade 4 group in our population. It is more likely that this group mostly had primary GBMs that expressed wild type IDH1/2, which would explain the lower prevalence of epilepsy in the grade 4 group than in the grade <4 group [27]. Since epilepsy is a symptom that can be suggestive of brain tumors, secondary GBMs might be diagnosed in an earlier stage, e.g. as an astrocytoma, which could explain the lower prevalence of secondary GBMs as well as the younger age at which they are diagnosed [26].

Intraoperatively, blood loss was greater in the grade <4 AC group than in the grade <4 GA group. This can be explained by the higher mean arterial blood pressure in awake

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patients. There was no indication that this results in a clinically relevant difference in outcome. The anesthesia time was longer in the grade <4 GA group than in the grade 4 GA group. The 1.4-hour difference between the groups could not be explained by the subanalysis, which showed a difference of 0.2 hours between the induction and preparation time between the grade <4 GA group and the grade 4 GA group. The difference between these groups cannot be fully explained. However, it can be more difficult to determine the borders of an insular LGG than the borders of an HGG, and therefore for this step may take longer when treating insular LGGs.

Limitations

This study had some limitations. First, this was a retrospective, single-center study of a disease that has a low incidence, so a larger sample size was not available. Some real differences may have been missed because of the size of the study. However, the sample size was comparable to or even larger than studies that have been published previously by other groups. Because the insula is a relatively common location for gliomas [3] and because insular gliomas have distinctive clinical features [10], this patient population is worth analyzing. Considering the low incidence of insular glioma, this study contributes to the existing body of knowledge about these patients.

Second, patients with WHO grade 4 glioma were compared with patients with grade <4 glioma, but it could be argued that WHO grade 3 and 4 groups should have been compared with WHO grade 1 and 2 groups. In this study, patients were divided based on similar clinical presentation and survival, but other authors have frequently grouped patients with grade 3 glioma with patients with grade 4 glioma [7]. However, the grade 4 group in this study was large enough to merit its own group, especially considering the distinctive clinical features of GBMs.

Finally, there are some limitations due to the retrospective design of the study, and additional prospective studies are needed to validate these observations. The advantage of our approach is that it provides a starting point for further study of additional research questions. For example, these results suggest that the value of AC for patients who present with linguistic dysfunction should be investigated further, as should the possible clinical relevance of higher blood loss during AC versus GA. Notably, there is an alternative technique that can be used to protect motor function in which the cortical processes are mapped using motor evoked potentials while the patient is under GA [28]. However, this technique was not performed at our hospital before 2015, so it is not discussed in this case series. It may be interesting to evaluate tumor extension into the temporal or frontal operculum as well as tumor extension medially beyond the lenticulostriate perforators; however, the subgroups were too small to draw any conclu-

sions. Use of the transcortical approach for the resection of this type of tumor is another technique that is not performed in our hospital, even though it may provide greater exposure of the insula and therefore might facilitate a greater EOR [29]. However, in our experience, this technique is not in widespread use, plus it should be critically evaluated as it involves the use of an approach through healthy brain tissue.

CONCLUSION

AC was used more often for the resection of dominant hemispheric tumors and oligo-dendrogliomas, while GA was used more often for astrocytomas and GBMs. However, both anesthesia techniques resulted in similar EORs, similar neurological outcomes, and similar 1- and 2-year survival in patients with similar tumor grades. Therefore, the added value of the more challenging AC procedure should be carefully considered for each patient. Prospective studies are needed to further evaluate the relative value of these techniques.

DISCLOSURE

The authors report no conflicts of interest.

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Chapter 10

Awake craniotomy versus craniotomy under general anesthesia for supratentorial glioblastoma in eloquent areas: A retrospective controlled- matched study.

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AWAKE CRANIOTOMY VERSUS CRANIOTOMY UNDER GENERAL ANESTHESIA FOR SUPRATENTORIAL GLIOBLASTOMA IN ELOQUENT AREAS: A RETROSPECTIVE CONTROLLED-MATCHED STUDY.

ABSTRACT

Background

Awake craniotomy with electrocortical and subcortical mapping (AC) has become the mainstay of surgical treatment of supratentorial low-grade gliomas in eloquent areas, but not as much for glioblastomas.

Objective

This retrospective controlled-matched study aims to determine whether AC increases gross total resections (GTR) and decreases neurological morbidity in glioblastoma patients as compared to resection under general anesthaesia (GA, conventional).

Methods

Thirty-seven patients with glioblastoma undergoing AC were 1:3 controlled-matched with one hundred eleven patients undergoing GA for glioblastoma resection. The two groups were matched for age; gender; preoperative Karnofsky Performance Score (KPS); preoperative tumor volume; tumor location; and type of adjuvant treatment. Primary outcomes were extent of resection and the rate of postoperative complications. The secondary outcome was overall postoperative survival.

Results

After matching, there were no significant differences in clinical variables between groups. Extent of resection was significantly higher in the AC group: mean extent of resection in the AC group was 94.89% (SD=10.57) compared to 70.30% (SD=28.37) in the GA group (p=0.0001). Furthermore, the mean rate of late minor postoperative complications in the AC group (0.03; SD=-0.16) was significantly lower than in the GA group (0.15; SD=0.39) (p=0.05).

Conclusion

These findings suggest that resection of glioblastoma using AC is associated with significantly greater extent of resection and less late minor postoperative complications as compared with craniotomy under GA. These data suggest that in patients with glioblastoma near eloquent areas AC should be implemented in standard treatment. A prospective randomized study is therefore warranted.

INTRODUCTION

Glioblastomas are malignant brain tumours with an annual incidence of six per 100,000. Treatment options include surgery, along with chemo(radio)therapy. Glioblastomas are of infiltrative nature, have a relatively poor radio- and chemotherapy sensitivity and are therefore invariably lethal. The median survival for glioblastoma multiforme (GBM) after treatment is approximately 15 months[1-3]. Due to the invasive nature of gliomas, complete resection in high grade gliomas is not possible. Surgeons strive to resect as much of the visible part of the tumor on MRI as possible, since the extent of this resection is correlated with survival and various predictive and prognostic factors[4-7]. Especially gross total resection (GTR) has been shown to increase survival in patients with high grade glioma, although at the risk of higher morbidity[4,8].

Awake craniotomy (AC) is the technique in which the patient is awake and cooperative during the resection of the tumor[9]. This allows the surgeon, together with cortical and subcortical mapping to prevent damage to eloquent cortical and subcortical areas during resection. AC is now widely used to optimize the extent of resection while minimizing the risk of complications[10,16]. Therefore, AC is mainly preferred over craniotomy under GA in patients with low-grade glioma because of the usually near-eloquent location of these tumors[10-12]. However, so far, AC has not yet been implemented routinely in high grade glioma surgery, although preservation of quality of life in these patients should be the first concern due to the limited prognosis. Only very few studies have reported the use of AC in glioblastomas, but are only descriptive or studied in a systematic review which included also low grade gliomas or WHO grade 3 gliomas[13,14].

This retrospective cohort-matched study aims to determine whether AC increases the extent of resection and decreases neurological morbidity in patients with high grade glioma as compared to resection under general anesthaesia (GA).

METHODS

Anesthesia, Surgical procedure and Postoperative Management

All patients in the AC group were extensively prepared for the procedure by the anesthetist with audiovisual media. AC-patients were sedated with propofol for craniotomy and closure and completely awake during resection of the tumor. Oxygen was provided by a nasal canula, patients were spontaneously breathing throughout the whole procedure. Local anesthesia was performed with Lidocaine 1% and Bupivacaine 0.25% and Adrenaline 1:200.000 for the pins of the Mayfield clamp and Bupivacaine 0.375% with Adrenaline 1:200.000 for the surgical field. After surgical incision, craniotomy and open-

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ing of the dura, propofol was discontinued, allowing the patient to wake up. During the resection of the tumor, standard electrocortical and subcortical stimulation and monitoring of speech and motor function were applied to resect the glioma[15]. After resection of the tumor the patient was sedated again with propofol until the termination of the operation.

GA patients were anesthetized with propofol, remifentanil and a non-depolarizing relaxant, intubated and mechanically ventilated throughout the procedure. In patients of both groups arterial blood pressure was measured invasively via the radial artery, and all patients received a urinary catheter. Mannitol, 200 ml 15% was given during the craniotomy period to all patients. After suturing, all patients were brought to the post-anesthesia-high-care-unit, where they spent the first 24 hours postoperatively. Morphine and paracetamol were given as postoperative analgesics routinely.

Inclusion criteria

Two cohorts were selected from a database of patients with supratentorial glioblastomas surgically treated using either AC or resection under GA at the Erasmus University Medical Center Rotterdam, Dept. of Neurosurgery, the Netherlands. All patients were treated for glioblastoma (WHO grade IV) between January 2005 and January 2015. Both techniques were used at the institute, but neurosurgeons not familiar with AC performed tumor resection under GA. Most neurosurgeons operated the patients with GBM under GA. In all cases, neuronavigation was used. Other adjuncts to surgery such as 5-ALA, intraoperative MRI or ultrasound were not used.

Criteria for inclusion in the study were as follows: 1) isolated GBM without evidence of multicentric or multifocal enhancement; 2) pathological diagnosis of glioblastoma multiforme (WHO Grade IV); 3) supratentorial lesion location; 4) preoperative KPS ≥60; 5) elective surgery; 6) No crossover between groups, meaning that no individuals underwent craniotomy under both AC and GA. No patients whose craniotomy was started as AC were converted to GA during the procedure.

Data collection

Patient characteristics were collected from a database and the hospital records, and presenting symptoms, neuroimaging findings, and data on pre- and postoperative neurological function and adjuvant treatment were documented. Preoperative KPS was assigned by the clinician at the time of evaluation and available in the chart for review in all cases. The MRI characteristics that were recorded included the lesion's size, specific lobe involvement, presence of a hemorrhagic component, and the degree of mass effect. The size of the lesion before and after surgery (residual tumor) was calculated based on T1-MR-images with contrast, using the method described by (among

others) Shah et al[18] in three directions. Extent of resection (EOR) as a percentage was calculated as: (preoperative tumor volume - postoperative tumor volume)/preoperative tumor volume. Operative data were reviewed for the use of AC with motor and langugage mapping. Postoperative complications were classified in four categories: early minor-, early major-, late minor-, and late major complications. Classification of postoperative complications was used as described in the meta-analysis of colleagues de Witt Hamer et al[13]. The distinction between early- and a late complication was 6 months postoperatively. Late complications, even minor-, are clinically important since these indicate permanent neurological complications from the surgery. Note that patients can experience multiple postoperative complications. To count more than one postoperative complication for one patient in the total number of complications (Table 6), the complications have to occur independently from each other. However, if a patient experiences an early complication that becomes permanent, this will solely be counted as an early complication.

Statistics: Matching procedure

The number of cases meeting the inclusion criteria was 37 in de AC group and 368 in the GA group. Patient characteristics of both groups before matching are shown in Tables 1 and 2. Because the number of patients who underwent craniotomy under GA in the same study period was disproportionately higher, a controlled matched selection of cases from the entire operative pool was performed based on the well known strongest prognostics[16,17]: 1) age, 2) gender, 3) preoperative KPS, 4) preoperative tumor volume, 5) tumor location, 6) type of adjuvant treatment (none, radiotherapy, chemotherapy, chemoradiotherapy). Propensity score matching was used to match conventional to awake patients based on the covariates gender, treatment, age, KPS_preop, Volume_preop, and Tumor_location. Balance between the conventional and awake

Variable	Levels	n	$\bar{x}$	s
Age	general anesthesia	368	57.3	12.9
	awake	37	45.7	15.1
$p < 0.0001$	all	405	56.2	13.6
KPS_preop	general anesthesia	368	85.6	11.2
	awake	37	89.7	11.2
$p = 0.03$	all	405	86.0	11.2
Volume_preop	general anesthesia	368	48063.6	38904.3
	awake	37	66278.8	64325.1
$p = 0.23$	all	405	49727.7	42086.2

Table 1: Summary statistics of continuous variables before matching

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Variable	Levels	$n_{generalanesthesia}$	$\%_{generalanesthesia}$	n_{awake}	$\%_{awake}$	n_{all}	$\%_{all}$
treatment	none	32	8.7	1	2.7	33	8.2
	chemo	6	1.6	0	0.0	6	1.5
	RT	87	23.6	12	32.4	99	24.4
	chemo+RT	238	64.7	24	64.9	262	64.7
	unknown	5	1.4	0	0.0	5	1.2
$p = 0.61$	all	368	100.0	37	100.0	405	100.0
Gender	male	217	59.0	23	62.2	240	59.3
	female	151	41.0	14	37.8	165	40.7
$p = 0.73$	all	368	100.0	37	100.0	405	100.0
Tumor_loc	frontal	104	28.3	16	43.2	120	29.6
	parietal	74	20.1	8	21.6	82	20.2
	temporal	156	42.4	13	35.1	169	41.7
	occipital	34	9.2	0	0.0	34	8.4
$p = 0.07$	all	368	100.0	37	100.0	405	100.0

Table 2: Summary statistics of categorical variables before matching

Abbreviations
chemo = chemotherapy; RT = radiotherapy; n = number; $\bar{x}$ = mean; $\tilde{x}$ = median; SD = standard deviation; IQR = interquartile range.

groups was checked with summary measures of QQplots comparing the covariates in the matched groups, and optimal results were achieved with a 1:3 matching ratio.

Statistics: Analysis after matching

111 cases were included in the GA cohort after matching. Patient characteristics of both groups after matching are shown in Tables 3 and 4. After matching, differences between the AC- and GA-groups in the matched data for the primary outcomes were tested: 1) extent of resection; 2) postoperative survival; and 3) rate of postoperative complications. Analysis of the matched data set was based on non-parametrics tests, namely for the outcomes Resection and Number of Complications Mann-Whitney tests were used, whereas for median survival the log-rank test was used. No adjustment for multiple testing has been done. The significance level was set to 5%.

Variable	Levels	n	$\bar{x}$	s
Age	general anesthesia	111	48.3	14.0
	awake	37	45.7	15.1
$p = 0.41$	all	148	47.7	14.3
KPS_preop	general anesthesia	111	89.3	9.9
	awake	37	89.7	11.2
$p = 0.64$	all	148	89.4	10.2
Volume_preop	general anesthesia	111	61946.6	47972.9
	awake	37	66278.8	64325.1
$p = 0.77$	all	148	63029.6	52335.4

Table 3: Summary statistics of continuous variables after matching

Variable	Levels	$n_{generalanesthesia}$	$\%_{generalanesthesia}$	n_{awake}	$\%_{awake}$	n_{all}	$\%_{all}$
treatment	none	5	4.5	1	2.7	6	4.0
	chemo	0	0.0	0	0.0	0	0.0
	RT	41	36.9	12	32.4	53	35.8
	chemo+RT	65	58.6	24	64.9	89	60.1
	unknown	0	0.0	0	0.0	0	0.0
$p = 0.87$	all	111	100.0	37	100.0	148	100.0
Gender	male	72	64.9	23	62.2	95	64.2
	female	39	35.1	14	37.8	53	35.8
$p = 0.84$	all	111	100.0	37	100.0	148	100.0
Tumor_loc	frontal	50	45.0	16	43.2	66	44.6
	parietal	23	20.7	8	21.6	31	20.9
	temporal	38	34.2	13	35.1	51	34.5
	occipital	0	0.0	0	0.0	0	0.0
$p = 1.00$	all	111	100.0	37	100.0	148	100.0

Table 4: Summary statistics of categorical variables after matching

Abbreviations

chemo = chemotherapy; RT = radiotherapy; n = number; $\bar{x}$ = mean; $\tilde{x}$ = median; SD = standard deviation; IQR = interquartile range.

RESULTS

Baseline characteristics

The AC and GA cohorts were matched for variables that could introduce bias: age, preoperative KPS, preoperative tumor volume, type of adjuvant treatment, gender and tumor location (Table 1-4). Before matching, there were significant differences in mean age (p<0.0001) and preoperative KPS (p=0.03) (Table 1 and 2).

Preoperative tumor volume (p=0.23), type of adjuvant treatment (p=0.61), gender (p=0.73) and tumor location (p=0/08) did not differ significantly between groups (Table 1 and 2).

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After matching, there were no significant differences between groups in mean age (p=0.41), preoperative KPS (p=0.64), preoperative tumor volume (p=0.77), adjuvant treatment (p=0.89), gender (p=0.84) or tumor location (p=1.00) (Table 3 and 4).

Furthermore, tumors were equally distributed between the left-right hemispheres in the groups (p>0.05).

Patient outcomes

Extent of resection

Resections under AC in glioblastoma patients proved to be superior to resections under GA regarding extent of resection. The mean extent of resection in the AC group was 94.89% (SD=10.57; IQR=6.76)), as compared to 70.30% (SD=28.37; IQR=44.76) in the GA group. The median extent of resection in the AC group was 100%, and 79.73% in the GA group. Table 5 and Figure 1 provide the extent of resection per group, showing significance (p < 0.0001, Mann-Whitney test).

Variable	Levels	n	$\bar{x}$	s	$\tilde{x}$	IQR
Resection	general anesthesia	111	70.30	28.37	79.73	44.76
	awake	37	94.89	10.57	100.00	6.76
$p < 0.0001$	all	148	76.45	27.27	87.67	36.31

Table 5: Summary statistics of percentage of tumor reduction after matching
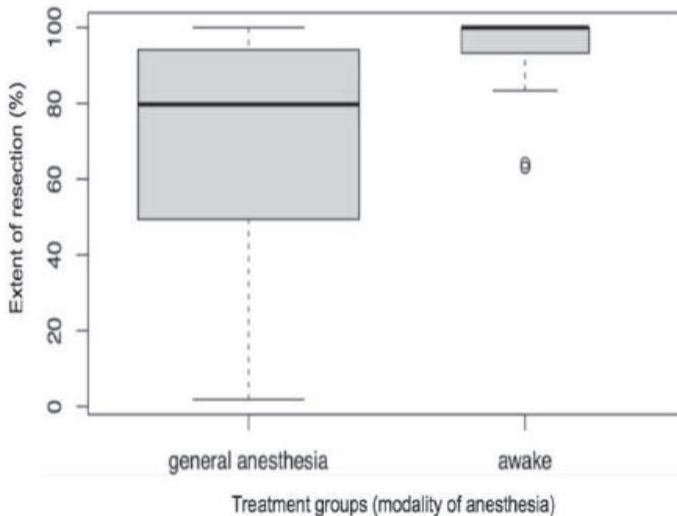
Figure 1: Box plot of extent of resection in both groups

Postoperative complications

Table 6 presents the distribution of postoperative complications in all patients before matching. The total number of postoperative complications in 405 patients was 260, of which 176 early- and 84 late postoperative complications. 16 of the 176 early postoperative complications occurred in the AC group (rate=0.43), and 160 in the GA group (rate=0.41). 3 of the 84 late complications occurred in the AC group (rate=0.081), and 81 in the GA group (rate=0.21).

	number of patients
major neurological deficits	early – late – total
hemiparesis	18 – 8 – 26
monoparesis grade 1-3	10 – 3 – 13
aphasia	33 – 6 – 39
dysphasia	11 – 3 – 14
aphasia + hemiparesis	14 – 4 – 18
hemianopsia	19 – 4 – 23
visual field deficit unspecified	0 – 5 – 5
vegetative/deceased	1 – 4 – 5
minor neurological deficits	early – late – total
monoparesis grade 4	11 – 9 – 20
nVII palsy	19 – 3 – 22
dysnomia	6 – 17 – 23
somatosensory syndrome	9 – 1 -10
parietal syndrome	19 – 13 – 32
cranial nerve deficit	6 – 4 – 10
total nr of patients	176 – 84 – 260

Table 6: Summary of postoperative complications before matching

Since the main objective of AC is to minimize postoperative complications while maximizing the extent of resection, the distribution and nature of the postoperative complications is of particular interest in this group. The 16 early postoperative complications in the AC group consisted of: N. VII palsy (n=5), aphasia (n=4), monoparesis grade 4 (n=3), unspecified cranial nerve deficit (n=2), hemiparesis (n=1) and parietal syndrome (n=1). The 3 late postoperative complications in the AC group consisted of: hemiparesis (n=2) and monoparesis grade 4 (n=1). The AC group experienced 19 complications in total (16 early and 3 late). These 19 complications were divided over 11 patients (total: 37; rate=0.30), while 182 of the 368 patients in the GA group experienced a complication (rate=0.49).

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Variable	Levels	n	$\bar{\text{x}}$	s	$\tilde{\text{x}}$	IQR
Comp_E_min	general anesthesia	111	0.22	0.46	0	0
	awake	37	0.24	0.64	0	0
$p = 0.71$	all	148	0.22	0.51	0	0
Comp_E_maj	general anesthesia	111	0.25	0.48	0	0
	awake	37	0.19	0.40	0	0
$p = 0.54$	all	148	0.24	0.46	0	0
Comp_L_min	general anesthesia	111	0.15	0.39	0	0
	awake	37	0.03	0.16	0	0
$p = 0.05$	all	148	0.12	0.35	0	0
Comp_L_maj	general anesthesia	111	0.12	0.32	0	0
	awake	37	0.05	0.23	0	0
$p = 0.27$	all	148	0.10	0.30	0	0

Table 7: Summary statistics of the number of postoperative complications after matching

Table 7 summarizes the rate of postoperative complications in both groups after matching (Mann-Whitney test). Complications were classified in four categories: early minor (E_min); early major (E_maj); late minor (L_min); and late major (L_maj). The mean rate of early minor postoperative complications in the AC group was 0.24 (SD=0.64), while this was 0.22 (SD=0.46) in the GA group (p=0.71). The mean rate of early major postoperative complications in the AC group was 0.19 (SD=0.40), as compared to 0.25 (SD=0.48) in the GA group (p=0.54). We found a significantly higher rate of late minor postoperative complications in the GA group than in the AC group: 0.15 (SD=0.39) versus 0.03 (SD=0.16) (p=0.05). The mean rate of late major postoperative complications was 0.05 (SD=0.23), and 0.12 (SD=0.32) in the GA group (p=0.27).
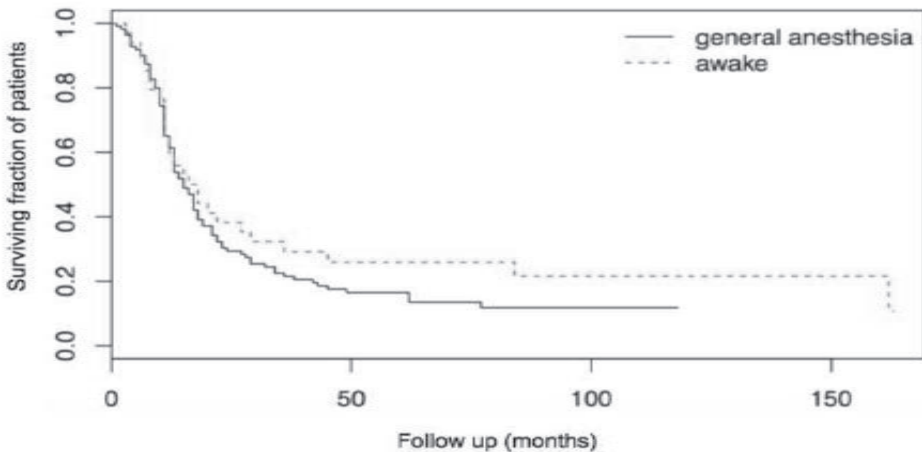
Figure 2: Kaplan-Meier curve of postoperative survival in both groups

Median postoperative survival

Groups were compared for postoperative survival using Kaplan-Meier curves (Figure 2, Logrank test). Although we found a trend towards longer median survival times in the AC group, this did not reach statistical significance (p=0.297; χ2=1.1). Median survival time in the AC group was 17 months (CI: 12.0; 36.0); as compared to 15 months (CI: 13.0; 18.0) in the GA group.

DISCUSSION

This matched controlled study shows that patients undergoing awake craniotomy for a single supratentorial GBM had significantly greater extent of resection of their tumor compared with patients undergoing resection under GA. Moreover, the rate of late minor postoperative complications in the AC group was significantly lower than in the GA group. Despite a higher resection percentage, no significant increase of median survival was found after AC. This could be explained by the low number of AC patients which remained after the matching procedure.

These results suggest that AC should be implemented as a routine technique for surgery of high grade tumors near eloquent areas of the brain. There is increasing evidence in the scientific literature that extensive resections are significant predictors of longer survival time in malignant glioma. However, a higher risk of morbidity has been reported before as the potential cost of pursuing gross-total resection (GTR)[4-8].

Surgical techniques have evolved, and the introduction of AC has proved to be a major stepping-stone in acquiring a greater extent of resection without an increased risk of morbidity. AC with cortical and subcortical stimulation has the advantage to control neurological function during brain tumor surgery and to increase the extent of resection in glioma surgery. However, AC has yet mainly been implemented for low-grade gliomas. Surgery of GBM is usually performed under GA. Hence, resections are not as aggressive as possible, due the chance of seriously damaging the patient with a rather low life expectancy. Our results show that surgery with the AC technique can preserve quality of life of these patients by decreasing the risk of postoperative morbidity. Our data also shows that an increased resection with AC can attain improvement in prognosis in GBM patients.

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Other studies have found similar results regarding postoperative complications and extent of resection after AC. De Witt Hamer et al[13] conducted an extensive meta-analysis including 8.091 adult patients who had surgery for supratentorial infiltrative glioma (high and low grade glioma), with or without intra-operative stimulation mapping (ISM;

e.g. awake craniotomy). They found that glioma resections using ISM were associated with fewer late major neurologic deficits and more extensive resection. Although this was a mixed group of patients, these findings are entirely in line with our results in glioblastoma patients.

Yoshikawa et al[14] conducted a study in 42 glioblastoma patients. They concluded that radical surgery with neurophysiological monitoring improved the functional outcome in glioblastoma patients. Moreover, Sacko et al[12] prospectively studied two groups of patients with supratentorial masses (n = 575), comparing AC with craniotomy under GA. They found that using AC in glioma surgery proved to be superior to craniotomy under GA regarding neurological outcome and quality of resection (p < 0.001). The findings from these studies are in harmony with our results. Peruzzi et al[11] add a new dimension by evaluating the length of hospital stay and inpatient costs after ICU care for glioma patients who were treated with AC and surgery under GA. They concluded that patients undergoing glioma resection using AC had a significantly shorter hospital stay with reduced inpatient hospital expenses after postoperative ICU care.

The major limitation is the retrospective nature of this study. Firstly, we expected a strong selection bias for patients operated with AC. Younger patients with higher KPS are usually selected for AC when the tumor is situated near eloquent areas. However, we minimized the risk for this bias by the using a matched controlled study design. Of course, biases caused by other factors than age, KPS, tumor location, tumor volume and type of adjuvant therapy could play a role, but are prevented as much as possible with this matched controlled study. The matching procedure also shows that many patients with tumors in eloquent areas were operated under GA. Secondly, the matching procedure did not take into account IDH-1 mutations which are associated with longer survival in patients with GBM. However, IDH-mutation is mainly present in younger patients and only expressed in 10%-20% of high grade gliomas. It is unlikely that these mutations would influence the matching procedure.

CONCLUSIONS

Resection of glioblastoma using AC is associated with significantly greater extent of resection and less minor late postoperative complications as compared with craniotomy under GA. No significant difference in median survival was found. Our findings confirm preliminary findings of other authors with smaller group sizes and urge the need for a randomized clinical trial to further reduce potential bias.

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VI

Postoperative pain management

Chapter 11

**Pain in neurosurgically treated patients:
a prospective observational study.**

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PAIN IN NEUROSURGICALLY TREATED PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY.

ABSTRACT

Object: This is the first observational study to compare perioperative pain character and intensity in patients undergoing different types of elective neurosurgical procedures.

Methods: A structured questionnaire was used to inquire about pain intensity, character, and management during the perioperative course, and the anticipated visual analogue scale (VAS) score in 649 patients during a 1-year period. The anticipated maximal postoperative VAS score was lower than the actual postoperative maximal VAS score and was independent of operation type and preoperative VAS score. Patients undergoing craniotomy experienced less pain than those undergoing spinal surgery. A majority of patients did not receive analgesic medication after surgery. Patients undergoing spinal surgery experienced higher preoperative VAS scores than those undergoing other neurosurgical treatments, with a shift from preoperative referred pain to postoperative local pain. After lumbar flavectomy, referred pain was greater than local pain. Patients with preoperative pain suffered significantly more postoperative pain than those without preoperative pain. In patients with postoperative surgery-related complications, VAS scores were higher than in those without complications.

Conclusions: Neurosurgical procedures cause more pain than anticipated. Anticipated pain intensity is independent of the operation type and preoperative pain intensity. Postcraniotomy on-demand analgesic medication is appropriate, if the nurses on the ward react quickly. Otherwise, patient-controlled analgesia might be an option. Other neurosurgical procedures require scheduled analgesic therapies. Spinal surgery requires intensive preoperative pain treatment; a shift in pain character from preoperative referred pain to postoperative local pain is expected. Patients with referred pain after lumbar flavectomy are prone to the most intense pain. Patients with preoperative pain experience more postoperative pain than those without preoperative pain and require more intensive pain management. Increased postoperative VAS scores are associated with surgery-related complications.

KEY WORDS • pain • neurosurgery • visual analog scale • observation • complication

Abbreviations used in this paper: ACS = aneurysm clip surgery; ANOVA = analysis of variance; ASA = American Society of Anesthesiologists; CS = cervical spondylodesis; LF = lumbar flavectomy; LTR = laminectomy with tumor resection; MCP = miscellaneous

cranial procedure; MEXP = miscellaneous extremity procedure; MSP = miscellaneous spinal procedure; SBICPM = skull boring with intracranial pressure measurement; THR = trephination and hematoma removal; TSO = transsphenoidal operation; TTR = trephination with tumor resection; VAS = visual analog scale; VPS = ventriculoperitoneal shunt; WHO = Word Health Organization

INTRODUCTION

Little is known about perioperative pain in patients undergoing neurosurgical procedures. There is a conventional accepted clinical impression that a trephination is associated with a small degree of postoperative pain whereas the opposite is true, for example, with spinal neurosurgical procedures.[8,10,26,27] There is controversy in the literature regarding the occurrence of pain and its intensity in patients undergoing neurosurgical procedures. [8,10] A different approach to postoperative pain management has been advocated for craniotomy procedures,[13,26,30] compared with lumbar disc surgery,[12] because the risk of severe sedation and cardiorespiratory instability seems lower. Moreover, different clinicians use different pain therapies for the same neurosurgical procedures,[27] and different types of pain therapy have been advocated for the same neurosurgical procedure.

[13,26,30] Risk factors for postoperative pain have been extensively investigated and include female sex, preoperative pain severity, younger age, surgical procedure, expected incision size, and psychological profile.[3,4,7,14,15,19,24,29] The authors of these studies, however, have not provided appropriate insights to allow comparison of all different types of neurosurgical procedures regarding pain intensity, character, and course after neurosurgical procedures. To our knowledge, no large observational study has been conducted to compare different types of neurosurgical procedures performed in one clinical center to determine perioperative VAS scores related to patient characteristics, pain type, pain intensity, and anticipation of postoperative pain. Therefore, we conducted a 1-year observational study on pain intensity and pain character covering all categories of patients undergoing an elective neurosurgical procedure in a university hospital.

CLINICAL MATERIAL AND METHODS

The study was approved by the Medical Ethical Committee of the University Medical Centre of the University of Cologne, Germany. The investigators fully respected and followed the declaration of Helsinki in the current version (Edinburgh, Scotland 2000). During a 1-year period, all patients undergoing an elective neurosurgical procedure were considered for inclusion in the study. Patients in same-day surgery (for example, those undergoing carpal tunnel release) were excluded from the study.

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The patients enrolled in this study were visited the day before surgery by one of two investigators. All patients were admitted to hospital the day before surgery. The first visit was on the evening before surgery. Further postoperative visits took place on the 1st, 3rd, and 5th postoperative days between 4:00 p.m. and 8:00 p.m. Each visit lasted approximately 5 to 10 minutes.

Patients were excluded from the study if any of the following variables applied to them: were unable to estimate the amount of pain because of decreased awareness; could not speak appropriate German; were undergoing an emergency operation; were unresponsive to questions; were not willing to cooperate; or were younger than 18 years of age.

On the first visit, the patient was informed about the study. Special attention was paid to the fact that the patient would be observed by the investigator, that these observations would be documented but that the patient would not receive special pain management, and that the anesthetic procedure planned by the anesthesiologist would not be changed. The neurosurgeon was responsible for pain management on the ward, and the patient could withdraw from the study at any time. Written informed consent was obtained from all patients. We made no differences in the pain management methods between patients undergoing procedures that were expected to cause significant (for example, most spine procedures) and those that were expected to produce only little pain (for example, all trephinations for tumors and aneurysms).

To measure the extent of pain, we used a VAS, in which the scores ranged from 0 (no pain) to 100 (worst pain imaginable). To record responses, the patient had to move a thin bar on a 10-cm line between the two extremes, which was demonstrated each time by our research team.

On the preoperative day, the current pain treatment and type of treatment were recorded. The patient's weight, age, sex, and ASA classification[18] (a reflection of the severity of preoperative comorbidities) were recorded. At the time of premedication, the preoperative VAS score was registered. The nature of the pain was characterized as follows: no pain, sharp local pain, diffuse local pain, referred pain, sudden-onset pain, normal headache, and other pain types. The patients were asked if they needed (further) pain treatment. Finally, the patients were asked about the maximal postoperative pain that they anticipated.[2]

During the perioperative period, the operation type and duration were noted. Moreover, after the operation had been performed, the investigators documented from the drug charts the type and dose of analgesics used on the day of operation.

On the 1st, 3rd, and 5th postoperative days, all patients were asked about the following: their VAS score at the initial visit, the pain character, if they had informed the staff about the pain, and whether they received adequate treatment after they had informed the staff. The patient was asked if they had received analgesic medication in the last 6 hours prior to the visit, and the kind of treatment was noted from the drug charts.

Some additional questions were asked. On the 1st postoperative day, the patient was asked to determine the maximal VAS score on the day of surgery and at what time this pain occurred.[1] On the 5th postoperative day, the medical staff was asked if any surgery-related complications (wound infection, reoperation, a second procedure, or a postoperative bleeding) occurred in any of the study patients.

With the visit on the 5th postoperative day, the period of observation ended. All enrolled patients were admitted to hospital until at least the 5th postoperative day. Participation in this study did not delay discharge from the hospital. The discharge decisions were made by the neurosurgeons only. It was current practice during the entire study period that patients undergoing lumbar flavectomy, for example, were hospitalized for at least 1 week postoperatively. Similarly, in the group of patients undergoing miscellaneous extremity procedures (for example, neurolysis of the median nerve), only two of the nine patients were monitored until postoperative Day 5. A patient was excluded from the study if still intubated 24 hours after surgery, if not aware enough to answer questions, or if unwilling to cooperate further, for any other reason.

Statistical Analysis

To analyze the data, the patients were grouped by surgical procedure. Each separate study group required 10 or more patients. There were 10 different procedures with 10 or more patients per group: TTR, VPS placement, TSO, SBICPM, THR, ACS, CS, LF, laminectomy, and LTR. One hundred nine patients underwent procedures that were performed fewer than 10 times (for example, lumbar fixation or frontobasal covering); these patients were divided into three groups: MSPs, MCPs, and MEXPs. The results of the preoperative interviews were analyzed if the patient was excluded on or after the 1st postoperative day. If a patient had to undergo reoperation for a surgery-related complication, the results obtained before the complication were still analyzed. The VAS scores and findings of the second operation were analyzed as if the data were obtained in a new case.

Intergroup comparisons for age, weight, operative time, maximal anticipated VAS score, maximal VAS score, and VAS score on the 1st, 3rd, and 5th postoperative days were conducted using an ANOVA with a Bonferroni posttest or a nonparametric Kruskal–Wal-

lis test when appropriate. Intergroup comparisons for ASA class distribution and male/female ratios were analyzed with the chi-square test for independence.

Intragroup comparisons of VAS scores over time were made using a repeated-measures ANOVA with a Bonferroni posttest or a Friedman nonparametric test when appropriate. A Student t-test was used to demonstrate a significant difference between the maximal anticipated VAS score and the maximal real postoperative VAS score.

Visual analog scale scores were stratified according to several characteristics: 1) age range (0–19, 20–39, 40–59, and ≥60 years); 2) sex; 3) ASA classification; 4) pain character over time, within the different treatment groups; 5) different types of postoperative pain medication (patients receiving no pain medication; those receiving WHO Class I, II, or III pain medication;[31,32] or different types of pain medication), within the different study groups; 6) whether patients asked for pain medication after surgery, within the different study groups; 7) whether patients received adequate treatment after informing the personnel about pain, within the different study groups; 8) a complicated compared with an uncomplicated postoperative course; and 9) whether patients had pain before surgery. **Table 1** provides a summary of WHO classes of pain medication.

TABLE 1 *WHO classification of pain treatment*

Class	Description	Examples
I	nonopioid analgesic drugs	nonsteroidal antiinflammatory drugs, acetaminophen
II	weak opioids (+ nonopioid analgesic drugs)	tramadol, codeine
III	strong opioids (+ nonopioid analgesic drugs)	morphine, piritramid, meperidine

Intergroup comparisons of VAS intensity scores were analyzed using an ANOVA with a Bonferroni posttest, a nonparametric Kruskal–Wallis test, or a t-test, as appropriate. Differences in patient numbers and pain character (distribution) within groups, after stratification, were analyzed using a chi-square test for independence. Intragroup VAS scores over time, measured after stratification, were compared using a repeated-measures ANOVA with a Bonferroni posttest or a Friedman nonparametric test, as appropriate.

Statistical significance was accepted at a probability value less than 0.05.

RESULTS

Clinical and surgical data are summarized in **Table 2**; significant intergroup differences are indicated. **Table 3** illustrates the VAS scores in the different study groups over time; significant differences between groups and over time are indicated. The maximal VAS score was significantly higher than the maximal anticipated VAS score overall and in the TSO, SBICPM, THR, LF, MSP, and MCP groups.

TABLE 2 *Summary of demographic and surgical data obtained in patients undergoing different neurosurgical procedures**

Factor	Total	TTR	VPS	TSO	SBICPM	THR	ACS	CS	LF	LAM	LTR	MSP	MCP	MEXP
no. of cases underwent op	666	161	44	17	12	18	11	80	192	12	10	55	45	9
included in study (%)	649 (97)	156 (97)	39 (89)	16 (94)	11 (92)	18 (100)	10 (91)	79 (99)	190 (99)	12 (100)	10 (100)	55 (100)	45 (10)	8 (89)
Day 1	619 (93)	144 (89)	35 (80)	15 (88)	10 (83)	16 (89)	9 (82)	79 (99)	187 (97)	12 (100)	10 (100)	53 (96)	42 (93)	7 (78)
Day 5	584 (88)	140 (87)	31 (70)	14 (82)	10 (83)	16 (89)	9 (82)	75 (94)	184 (96)	12 (100)	10 (100)	48 (87)	33 (73)	2 (22)
age (yrs)	51.0 ± 16.3	52.3 ± 15.8	47.8 ± 21.0†	42.1 ± 17.7†	61.9 ± 17.3	65.1 ± 11.6	46.1 ± 11.4	51.8 ± 13.5	51.6 ± 15.4†	56.5 ± 15.4	53.6 ± 13.4	51.5 ± 16.2	38.2 ± 16.0†‡§‖¶**††	58.0 ± 10.4
weight (kg)	75.8 ± 15.4	74.7 ± 14.8	74.2 ± 20.3	77.3 ± 17.7	75.0 ± 15.0¶‖	73.4 ± 10.4†§.§§¶	67.6 ± 14.9†‖	75.5 ± 14.7††§.§§	78.2 ± 14.6††§.§§	85.5 ± 23.6§‖¶	71.0 ± 13.8¶	75.9 ± 13.8	73.3 ± 16.2¶	68.8 ± 17.2††¶
M/F ratio	364:302	81:80	24:20	6:11	8:4	10:8	2:9	51:29	115:77	5:7	3:7	32:23	25:21	2:6
op time (mins)	165.9 ± 119.0	281.2 ± 134.4	76.1 ± 19.7†	137.5 ± 38.6†,‡‡	28.9 ± 12.4‡	55.0 ± 41.2‡	256.1 ± 81.0†§¶§§	161.0 ± 73.9††§.§§	105.6 ± 43.7†‖	156.7 ± 81.9†§	280.6 ± 143.5†§‖¶§§	183.5 ± 128.1†§¶§§	124.0 ± 102.5†,‡‡‖	165.0 ± 97.9
ASA Class (%)														
I	145 (22)	30 (19)	4 (9)	2 (12)	1 (8)	2 (11)	2 (18)	23 (29)	57 (30)	2 (17)	1 (10)	10 (18)	9 (20)	2 (25)
II	306 (46)	71 (49)	17 (39)	12 (71)	3 (25)	7 (39)	3 (27)	45 (57)	88 (46)	8 (67)	6 (60)	25 (45)	19 (42)	4 (50)
III	192 (29)	54 (34)	22 (50)	3 (18)	8 (67)	1 (6)	6 (55)	12 (15)	46 (24)	1 (8)	3 (30)	20 (36)	14 (31)	2 (25)
IV	15 (2)	5 (3)	0 (0)	0 (0)	0 (0)	8 (44)	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)	1 (2)	0 (0)
V	1 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

* Data are expressed as means ± standard deviation (SDs), where applicable. Abbreviation: LAM = laminectomy. † Statistically significant compared with THR group. ‡ Statistically significant compared with TTR group. § Statistically significant compared with SBICPM group. ‖ Statistically significant compared with CS group. ¶ Statistically significant compared with LF group. ** Statistically significant compared with LAM group. †† Statistically significant compared with MSP group. ‡‡ Statistically significant compared with ACS group. §§ Statistically significant compared with LTR group. ¶¶ Statistically significant compared with VPS group. ‖‖ Statistically significant compared with ACS group. ¶¶ Statistically significant compared with TSO group

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TABLE 3 *Summary of VAS score–related data stratified by treatment group**

VSA Data	Total	TTR	VPS	TSO	SBICPM	THR	ACS	CS	LF	LAM	LTR	MSP	MCP	MEXP
max anticipated score	35.7 ± 22.1†	29.9 ± 21.1	41.2 ± 18.4	36.6 ± 17.1†	33.6 ± 24.7†	27.3 ± 18.6†	43.1 ± 11.4	35.4 ± 23.0	37.1 ± 23.1†	39.2 ± 13.7	47.9 ± 31.7	44.1 ± 21.4‡	34.0 ± 21.9†	29.5 ± 20.9
preop score	21.5 ± 24.7†§	4.1 ± 10.6†§||	15.7 ± 22.3†§	5.8 ± 8.1†§¶†**	8.7 ± 16.0†**	17.2 ± 20.8†	17.9 ± 20.0	26.0†||††	33.3 ± 26.1†§||††‡‡	23.7 ± 21.8	13.2 ± 14.5	33.2 ± 23.3†‡§||††‡‡§§||||	22.0 ± 24.9††	6.5 ± 16.8**
max score	42.8 ± 29.4§||††	26.5 ± 27.6§||††	39.6 ± 25.8§‡‡	55.3 ± 30.9†§||‡‡	41.4 ± 25.6||‡‡	63.1 ± 29.1§||††	51.4 ± 28.9	40.4 ± 26.0†§||‡‡	47.1 ± 26.7†§||‡‡	47.3 ± 26.6||‡‡	28.9 ± 34.9	61.2 ± 26.2†§||¶††‡‡¶¶	53.5 ± 29.0†§||‡‡	16.6 ± 26.4†§
score														
Day 1	24.1 ± 21.9||‡‡	14.7 ± 18.4‡‡	24.9 ± 23.7	32.5 ± 24.1‡‡	17.6 ± 17.1	26.2 ± 27.9	37.0 ± 21.1	23.8 ± 19.8‡‡	26.2 ± 20.4||‡‡	27.0 ± 16.6	24.1 ± 26.3	34.2 ± 22.4||‡‡	29.3 ± 26.7†||‡‡	5.7 ± 7.1
Day 3	17.2 ± 20.3‡‡	10.6 ± 16.0‡‡	23.4 ± 24.6†	18.7 ± 28.1	10.6 ± 14.2	14.8 ± 16.8	24.8 ± 18.8	17.8 ± 20.5	18.7 ± 20.1†,‡‡	15.7 ± 15.0	15.4 ± 17.5	22.7 ± 21.0†,‡‡	19.8 ± 21.8	0.0 ± 0.0
Day 5	11.8 ± 17.1	6.6 ± 11.1	13.5 ± 20.6	8.2 ± 10.3	3.8 ± 6.8	16.2 ± 21.0	26.7 ± 28.0‡	14.1 ± 19.1	12.3 ± 16.9	14.5 ± 15.2	13.7 ± 18.4	17.9 ± 20.9‡	11.5 ± 15.4	0.0 ± 0.0

* Data are expressed as means ± SDs. † Statistically significant compared with maximal VAS score. ‡ Statistically significant compared with TTR group. § Statistically significant compared with VAS score on Day 1. || Statistically significant compared with VAS score on Day 3. ¶ Statistically significant compared with CS group. ** Statistically significant compared with LF group. †† Statistically significant compared with VPS group. ‡‡ Statistically significant compared with VAS score on Day 5. §§ Statistically significant compared with TSO group. |||| Statistically significant compared with SBICPM group. ¶¶ Statistically significant compared with LTR group.

TABLE 4 *Summary of changes in pain status stratified by treatment group*[*]

Pain Status	TTR	VPS[a]	TSO	SBICPM[g]	THR[a]	ACS	CS[abcdgh]	LF[abcdegh]	LAM[abcfg]	LTR[ef]	MSP[abfg]	MCP[aefg]	MEXP[ef]
preop													
overall no.	156	39	16	11	18	10	79	190	12	10	55	45	8
no pain	77	51	56	55	33	40	14	9	8	40	15	31	63
local pain	1	15	0	0	11	10	13	7	17	20	25	18	0
diffuse pain	5	8	13	0	28	10	4	1	0	0	4	22	13
referred pain	1	5	0	0	11	0	63	77	50	20	51	4[klm]	0
sudden onset	1	0	0	0	0	0	1	5	0	0	2	0	13
normal headache	5	18	13	18	6	10	0	0	0	0	0	11	0
other pain	10	5	19	27	11	30	5	1	25	20	4	13	13
	TTR[n]	VPS[n]	TSO[an]	SBICPM[an]	THR[n]	ACS	CS[abcdghn]	LF[abcdghn]	LAM[an]	LTR	MSP[an]	MCP[fn]	MEXP[f]
Day 1													
overall no.	144	35	15	10	16	9	79	187	12	10	53	42	7
no pain	35	14	0	20	6	11	10	8	0	20	2	14	43
local pain	38	54	53	50	69	44	56	67	92	70	66	38	43
diffuse pain	11	14	33	10	19	11	4	1	0	0	6	14	0
referred pain	2	3	0	0	6	0	16	18	8	10	17	10	0
sudden onset	0	0	0	0	0	0	0	1	0	0	0	0	0
normal headache	4	9[k]	7	20	0	11	0	1	0	0	0	7	14
other pain	8	6	7	0	0	22	14	5	0	0	9	17	0
	TTR[e]	VPS[an]	TSO	SBICPM	THR	ACS	CS[ano]	LF[abcgfhno]	LAM[ab]	LTR[e]	MSP[ano]	MCP[f]	MEXP
Day 3													
overall no.	140	34	15	10	16	9	77	187	12	10	50	37	4
no pain	48	24	20	50	31	11	30	19	17	30	18	30	100
local pain	23	38	40	30	56	56	32	48	42	70	44	22	0
diffuse pain	11	12[k]	7	0	6	22	5	2	0	0	4	11	0
referred pain	2	0	7	0	6	0	18	22[k]	25	0	20	5	0
sudden onset	0	0	0	0	0	0	0	2[k]	8	0	0	0	0
normal headache	8	3	13	10	0	11	3	1	0	0	4	11	0
other pain	8	24	13	10	0	0	12	6	8	0	10	22	0
	TTR[no]	VPS[o]	TSO[an]	SBICPM	THR[a]	ACS[a]	CS[abchno]	LF[abcdgfnop]	LAM[abch]	LTR[h]	MSP[abcen]	MCP	MEXP
Day 5													
overall no.	140	31	14	10	16	9	75	184	12	10	48	33	2
no pain	54	48	21	70	31	22	40	35	17	40	10	42	50
local pain	26	23	36	20	25	11	21	33	42	60	50	18	0
diffuse pain	6	10	14	0	25	22	4	1	0	0	2	9	0
referred pain	1	0	14	0	13	0	25	23[k]	33	0	21[k]	6	0
sudden onset	0k	3	0	0	0	0	3	2	0	0	0	0	0
normal headache	4	6	0	10	0	33	0	0	0	0	0	6	0
other pain	9	10	14	0	6	11	7	6	8	0	17	18	50

[*] Data are presented as percentages of the total, except overall number of patients ("overall no."). [a] Statistically significant difference in pain distribution compared with TTR group. [b] Statistically significant difference in pain distribution compared with VPS group. [c] Statistically significant difference in pain distribution compared with SBICPM group. [d] Statistically significant difference in pain distribution compared with THR group. [e] Statistically significant difference in pain distribution compared with CS group. [f] Statistically significant difference in pain distribution compared with LF group. [g] Statistically significant difference in pain distribution compared with TSO group. [h] Statistically significant difference in pain distribution compared with ACS group. [i] Statistically significant difference in pain distribution compared with LAM group. [j] Statistically significant difference in pain distribution compared with MSP group. [k] Statistically higher VAS score compared with that for local pain. [l] Statistically higher VAS score compared with that for diffuse pain. [m] Statistically higher VAS score compared with that for normal headache. [n] Statistically significant difference in pain distribution compared with preoperative time point. [o] Statistically significant difference in pain distribution compared with Day 1. [p] Statistically significant difference in pain distribution compared with Day 3

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TABLE 5 *Summary of data obtained in patients who did and did not ask for analgesic medication*

Analgesic Request	Overall	TTR	VPS[a]	TSO	SBICPM	THR[a]	ACS[a]	CS[a]	LF[a]	LAM	LTR	MSP[a]	MCP[a]	MEXP
preop no.														
overall	647	156	38	16	11	18	10	79	189	12	10	55	45	8
% did not ask	92	99	89	100	100	89	80	90	89	92	100	89	87	100
% did ask	8[e]	1	11[e]	0	0	11	20	10[e]	11[e]	8	0	11[e]	13[e]	0
Day 1														
overall	618	143	35	15	10	16	9	79	187	12	10	53	42	7
% did not ask	88	94	80	87	100	94	56	87	89	83	90	85	83	86
% did ask	12[e]	6[e]	20[e]	13	0	6	44[e]	13[e]	11[e]	17	10	15[e]	17[e]	14
Day 3														
overall	599	139	34	15	10	16	9	76	187	12	10	50	37	4
% did not ask	94	97	82	87	90	100	78	95	93	100	90	94	100	100
% did ask	6[e]	3[e]	18[e]	13	10	0	22	5[e]	7[e]	0	10	6[e]	0	0
Day 5														
overall	581	139	30	14	10	16	9	74	184	12	10	48	33	2
% did not ask	96	99	100	100	100	94	78	96	95	92	90	96	97	100
% did ask	4[e]	1	0	0	0	6	22	4[e]	5[e]	8	10	4[e]	3	0

[a] Statistically Significant difference compared with TTR group. [b] Statistically significant difference compared with SBICPM group. [c] Statistically significant difference compared with THR group. [d] Statistically significant difference compared with ACS group. [e] Statistically higher VAS score compared with that in patients who did not ask for pain medication.

TABLE 6 *Summary of data obtained in patients with and without the subjective feeling of adequate treatment after informing personnel about pain*

	Overall No.	TTR	VPS	TSO	SBICPM	THR	ACS	CS	LF	LAM	LTR	MSP	MCP	MEXP
Day 1														
overall no.	619	144	35	15	10	16	9	79	187	12	10	53	42	7
% informed	60	34	69	73	50	69	67	62	67	67	40	81	67	14
% adequate	54	32	57	73	40	63	56	57	61	67	30	70	57	14
% not adequate	6*	2	11*	0	10	6	11	5*	6*	0	10	11*	10	0
Day 3														
overall no.	601	141	34	15	10	16	9	76	187	12	10	50	37	4
% informed	41	28	56	47	40	50	56	39	40	58	20	50	57	0
% adequate	37	26	53	40	30	44	44	37	37	58	20	40	57	0
% not adequate	3*	3*	3	7	10	6	11	3	2*	0	0	10*	0	0
Day 5														
overall no.	584	140	31	14	10	16	9	75	184	12	10	48	33	2
% informed	29	19	39	36	0	44	67	27	28	25	40	42	36	0
% adequate	26	19	35	36	0	38	44	23	26	25	30	33	30	0
% not adequate	3*	1	3	0	0	6	22	4*	2*	0	10	8*	6	0

* Patients had a statistically higher VAS score than that in patients who reported adequate treatment. There was no intergroup difference in distribution of patients who did and did not receive adequate treatment.

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The distribution in pain character over time, with different operation types, is shown in **Table 4**; significant differences in pain distribution and VAS scores for the different pain categories are indicated. **Table 5** illustrates data pertaining to patients who did and who did not ask for analgesic medication; significant differences are indicated. **Table 6** provides a summary of data pertaining to patients who did and did not feel the relief of pain was adequate after receiving analgesic medication, with significant intergroup differences indicated.

On the 1st postoperative day, the VAS scores were significantly lower among patients receiving WHO Class I medication than those receiving WHO Class II medication overall and in the CS and LF groups; however, the scores were lower than those in patients receiving WHO Class III medication overall. On the 1st postoperative day the VAS score was significantly lower in patients receiving WHO Class III medication than in those receiving Class II medication in the LF group. On the 3rd postoperative day, the VAS score was significantly lower in patients receiving WHO Class I medication than in those receiving WHO Class II medication overall and in those in the LF group, and lower than those in patients receiving WHO Class III medication in the overall population. Finally, on the 5th postoperative day, the VAS score was significantly lower in patients receiving WHO Class I medication compared with WHO Class II medication overall and in the CS and LF groups; they were also lower than in patients receiving WHO Class III medication overall and in the LF group.

In the overall patient population, the VAS scores on the 1st, 3rd, and 5th postoperative days were significantly lower in patients without preoperative pain (16.6 ± 19.7; 10.2 ± 14.9; and 6.1 ± 12.9, respectively) than in patients with preoperative pain (28.1 ± 21.8; 20.7 ± 21.4; and 15.0 ± 18.0, respectively). The pain character was also significantly different between patients with and without preoperative pain.

Patients with pain before surgery experienced significantly more sharp and referred pain after surgery (on Days 1, 3, and 5). Patients without pain before surgery more often reported "no pain" during the postoperative period (on Days 1, 3, and 5). Additionally, the VAS scores were significantly lower in patients without presurgical pain than in those with pain before surgery on Days 1, 3, and 5 in patients in the TTR and MSP groups; on Day 1 for those in the TSO group; on Days 3 and 5 for those in the LF group; and on Day 5 for those in the VPS placement, SBICPM, THR, and LTR groups.

The VAS score was independent of patient's gender. On the 5th postoperative day, patients with ASA Class III morbidities suffered significantly more pain than those with ASA Class I morbidities. The preoperative VAS score was significantly higher in patients in the 40 to 59–year-old age group than in those 0 to 19 years of age. The maximal

postoperative VAS score was significantly higher in patients in the 20 to 39–year-old age group than in those older than 60 years of age.

Overall, 36 patients sustained relevant surgery-related complications such as delayed wound healing (one case), meningitis (two cases), fluid-filled fistula (three cases), early VPS-related problems (three cases), and early relapse of lumbar hernia (10 cases). Seventeen patients had to undergo a reoperation during the study period (one each in the THR, ACS, and MSP groups; four in the CS group; and 10 in the LF group).

In the overall patient population, the VAS scores were significantly higher on the 3rd and 5th postoperative days in patients with surgical complications (30.5 ± 24.8 and 38.4 ± 28.8) than in those without surgical complications (16.4 ± 19.0 and 11.2 ± 15.5, respectively). The same applied on Day 5 to patients in the MCP group (53.0 ± 1.4 compared with 9.8 ± 11.62); on Days 3 and 5 to patients in the TTR group (27.8 ± 29.4 and 31.0 ± 30.0 compared with 10.47 ± 15.7 and 6.73 ± 10.0) and to patients in the LF group (29.8 ± 28.6 and 45.0 ± 24.8 compared with 18.1 ± 18.2 and 11.8 ± 15.2); and on Days 1, 3, and 5 in the CS (44.13 ± 14.0, 45.8 ± 16.7, and 59.5 ± 28.3 compared with 22.63 ± 19.8, 16.8 ± 21.0, and 12.1 ± 16.6) and MSP (58.3 ± 36.1, 51.0 ± 24.9, and 48.7 ± 42.2 compared with 30.9 ± 20.9, 20.8 ± 19.8, and 16.1 ± 17.9) groups, respectively.

DISCUSSION

Not surprisingly, in the different surgical groups, VAS scores decreased significantly over time after surgery. More interestingly, the patients in the TTR group had significantly less pain on the day of operation and on postoperative Days 1, 3, and 5 than those in the other groups (except for the SBICPM group), and this was significantly different from groups CS and LF. This finding is supported by another study in which investigators found that craniotomy procedures were associated with lesser analgesic requirements than extracranial procedures.[10] Some patients undergoing trephination, however, do suffer serious postoperative pain.[22] In those patients, codeine phosphate has been shown to be more effective than tramadol.[4] Scalp nerve blocks can decrease the pain severity after craniotomy, and this effect is long lasting, possibly due to a preemptive mechanism.[20] In patients undergoing craniotomy, postoperative pain is treated insufficiently with acetaminophen alone and should be combined with tramadol or nalbuphine.[30] In contrast to the general accepted clinical impression that craniotomy is associated with less perioperative pain, De Benedittis and coworkers[8] have indicated that postoperative pain in patients undergoing craniotomy is an important and neglected clinical problem that, to provide better and more appropriate treatment, deserves greater attention by surgical teams. In our study, in the preoperative phase,

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the patients in the TTR group asked for analgesic agents less frequently than those in the other groups. Most patients in this group did not receive any analgesic medication before surgery (150 cases), although a few did (six cases). Also in the postoperative phase, the mean VAS scores in the TTR group were lower than those in the other groups, except for the SBICPM group. Directly after surgery, 99 of the 145 patients undergoing TTR required no analgesic agents. On Days 1, 3, and 5 after surgery, only 38 of 145, 21 of 141, and 20 of 140 patients, respectively, needed analgesic medication. When these patients needed analgesic relief, more than 60% of them used WHO Class II medication, a finding in agreement with data published in the current literature. There were no significant differences in VAS scores in the patients receiving different WHO class medications. Based on these data, we conclude that for patients undergoing trephination, on-demand analgesic treatment seems justified.

Compared with the TTR group, patients undergoing neurosurgical spinal procedures experience a different perioperative course in terms of pain character and pain intensity. Patients in the CS and LF groups suffered more pain before surgery than those in the TTR and VPS placement groups. Interestingly, however, all patients in the different groups expected to have the same amount of postoperative pain, despite their varying preoperative pain scores. Moreover, the maximal anticipated VAS score was lower than the actual maximal VAS score in the following groups: TSO, SBICPM, THR, ACS, CS, LF, laminectomy, MSP, and MCP. This leads us to conclude that the anticipated maximal VAS score is independent of the neurosurgical procedure or the extent of preoperative pain and that postoperative pain in patients who have undergone a neurosurgical procedure is greater than anticipated. However, anticipated pain might be influenced by preoperative teaching. In our study, we did not take this into account. When visited by the examiner preoperatively, only approximately one half of the patients were informed by the surgeon. Additional studies may be undertaken to evaluate the impact of adequate preoperative teaching about pain management options on postoperative pain and patient satisfaction.

Referred pain can be described as a radicular pain with a possible projecting and/or neuropathic component. Because this pain is difficult to treat with opioid agents, the use of anticonvulsant and antidepressive drugs should be seriously considered. The mean VAS score in patients with referred pain was significantly higher than that in patients with local pain in the LF group on the 3rd and 5th postoperative days, whereas in patients undergoing TTR and VPS placement normal headache was more painful than local pain, as measured on the 5th relative to the 3rd postoperative day. These findings underscore that the pain character can direct the physician to the patients who are expected to suffer the most intense postoperative pain. In addition, in the CS and LF groups there was a shift from preoperative referred pain to local pain postoperatively. This finding

suggests that after spinal surgery nerve decompression decreases the extent of referred pain and the pain originates in the operative wound, resulting in local pain; however, some patients still suffered from referred pain after surgery. These patients experienced greater pain than those with other pain characteristics, which suggests that patients with referred pain after CS and LF require more intensive pain management than do those with local pain.

During the entire observation period in the CS and LF groups, there was significantly more referred pain than in the other groups. The following factors have been found to be predictive of surgical outcome after lumbar disc surgery: prolonged current pain attack, report of long-term illness, anxiety, severe pain reported immediately after surgery, employment status, and the presence of complete herniation at surgery.[25] The authors of another study also found a predictive value for the outcome after anterior cervical decompression; [21] the main value by which to predict postoperative pain intensity was the magnitude of the preoperative kyphosis. In our study, age, ASA class, and sex were not predictive of pain character, pain intensity, or the need for reoperation in any treatment group. Overall, however, the mean VAS score for patients with a postsurgical complication was significantly higher than that for patients without complications. This finding may suggest that clinicians should be mindful of patients with extremely high VAS scores because postoperative complications may occur. We realize, however, that patients who experience surgery-related complications may have anxiety or other factors that could influence the VAS score. We are also aware of the fact that in patients who must undergo a second procedure, some tolerance or tachyphylaxia to the analgesic medication used may have developed. This might bias the results. Ours, however, was an observational study reflecting daily clinical routine; thus, the number of patients undergoing a second procedure during the study period was small. The impact of a reoperation on pain medication requirements may well be the subject of another study.

Analysis of our results shows that patients with preoperative pain suffer significantly more postoperative pain than patients without preoperative pain. In another study investigators also found that patients with preoperative pain suffer more pain postoperatively;[14] however, they investigated all surgical procedures except heart and intracranial neurosurgical procedures. Using a scoring system to assess quality of recovery after cranial and spinal surgery, one group has reported that postoperative pain and neurological deficits correlated with poor postoperative recovery.[17] Evaluation of our data also suggests that neurosurgical patients who suffer preoperative pain require more intensive pain management after surgery than patients without preoperative pain. Age, sex, expected incision size, and surgical procedure have also been shown to affect the postoperative pain intensity.[14] We found no significant difference between males and

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females in terms of pain intensity, but we did find a correlation with age. Whereas there was a trend toward higher preoperative VAS scores in older patients, there was likewise a trend toward higher postoperative VAS scores in younger patients. Therefore, in young patients the increase in pain during the entire observation period was greater than that in old patients. Moreover, patients with ASA Class III morbidity had significantly more pain than those with ASA Class I morbidity on the 5th postoperative day; however, this was an isolated finding, and it may be too early to draw any conclusions from it.

The mean VAS score for patients who asked for medication was significantly higher than the VAS score for those who did not ask for medication. On Days 1 and 3, patients in the ACS group asked for pain medication significantly more often than those in the other groups; however, we assumed that this group was adequately treated with the given pain medication because, during the observation period, significantly increased VAS scores were not documented in these patients. It has been reported that patients are not afraid to ask for analgesic drugs[6] and that nurses underestimate postoperative pain intensity of patients.[11] Moreover, there are indications that individual pain assessment is poorly documented and that a nurse's record of a patient's postoperative pain experience differed from the patient's self-assessment.[5] Analysis of our data showed that in patients who asked for pain medication VAS scores were significantly higher and the patients needed to be treated accordingly. The mean VAS score in patients who felt they had not been adequately treated was significantly higher than that in patients who felt they had received adequate treatment. This finding suggests that the VAS score is not only useful for estimating pain intensity but can also be used to review current pain management protocols.

In patients who underwent CS and LF and who received WHO Class I medication, the mean VAS score was significantly lower during the postoperative period than that in patients receiving WHO Class II medication, whereas the mean VAS score in patients receiving WHO Class III medication was lower again. This leads us to conclude that in a subgroup of patients undergoing CS or LF and who do not benefit from WHO Class I medication alone, WHO Class II medication is also insufficient, and the patient should be treated with WHO Class III medication directly.

One limitation of the present study may have been that we did not separate the different opioid agents used intraoperatively; however, the anesthesiologists were not involved in the study, and the use of opioid agents was left to their discretion. Thus, the results of this observational study reflect a clinical routine. Older patients reported greater pain before surgery than younger patients whereas younger patients reported more pain after surgery than older patients. The postoperative recovery takes longer in patients with serious comorbidity compared with a faster recovery in otherwise healthy patients.

The anticipated pain intensity is independent of the operation type or the preoperative pain intensity perceived.

CONCLUSIONS

Based on our findings, we can conclude that neurosurgical procedures are more painful than anticipated by the patient. The idea that pain associated with neurosurgical procedures is insufficiently managed was recently addressed in an editorial titled, "Postcraniotomy pain remains a real headache!"[28] However, considering the high number of patients without postoperative pain, patients undergoing craniotomy can be treated with on-demand analgesic medication, but only if the nurses on the ward react promptly. Therefore, patient-controlled analgesia may be an effective and safe option. [23] Recently, a detailed review on acute and chronic postcraniotomy pain was published; the authors addressed the different modes of pain treatment after craniotomy and the causative factors for the development of chronic postcraniotomy pain.[9]

Patients undergoing all other types of neurosurgical procedures should receive scheduled treatment of analgesic drugs at least on the 1st postoperative day. Patients undergoing spinal surgery need intensive pain treatment in the preoperative phase; in these patients, a shift in pain character from referred pain preoperatively to local pain postoperatively is expected. A referred pain character after LF can direct the physician to those patients expected to suffer the most intense pain. In patients with preoperative pain, postoperative pain is more intense than in those without pain before surgery, and clinicians must undertake more intensive pain management in the patients after surgery. Patients who ask for analgesics or those who claim to be undertreated need to be taken seriously and treated accordingly. Receiving more pain treatment does not always lead to lower pain scores. Increased analgesic intake might still not be enough for some patients. It should be anticipated in patients with increased postoperative VAS scores that surgery-related complications will occur. In patients undergoing spinal surgery, there is a subset that does not benefit from WHO Class I medication alone, and WHO Class III medication should be provided directly.

In summary, we have shown the importance of pain and its sufficient treatment after neurosurgical procedures in an observational study setting. At present, pain is considered to be the "fifth vital sign."[16] Patients and regulatory agencies (for example, the Joint Commission on Accreditation of Healthcare Organizations) are paying much more attention to the appropriate and timely treatment of pain. It is our hope that the findings of this study will be used by neurosurgeons and neuroanesthesiologists as a reference for future studies in an effort to optimize pain management after neurosurgical procedures.

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VII

General discussion

GENERAL DISCUSSION

In the last 22 years the author has provided anesthesiological care for much more than 300 patients undergoing an awake craniotomy for brain tumor resection. Over the years, the anesthesiological regimen has not changed much. Based on clinical observations, small modifications were performed to increase patients' comfort and safety. These measures and the scientific evaluation of their effects has been described in the previous chapters. This chapter provides a summarizing view on the procedure and the presented findings, together with a perspective on the ongoing discussions and future developments:

This thesis:

Chapter 1 and 2 describe the anesthesiological practice of the awake craniotomy at Erasmus University Medical Center Rotterdam. Relevant aspects of patient selection, patient preparation and monitoring are discussed in chapter 1, whilst chapter 2 focusses on the use of local anesthetics in these patients. In summary, we have developed a quite "minimalistic" regimen (no complex airway management, anesthesia relying on local anesthesia by surgical field infiltration combined with propofol-sedation during craniotomy and closure), which has turned out to be safe and feasible. This regimen pays a lot of attention to the psychological preparation of the patient and 'vocal anesthesia'.

Despite practice for years and a lot of successful and positive examples are described in scientific and non-scientific media, the idea of being awake whilst the neurosurgeon is operating inside their brain still is supposed to be stressful and frightening for many patients. Chapters 3 and 4 provide clear evidence, that the metabolic stress-response of patients undergoing an awake craniotomy is definitively not higher and maybe even lower than in patients undergoing a tumor resection under general anesthesia. Chapter 5 summarizes the current ideas to improve patient's comfort during an awake craniotomy and brain tumor resection. Much attention should be paid to basic comfort measures (e.g. lying on the table, temperature management, treating a dry mouth) and psychological guidance (vocal anesthesia) of the patient.

In chapter 6 and 7 we addressed the question: how awake is awake? Surprisingly, we found that patients have a) very limited and b) mostly positive memories of their awake craniotomy, despite the fact that they were completely awake and cooperative for long parts of the procedure. These findings show, that planned intraoperative awareness is experienced by patients completely different to unexpected, unplanned (and maybe even painful), accidental intraoperative awareness. On the other side, we could show that those patients who report more memories have also more positive memories. Being awake and cooperative does not automatically include the creation of memories – we

observed a lot of amnesia. On the other side, the association of a higher quantity with the better quality of the memories suggests, that the psychological coping with such a major life event is not automatically improved by amnesia.

In chapters 8, 9 and 10 the added value of an awake craniotomy in selected, less common patient groups is discussed. Chapter 8 is a case-report about a brain tumor resection in a 9-year old boy. Next to the psychological guidance of the child and its parents through the perioperative period, another important aspect is the possible limitation of the amount of local anesthetics, which can be used due to the weight-dependency of the toxic upper dose limit. In chapter 9 we studied patients operated for an insular glioma, a rare, but challenging tumor location, which requires a special surgical approach, a fissurotomy, which makes it lasting longer than a standard cortical tumor resection. In these patients, awake craniotomy is much more exhausting for the patient than in case of cortical tumors. In this population, the added value of an awake craniotomy seems limited: when the tumor resection is performed under general anesthesia, a comparable extent of resection with a comparable risk of neurological damage can be achieved. This is in contrast with the findings of chapter 10: here we examined patients scheduled for resection of a glioblastoma multiforme. This most devastating tumor has a very poor prognosis - with and without surgery. However, there is a clear link between the extent of resection and the duration of survival. Our retrospective data support the use of the awake technique for a more radical resection and less neurological long-term deficits. However, these data have to be confirmed by a prospective study before a new standard can be established.

Postoperative pain control after craniotomy is the topic of chapter 11. Here we studied the pain experience and the analgesic needs of neurosurgical patients. Our data show, that the level of pain experienced after a craniotomy is in average low, but shows a broad variation. From low pain with no need of an opioid to severe pain with repeated need of opioids all can be observed.

In summary, the safety and feasibility of the technique of awake craniotomy for brain tumor resection has been clearly demonstrated, even under challenging circumstances like in children or for insula gliomas.

Ongoing scientific discussions:

When looking at the ongoing discussions in scientific literature referring to the technique of awake craniotomy, 2 major aspects get a lot of attention: the airway-management and the sedation regimen.

Whilst our airway management may be called "minimalistic", there is a lot of literature recommending much more invasive measures and devices: Sivasankar et al. promote the use of a nasopharyngeal airway[1], Matsunami et al. recommend the use of the i-gel laryngeal mask airway [2], whilst others perform the craniotomy with a laryngeal mask airway and intubate the patients endotracheally for closure after the resection [3] – just to give some ideas of the current practice. There is mutual link between the airway management and the sedation regimen: the more invasive the airway management, the more sedation is needed to make the patient tolerating it and vice versa: the more sedation is given, the more respiratory depression might occur and the more invasive airway measure might become necessary. It should be stressed, that the use of sedation during an awake craniotomy is a comfort measure, and that the use of one sedative drug, e.g. propofol, should be sufficient, as long as the local anesthesia is performed well.

Therefore, we have decided to use a "minimalistic" sedation regimen, too, as we work with propofol only. During the last years, dexmedetomidine has become the most frequently used alternative as sedative agent [4], but other authors routinely use combinations of propofol and remifentanil in doses requiring invasive airway management [5].

Future perspectives:

Right now, the value of the awake craniotomy for a maximum of brain tumor resection with a minimal risk of functional damage has been established worldwide. Future developments are, the combination of this technique with other techniques to further increase the extent of (safe) tumor resection. One option is the use of an intraoperative MRI-scan in patients undergoing an awake craniotomy [6]. Another is the use of 5-aminolevulinic acid (Gliolan®) in combination with an awake craniotomy [7]. However, most of these reports show only limited added value of the extra techniques, so that there still remains an open field for future developments. It should be noted, that all extra techniques applied intraoperatively are more or less time-consuming, and the possible duration of surgery is limited by a) the effect of the local anesthesia and b) the ability of the patient to cooperate.

Another aspect getting more and more attention is the possibility to perform a brain tumor resection as an outpatient / day-care-procedure [8]. Because the neurosurgical procedure of brain tumor resection is more or less the same in awake and anesthetized patients, it has been shown, that it can be done not only for patients after an awake craniotomy, but also after a general anesthesia. However, careful patient selection is a keystone when doing so, and "outpatient" in the most studies publishing on this topic means "in a hotel close to the hospital", because postoperative bleeding still remains the most threatening early complication after these procedures.

Now, after the safety and feasibility of the awake craniotomy have been demonstrated, an extension of the indications is coming up: The first series of successfully awake clipped cerebral aneurysms are published [9]. 13 years after our case report of successful awake craniotomy in a 9-years old child, in 2017 the case of an 8-years old child who has undergone successful awake resection of a frontal brain tumor was published [10]. Several case reports describe the successful use of an awake craniotomy-technique for tumor- and non-tumor-neurosurgery in patients with congenital heart disease and/or pulmonary hypertension, which make a general anesthesia with mechanical ventilation very risky [e.g. 11]. Recently, the ongoing extension of indications cumulated in the question, whether a tumor resection under general anesthesia for some patients (low grade glioma with no or little functional deficits) still is ethically acceptable and whether not only language, but also sensorimotor, visuospatial, higher cognitive and emotional functions must be monitored intr aoperatively in the awake patient [12]?

Finally, there is also a rising interest in psychosocial and ethical aspects of the awake craniotomy, which can be felt in discussions on conferences, but is not yet fully mirrored in scientific literature: the first cases of post-traumatic stress disorder after an awake craniotomy have been diagnosed and described [13], which we did not observe in our patients up to now.

Two other very important questions remain still unanswered: what does it do with the patient and the medical team, when despite mapping and neuromonitoring an intraoperative functional decline (not only a temporary epileptic insult) occurs? In practice, we see emotional reactions of all people involved, and mostly the decision is taken to stop further resection attempts. However, this phenomenon is not yet covered in a scientific manner.

The other question is even more difficult to answer: is there any non-functional brain? Until now, the surgeon removes the (suspect) tissue, if during cortical and subcortical stimulation no functional changes occur, always aiming for a maximum resection. However, during these stimulations one can only monitor the functions you are searching for, possibly missing others, which are less overt. More input from basic-neuroscientists is strongly needed to get a clearer picture of the complexity of the brain and its possibly hidden functions.

In summary, after the publication of this thesis, there remain a lot of unanswered questions and challenges for the patient undergoing and the team performing an awake craniotomy for brain tumor resection. There is no doubt, that all efforts must be taken, to make the procedure for the patient as safe, as effective, and as pleasant as possible.

This is most probably warranted by an experienced and dedicated team, with intensive counselling of the patient [14] – which is routine at Erasmus MC.

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VIII

Summary

SUMMARY

This thesis aims to provide a solid framework of the anesthesiological aspects linked to an awake craniotomy procedure for brain tumor resection. To begin with, it should be clarified, that the term 'anesthesiological' in case of the awake craniotomy covers the whole non-operative/non-surgical context, including metabolic and psychological aspects, too - and not only sedation and analgesia.

The **introduction** shows the historical developments in the fields of anesthesiology (e.g. local anesthetics, injection needles, fast-in-fast-out sedatives) and neurosurgery (e.g. microsurgery, functional anatomy of the brain) that were mandatory to make this procedure safe and feasible. Based on this background, 5 key-questions are addressed in the findings presented here:

Question 1: What are the pre-requisites for a successful awake craniotomy?
Chapter 1 addresses the unique role of the anesthetist in a setting, where no general anesthesia is applied, whilst open brain surgery is performed: a careful patient selection, an intensive preparation of the patient, a minimalistic anesthesia regimen (no invasive airway management, light sedation with propofol) and a goal directed (psychological) guidance of the patient throughout the procedure ("vocal anesthesia") are described as the cornerstones. **Chapter 2** focusses on the use and the added value of local anesthetics for brain tumor resections. Next to the surgical field block, the technique of direct nerve/scalp block is described and discussed in detail; whilst the first must be considered the easy and reliable routine technique, the second remains a useful tool in extraordinary situations (e.g. small patients, re-craniotomies).

Question 2: Is an awake craniotomy for the patient more or less stressful than a brain tumor resection under general anesthesia?
Chapter 3 and 4 are biochemical approaches to address the metabolic response of the patient on the theoretical stress of an awake brain tumor resection. Because all patients received dexamethasone, measuring cortisol was not an option. Therefore, levels of plasma amino acids and inflammatory mediators were measured as alternative "objective" stress-markers. Our studies showed, that - in contrast with what many people might expect - undergoing an awake craniotomy in our routine setting is not more, but maybe even less stressfull than a brain tumor resection under general anesthesia. The fact that awake-craniotomy patients have a shorter length of stay in the hospital supports these findings.

After the safety and feasibility of the awake craniotomy has been established, the next level is the maximization of patients' comfort. This topic is addressed in **chapter 5**, where

several technical solutions (e.g. transparent drapes, music) and other measures (e.g. not keeping the patients fasted) are reviewed.

Question 3: The patients undergoing an awake craniotomy must be cooperative during the procedure, but: what do they remember of the perioperative period and how do they deal with it?

Chapter 6 shows, that patients undergoing an awake craniotomy, have only partial (and mostly positive) memories of their procedure. This is surprising, because they are awake for more than an hour intraoperatively and cooperate closely whith the whole team. Furthermore, we could demonstrate, that planned and pain-free intraoperative awareness does not have to cause a problem for the coping of the patient. These findings were confirmed by the research presented in **chapter 7**. Here we found, that patients undergoing an awake craniotomy have more, and more positive memories of the perioperative period than patients operated for an intracranial tumor under general anesthesia. Furthermore, we could identify that being operated - awake or not - has more impact on the quality and quantity of memories than the question whether a benign or malignant tumor has been resected. We also addressed anxiety in patients and their relatives and found that the patients experienced their relatives as more anxious than themselves. This finding deserves attention in future research.

Question 4: What is the added value of an awake craniotomy in selected patient populations?

Within the large patient population treated, some selected sub-groups asked for special attention. **Chapter 8** gives a detailed description of an awake craniotomy in a 9-year-old boy who underwent an awake craniotomy for glioblastoma resection. Next to the biological age and weight of the patient (e.g. dose of local anesthetics), especially the psychological guidance of the child and the parents throughout the perioperative period are challenging. However, the encouraging result of this case is, that it can be done safely and successfully.

   Chapter 9 describes the choices for and against awake craniotomies and the related outcomes in patients suffering from a brain tumor in the insula. Surgery in this part of the brain is challenging even under general anesthesia, and not frequently performed nor published. However, we could show, that with a careful patient selection, it is not mandatory to perform all these insula-tumor resections as an awake craniotomy. Complications and long-term-prognosis after general anesthesia are similar. This must be taken into account when counselling future patients. In **chapter 10** the question, whether patients suffering from a (suspected) glioblastoma multiforme have advantage by an awake craniotomy is addressed by a retrospective, controlled-matched study. It turned out, that resection of glioblastoma as an awake craniotomy is associated with

significantly greater extent of resection and less late minor postoperative complications as compared with craniotomy under general anesthesia. We hope that in the future a prospective randomized trial can be performed clarifying this issue definitively.

Question 5: What is the adequate postoperative pain-treatment after an (awake) craniotomy?

Chapter 11 shows that patients after a trepanation for brain tumor resection have a relatively low pain score and do not require opioids postoperatively routinely. However, there are patients, who experience severe post-craniotomy pain, and therefore the access to fast and strong working opioids must be warranted.

In the final **general discussion**, the findings of the presented papers are reviewed and future research perspectives are addressed.

vocal ANESTHESIA

MEMORY PAIN

TRUST

IX

Nederlandstalige Samenvatting

NEDERLANDSTALIGE SAMENVATTING

Dit proefschrift heeft als doel een onderbouwd overzicht te bieden van de anesthesiologische aspecten die bij een wakkere hersentumor resectie aan bod komen. Om te beginnen: het moet helder zijn dat "anesthesiologisch" in deze samenhang niet alleen sedatie en pijnbestrijding, maar alle niet-chirurgische aspecten omvat, en dus ook metabole en psychologische effecten worden bekeken.

De **inleiding** vat de historische ontwikkelingen samen op de gebieden van de anesthesie (zoals locale anesthetica, injectienaalden, snelwerkende sedativa) en van de neurochirurgie (zoals microchirurgie, functionele anatomie van de hersenen). Deze waren noodzakelijk om de wakkere craniotomie veilig en überhaupt uitvoerbaar te maken. Tegen deze achtergrond worden in dit proefschrift vijf sleutelvragen besproken:

Vraag 1: Wat zijn de randvoorwaarden van een succesvolle wakkere craniotomie?
Hoofdstuk 1 behandelt de unieke rol van de anesthesioloog bij een operatie waar geen algehele anesthesie wordt toegediend, terwijl open hersenchirurgie wordt uitgevoerd: een zorgvuldige selectie van de patiënten, intensieve voorbereiding van de patiënt, een minimalistisch anesthesie-beleid (geen invasief luchtwegmanagement, lichte sedatie met propofol) en een doelgerichte (psychologische) sturing van de patiënt door de hele procedure heen ("vocale anesthesie") zijn de beschreven hoekstenen. **Hoofdstuk 2** focust op het gebruik en de toegevoegde waarde van locale anesthetica bij hersentumorresecties. Naast het chirurgische veldblok wordt de techniek van het directe zenuw/scalp-blok beschreven en bediscussiëerd. Terwijl het veldblok een simpele en betrouwbare routinetechniek is, is het directe zenuwblok een reservemiddel voor buitengewone omstandigheden (bijvoorbeeld kleine/lichte patiënten, re-operaties).

Vraag 2: Is een wakkere craniotomie voor de patiënt meer of minder stressvol dan een hersentumorresectie onder algehele anesthesie?
Hoofdstuk 3 en 4 beschrijven biochemische pogingen om het metabole antwoord van de patiënt op de theoretische stress van een wakkere hersenoperatie in kaart te brengen. Gezien alle patiënten met dexamethason worden behandeld, is het "gewoon" meten van cortisol hiervoor geen optie. Daarom werden de plasmaspiegels van aminozuren en ontstekingsmediatoren gemeten als alternatieve "objectieve" stressmarkers. Onze resultaten laten zien dat - anders dan men zou verwachten - onze klinische standaardwerkwijze voor een wakkere hersenoperatie voor de patiënt zeker niet meer, en mogelijk zelfs minder stressvol is dan een operatie onder algehele anesthesie. Het feit, dat patiënten na een wakkere hersenoperatie een kortere ziekenhuisopname hebben dan na een algehele anesthesie ligt in lijn met deze bevindingen.

Nadat de veiligheid en haalbaarheid van de wakkere craniotomie duidelijk gemaakt waren, stond de verhoging van het comfort van de patiënt in het centrum van de aandacht. **Hoofdstuk 5** is hierop gericht en beschrijft verschillende technische oplossingen (zoals transparante afdekdoeken, muziek op de operatiekamer) en andere maatregelen (bijvoorbeeld de patiënten voor een wakkere hersenoperatie niet volledig nuchter houden).

Vraag 3: Patiënten die een wakkere craniotomie ondergaan moeten tijdens de operatie coöperatief zijn, maar: wat herinneren zich de patiënten uiteindelijk nog van de ingreep en hoe gaan zij hiermee om?

Hoofdstuk 6 laat zien, dat patiënten na een wakkere hersenoperatie alleen gedeeltelijke (en meestal positieve) herinneringen van hun operatie overhouden. Dit is enigszins verrassend gezien de patiënten meer dan een uur tijdens de operatie wakker zijn en nauw en actief samenwerken met het hele behandelteam. Verder konden wij aantonen, dat het gepland, pijnvrij intra-operatief wakker zijn op zich geen probleem hoeft te betekenen voor de verwerking door de patiënt. Deze bevindingen werden bevestigd door het onderzoek beschreven in **hoofdstuk 7**. Hier vonden wij dat patiënten die een wakkere hersenoperatie ondergaan meer - en positievere herinneringen aan hun procedure hebben dan patiënten die onder algehele anesthesie zijn geopereerd. Hiernaast konden wij aantonen dat de vraag of men al dan niet wakker geopereerd werd, meer invloed heeft op de kwaliteit en de kwantiteit van de herinneringen bij de patiënt dan de vraag, of er een goed- of kwaadaardige tumor werd verwijderd. We konden ook laten zien dat de meeste patiënten hun naasten rondom de operatie als angstiger dan zichzelf ervaren. Dit vraagt zeker om aandacht bij toekomstig onderzoek.

Vraag 4: Wat is de toegevoegde waarde van de wakkere hersenoperatie bij geselecteerde patiëntengroepen?

Binnen de grote patiëntenpopulatie die behandeld werd, verdienen enkele geselecteerde subgroepen bijzondere aandacht. **Hoofdstuk 8** geeft een gedetailleerde beschrijving van een wakkere craniotomie bij een 9-jarige jongen met een glioblastoom. Naast de biologische leeftijd en het gewicht (in samenhang met de dosis van locale anesthetica) ligt hier een bijzondere uitdaging in de psychologische begeleiding en sturing van patiënt en ouders door de hele perioperatieve periode. Niettemin is het motiverende resultaat van deze casus, dat ook bij dermate jonge kinderen de procedure veilig en succesvol uitgevoerd kan worden.

Hoofdstuk 9 beschrijft de afwegingen voor of tegen een wakkere craniotomie en de hieraan gerelateerde uitkomsten bij patiënten met een hersentumor in de insula-regio. Chirurgie in deze onderdelen van de hersenen is bijzonder uitdagend, ook onder

algehele anesthesie. Hierdoor wordt dit soort operatie niet vaak uitgevoerd en ook niet gepubliceerd.

In onze grote patiëntengroep konden wij aantonen, dat met zorgvuldige selectie van de patiënten het zeker niet altijd nodig is, om een tumor in de insula-regio wakker te opereren. De complicaties en langetermijnsuitkomsten na een operatie onder algehele anesthesie zijn vergelijkbaar. Dit behoort bij de indicatiestelling meegenomen te worden.

In **hoofdstuk 10** wordt de vraag of patiënten met een (verdenking op) glioblastoom voordeel hebben van een wakkere hersenoperatie geadresseerd door middel van een retrospectieve, controlled-matched studie. Het resultaat is, dat de tumorverwijdering in vorm van een wakkere craniotomie een significant ruimere resectie mogelijk maakt en tot significant minder late postoperatieve complicaties leidt. Wij hopen daarom ook, dat deze vraag voor de toekomst door middel van een prospectief gerandomiseerd onderzoek definitief beantwoord kan worden.

Vraag 5: Hoe ziet de adequate postoperatieve pijnstilling na een (wakkere) craniotomie eruit?

Hoofdstuk 11 laat zien, dat patiënten na een hersentumorresectie in het algemeen relatief lage pijnscores aangeven en niet routinematig postoperatief een behandeling met opioiden nodig hebben. Maar, er zijn ook enkele patiënten, die ernstige post-craniotomie-pijn ervaren, en daarom vinden wij dat sterke en snelwerkende opioiden voor deze patiëntengroep onmiddellijk beschikbaar moeten zijn, indien nodig.

In de afrondende **general discussion** worden de resultaten van de gepresenteerde onderzoeken beschouwend samengevat en toekomstige onderzoeksperspectieven voorgesteld.

X

Dankwoord

DANKWOORD

Promoveren doe je niet alleen, zeker niet als je daar een tijdje over doet; en vandaar is het een behoefte en genoegen, dat ik hier **alle vrienden en collega's** (**specialisten, arts-assistenten en physician assistants van de afdelingen Anesthesiologie en Neurochirugie, anesthesiemedewerkers, neuropsychologen en klinisch linguisten, operatieassistenten van "OK 1 en 3", de verpleegkundigen van de PACU** (in het bijzondere van "bedje 4" ☺)**, afdeling 7 Zuid en het acute pijnteam, studenten, onderzoekers, de medewerkers van de preoperatieve polikliniek Anesthesiologie, het planbureau Neurochirurgie en "mijn" secretariaat**) kan bedanken voor de jarenlange prettige samenwerking in de zorg (niet alleen) voor de wakkere patiënten en hun bijdrage, die dit mooi resultaat mede mogelijk heeft gemaakt.

Promoveren over een klinisch onderwerp lukt ook niet zonder de medewerking en het vertrouwen van de **patiënten,** die bereid waren om bloed te geven, vragenlijsten in te vullen en hun ervaringen met ons te delen – hiervoor dank en respect!

Bijzondere dank gaat aan **Prof. dr. Robert Jan Stolker**: Robert Jan, mijn promotor. Jouw vertrouwen, jouw belangstelling en geduld, jouw adviezen en jouw "zachte dwang" - en alles op de juiste tijdstip en met de juiste dosis - hebben uiteindelijk ervoor gezorgd, dat dit project rond is gekomen. Ik had mij geen betere promotor kunnen wensen en ben blij, dat onze samenwerking hier zeker niet mee zal stoppen!

De leescommissie: **Prof. dr. Clemens Dirven, Prof. dr. Peter Sillevis Smit en Prof. dr. Tony Absalom** – het voelt als een bijzondere eer, dat jullie de moeite hebben genomen om het manuscript door te nemen en te opponeren bij mijn verdediging. Onze gemeenschappelijke motivatie om mensen met een hersentumor en andere neurologische/ neurochirurgische aandoeningen een langer leven in goede kwaliteit te bieden, heeft de afgelopen jaren al tot veel wederzijdse inspiratie geleid, en ik vertrouw erop dat dit ook na vandaag nog door zal blijven gaan.

De leden van de grote commissie: **Univ.-Prof. (em.) Dr. med. Walter Buzello** – lieber Walter, ich freue mich besonders, diesen Tag auf diese Weise auch mit Dir zu erleben. Die Ausbildung und Begleitung, aber auch die Freiheit und das Vertrauen, das ich in Köln unter Deiner Regie erfahren durfte, sind für mich immer noch vorbildlich. **Prof. em. Dr. Hans Knape** - beste Hans, van harte bedankt dat jij - naast Tony als de huidige voorzitter van het Nederlands Neuroanesthesiologisch Gezelschap - ook als oud-voorzitter hier aan tafel wilt zitten – een van de vele banden die wij hebben. **Prof. dr. Jan van Busschbach** en **Prof. dr. Frank Huygen** - bedankt voor de bereidheid tot deelname aan de oppositie. Zoals in de samenvatting beschreven gaat het bij de "anesthesiologische aspecten" in

dit proefschrift om meer dan alleen de intra-operatieve momenten, en ik ben blij dat dankzij jullie expertise ook de aspecten psychologie/psychiatrie en postoperatieve pijn de nodige aandacht krijgen.

Veel dank ook aan **alle co-auteurs** voor hun bijdrage tot de hier verzamelde stukken**,** waaronder ook mijn hooggewaardeerde neurochirugische collega's **dr. Arnaud Vincent** en **drs. Joost Schouten**. Het was en is altijd een plezier om met jullie samen "een wakkere te doen", en ik weet zeker dat wij ook nadat dit boekje nu af is niet met de klinische en wetenschappelijke output zullen stoppen: de KWF-fonds voor de SAFE-trial staat al klaar!

Dr. med. Christoph Weigand – lieber Christoph, es war am 14. März 1996, als wir im "Ausweich-OP" der Kieferchirurgie in Köln gemeinsam unsere erste Wachkraniotomie anästhesiologisch begleiteten. 22 Jahre und mehr als 350 Patienten später mache ich zu 90% die Dinge noch so, wie wir sie uns damals ausgedacht haben! Du warst mein klinischer Lehrmeister - nicht nur in der Neuroanästhesie - und ich bin froh und dankbar, dass sich aus unserem "Ober-und-Assistenzarzt–Verhältnis" schon zu Kölner Zeiten eine echte Freundschaft entwickelt hat.

Univ.-Prof. Dr. med. Ulf Börner – Lieber Ulf, Du bist leider viel zu früh gestorben. Als "Doktorvater" meiner Deutschen Promotion betrachte ich Dich noch immer als meinen wissenschaftlichen Lehrmeister. Ich weiss, dass Du auch sehr gerne dabei gewesen wärst, wenn ich meine Niederländische Promotion verteidige. Unsere Schilddrüsen-Forschung brachte uns in Kontakt mit **Prof. dr. ir. Theo Visser**, die vandaag ook helaas niet meer aanwezig kan zijn. Beste Theo, in jouw lab heb ik 1999 mijn eerste contacten met Rotterdam gehad en echt genoten van de inspirerende besprekingen met jou en **Prof. em. dr. Georg Henneman**. Mede dankzij deze tijd beschouw ik mezelf nog steeds als een "endocrinofiele anesthesioloog".

Prof. dr. Jan Klein – beste Jan, je hebt mij in 2001 naar Rotterdam gehaald en alle vrijheden gegeven om me op alle vier domeinen (patiëntenzorg, onderwijs/opleiding, onderzoek en management/organisatie) te ontplooien. Dankzij jouw vertrouwen en die van **Prof. em. dr. Cees Avezaat** kon ik - in het begin trouw ondersteund door **Steven Roubos** en later samen met **drs. Chris Jansen, Dr. Aloys Oberthür**, **dr. Ismail Eralp** en **alle andere anesthesiemedewerkers** - de wakkere craniotomie vanuit de anesthesiologie voor Rotterdam neerzetten.

Om de klinisch-wetenschappelijke uitdagingen van het schrijven van een proefschrift te kunnen meesteren, heb je ook een goed "persoonlijk milieu" nodig. Dit veld om je

heen zorgt ervoor, dat je mentaal en fysiek enigszins "normaal" blijft, terwijl je enigszins "buitengewone" dingen doet. Alle mensen die hier een bijdrage aan hebben geleverd, mogen in dit dankwoord beslist niet worden vergeten:

Mr. drs. Rembrandt Zuijderhoudt – beste Rembrandt, we hadden een afspraak… en hier is het resultaat. Een cognitieve dissonantie is toch iets anders dan een emotionele dissonantie, en soms heb je iemand nodig, die je hiervoor de ogen opent. Dank voor onze inspirerende gesprekken!

Ton Dunk jr. en de co-trainers van de Rotterdamsche Boksvereniging van 't Hof: jullie zijn verantwoordelijk voor het feit dat ik fitter uit mijn promotietraject eruit kom dan dat ik erin ben gegaan – dank voor alle motivatie en blessurevrije uitputting! Dit boek is nu af, maar ik zal zeker blijven komen trainen!

Liebe Freunde, lieve vrienden, dear friends – I tried not to bother you with this project and maybe it comes even as a surprise (at least for some of you) that I finally did it, but be sure: without you I never would have made it! Whenever I need(ed) some distraction, I knew and still know to find you! Thank you so much for all the moments we enjoy(ed) together, I am absolutely sure: there will be even more opportunities after today!

Mijn paranimfen, **drs. Eldert Boudesteijn** en **drs. Mark Buunen**. Jullie zijn twee lieve, langjarige vrienden, met wie ik al meerdere hoogte- en dieptepunten van mijn en jullie leven mocht delen. Ik waardeer het bijzonder, dat jullie onmiddellijk bereid waren om van deze dag een gemeenschappelijk hoogtepunt te maken; dit voegt nog een extra dimensie toe aan onze al bijzondere vriendschappen!

Ilona Klimek und **Guido Löhrer -** ganz herzlichen Dank für das aussagekräftige Titel-Design. Ihr habt da – ganz wie in alten Zeiten – zusammen mit **Andrea Bartsch** mal wieder etwas richtig Tolles gemeinsam gezaubert! Auch **Hilmer Tasto** als Modell darf hier nicht vergessen werden!

Meine **liebe Familie en lieve schoon-familie** – dankzij onze regelmatige zomervakanties in Domburg kan ik in mijn Nederlandse proefschrift ook het dankwoord voor jullie gewoon in het Nederlands schrijven en jullie snappen het allemaal (en andersom in het Duits zouden jullie van de schoon-familie er ook geen problemen mee hebben): wat ben ik blij dat jullie er zijn en dat jullie ook onderling zo'n fijne verstandshouding hebben! Bedankt voor jullie oprechte belangstelling en betrokkenheid, het is heel fijn om te weten dat ik op jullie altijd terug kan vallen, en dat ik ook ben meegenomen in jullie gebeden.

Lieve **Thomas** – het is zo ongelooflijk fijn, dat wij elkaar gevonden hebben, dat wij elkaar steun en uitdaging, maar ook ontspanning en afleiding kunnen bieden, dat wij samen de wereld verkennen, maar ook thuis gewoon samen muziek maken, Tatort-kijken of lekker koken en eten. Zonder jou was dit boekje mogelijk wat eerder rond geweest, maar dankzij jou waren de afgelopen jaren dermate veel leuker, dat ik dit helemaal niet erg vind – in tegendeel! Want uiteindelijk is het toch klaar: the dream-team did it again! Op naar de volgende gemeenschappelijke uitdagingen en ontspanningen, ik houd van je! DT4E!XXX

vocal ANESTHESIA

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Curriculum Vitae

CURRICULUM VITAE

Markus Klimek was born on October 18, 1968 in Cologne, Germany. He attended pre-university education at Friedrich-Wilhelm-Gymnasium Cologne, Germany and finished 1987 "with excellence". After the military service, he started in October 1988 his medical studies at the Albertus-Magnus-University of Cologne. At that time, he already knew that he wanted to become an anesthesiologist and started to work on a research project at the Department of Anesthesiology at the University Hospital of Cologne. Next to his medical studies he followed courses and lectures in psychology, philosophy, Dutch philology and economy.

In 1995 he finished his Medical studies "with excellence" and became resident in training at the Department of Anesthesiology and Intensive Care at the University Hospital of Cologne by January 1, 1996 (Chairman: Univ.-Prof. Dr. med. W. Buzello). In December 1997, his research project was successfully rounded up by a doctoral thesis (Promotor: Univ.-Prof. Dr. med. U. Börner †) with the title "Einfluss volatiler Anästhetika auf die Freisetzung und den Metabolismus der Iodothyronine in vitro und in vivo" and graded with "summa cum laude". This project was followed by some clinical research, which brought him in first contact with Rotterdam, especially with the Thyroid Laboratory of the Department of Endocrinology of the former "Academic Hospital Rotterdam" in 1999 (head: Prof.dr.ir. Th. Visser †). During his training Markus developed and deepened his special interest in Neuroanesthesiology, but also in teaching and in Emergency Medicine: He was medical head of the school for paramedics at the Johanniter Unfallhilfe Köln for several years, and was certified as "Notarzt", "Leitender Notarzt", and "Ärztlicher Leiter Rettungsdienst".

In February 2001 he became certified as anesthesiologist (and later also as intensivist) in Germany. A few months later he followed the Rhine downwards and became staff anesthesiologist in Rotterdam in July 2001. In 2002 he was announced as chairman of the sector "Center Location", in 2003 he became the vice-chairman of the department of Anesthesiology at Erasmus MC. In 2007 he became the vice-head of the residency training program. He also succeeded with the D.E.A.A. and the E.D.I.C, the European certificates as anesthesiologist and intensivist, and is now examiner for the EDAIC part II as well as the Dutch board exam. Next to his managerial and clinical activities - mostly as a dedicated neuroanesthesiologist - Markus is certified as clinical teacher with the Senior Teaching Qualification (SKO), chairman of the Committee for professional behaviour of medical interns (CLBC) at Erasmus MC, Board member and course director at ATLS-The Netherlands. Finally, his dedication to patient safety is reflected in his role as chairman of the Critical Incident Reporting System-Committee at Erasmus MC.

In their life outside their respective hospitals, Markus and his life partner Thomas enjoy making music, cooking, travelling and spending time together with family and friends.

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Portfolio

COURSES AND CERTIFICATES (SELECTION)

3/11	Workshop: "**Neuromonitoring**" (German Anesth. Soc., DGAI)
7/14	Certificate: **BKO – Basiskwalificatie Onderwijs / UTQ – University Teaching Qualification**
6/15	Certificate: **SKO – Senior Kwalificatie Onderwijs / STQ – Senior Teaching Qualification**
1/17	**BROK-certificate** (legislation and organization of clinical research)
3/18	Training „**Diversity and inclusivity on the workfloor**"

ACTIVITITES AS EDITOR/REVIEWER FOR SCIENTIFIC JOURNALS

5/07-1/09 and 1/12-12/12	Vice-Editor in Chief **Nederlands Tijdschrift voor Anesthesiologie (Dutch Anesthesia Journal)**
1/09-12/11	Editor in Chief **Nederlands Tijdschrift voor Anesthesiologie**
since 1999	Reviewer for several jounals, among others:

Acta Anaesthesiologica Scandinavica
British Journal of Anaesthesia
British Journal of Surgery
Cochrane Anaesthesia Group
Der Anästhesist
Frontiers in Physiology
Journal of Clinical Anesthesia
Journal of Clinical Endocrinology and Metabolism
Journal of Critical Care
Neurological Research

LIST OF PUBLICATIONS NOT PRESENTED IN THIS THESIS (SELECTION)

I. Original articles:

M.L. Buis, I.M. Maissan, S.E. Hoeks, **M. Klimek**, R. Stolker:
Defining the learning curve for endotracheal intubation using direct laryngoscopy: A systematic review.
Resuscitation 99;63-71 (2016)

H. Mijderwijk, R.J. Stolker, H. Duivenvoorden, **M. Klimek**, EW Steyerberg:
Clinical prediction model to identify vulnerable patients in ambulatory surgery: towards optimal medical decision making.
Can J Anaesth 63;1022-32 (2016)

M. Heesen, **M. Klimek**, S.E. Hoeks, R. Rossaint:
Prevention of spinal anesthesia-induced hypotension during cesarean delivery by 5-hydroxytryptamine-3 receptor antagonists: a systematic review and meta-analysis and meta-regression.
Anesth & Analg 123;977-88 (2016)

J. Hattler, **M. Klimek**, R. Rossaint, M. Heesen:
The effect of combined spina-epidural versus epidural analgesia in laboring women on nonreassuring fetal heart rate tracings. Systematic review and meta-analysis.
Anesth & Analg 123;955-64 (2016)

J.C. Sierink, K. Treskes, M.J. Edwards, B.J. Beuker, D. den Hartog, J. Hohmann, M.G. Dijkgraaf, J.S. Luitse, L.F. Beenen, M.W. Hollmann, J.C. Goslings, **REACT-2-study group**:
Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial.
Lancet 388;673-83 (2016)

H. Mijderwijk, **M. Klimek**, S. van Beek, R.H. van Schaik, H.J. Duivenvoorden, R.J. Stolker:
Implication of UGT2B15 Genotype Polymorphism on Postoperative Anxiety Levels in Patients Receiving Lorazepam Premedication.
Anesth Analg 123;1109-15 (2016)

M. Heesen, **M. Klimek**, R. Rossaint, G. Imberger, S. Straube:
Paravertebral block and persistent postoperative pain after breast surgery: Meta-analysis and trial sequential analysis.
Anaesthesia 71;1471-81 (2016)

S. van Beek, **M. Klimek**, J. Koopmans, R.J. Stolker:
Metamizole postoperatively for one single day: short report of a retrospective cohort study.
Eur J Anaesthesiol 34;320-2 (2017)

M. Heesen, S. Weibel, **M. Klimek**, R. Rossaint, L.R. Arends, P. Kranke:
Effects of epidural volume extension by saline injection on the efficacy and safety of intrathecal local anaesthetics: systematic review with meta-analysis, meta-regression and trial sequential analysis.
Anaesthesia 72;1398-1411 (2017)

M. Heesen, **M. Klimek**, G. Imberger, S.E. Hoeks, R. Rossaint, S. Straube:
Co-administration of dexamethasone with peripheral nerve block: intravenous *vs* perinerual application: systematic review, meta-analysis, meta-regression and trial-sequential analysis.
Brit J Anaesthesia 120;212-27 (2018)

M. Klimek, R. Rossaint, M. van de Velde, M. Heesen:
Combined spinal-epidural vs. spinal anaesthesia for caesarean section: meta-analysis and trial-sequential analysis.
Anaesthesia 13 Jan (2018), epub ahead

J.A. Calvache, C. Daza-Perdomo, J. Gomez-Tamayo, E. Benavides-Hernandez, A. Zorrila-Vaca, **M. Klimek**:
Ultrasound guidance for central venous catheterization: A Colombian national survey.
Int J Qual Health Care 9 April (2018), epub ahead.

H. Mijderwijk, R.J. Stolker, H.J. Duivenvoorden, **M. Klimek**, E.W. Steyerberg:
Prognostic model for psychological outcomes in ambulatory surgery patients: A prospective study using a structural equation modeling framework.
PLoS One 13(4):e0193441 (2018)

II. Non-systematic, invited and uninvited reviews, Editorials:

M. Heesen, **M. Klimek**:
Obstetric analgesia – update 2016 - Review
J Perinat Med 45;281-9 (2017, epub ahead juli 2016)

F. Grüne, **M. Klimek**:
Cerebral blood flow and its autoregulation – When will there be some light in the black box? - Editorial
Brit J Anaesth 119;1077-9 (2017)

M. Heesen, **M. Klimek**, S.E. Hoeks:
Restrictive or responsive? Outcome classification and unplanned sub-group analyses in meta-analyses. - Editorial
Anaesthesia 73;279-83 (2018)

III. Book chapters / E-learning / Applications:

M. Klimek, T.H. Ottens:
Fluid Management in Neuroanesthesia
In: K. Ruskin (Ed.): Fundamentals of Neuroanesthesia
Oxford University Press (2013)

T.H. Ottens, **M. Klimek:**
Pharmacology
In: Matthes, Urman, Ehrenfeld (Eds.) Anesthesiology: a comprehensive
board review for primary and maintenance of certification
Oxford University Press (2013)

M. Klimek:
Anesthesie voor een wakkere hersentumoroperatie
In: I.F. Panhuizen et al. (Eds): Probleemgeorienteerd denken voor gebruikers van lokaal anesthetica
Uitgeverij tijdstroom (2015)

M. Klimek, A.R. Absalom**:**
Er zit iets in mijn hoofd – Anesthesie voor hersentumor-operaties
In: D.G. Snijdelaar et al. (Eds.) Probleemgeorienteerd denken in de
anesthesiologie, 2de uitgave,
Uitgeverij tijdstroom (2016)

D. Snijdelaar, **M. Klimek:**
Een slap handje – Anesthesie bij myasthenia gravis
In: D.G. Snijdelaar et al. (Eds.) Probleemgeorienteerd denken in de
anesthesiologie, 2de uitgave,
Uitgeverij tijdstroom (2016)

M. Klimek, L.A. Steiner, F.A. Lobo, C.J.K. Kalkman:
Neuroanaesthesia
In: Hardman, Hopkins, Struys [Eds.]: Oxford Textbook of Anaesthesiology
Oxford University Press (2017)

M. Klimek, J. Hamming, I. Wallenburg**:**
Patientveiligheid in de opleiding
In: Dillmann, Wagner, Schellekens, Klein, Jager, van der Grinten
[Eds.]: Handboek Patientveiligheid
Uitgeverij tijdstroom (2016)

M. Klimek:
Basale fysica
In: Noordzij, **Klimek**, Landman: Klinische Anesthesiologie
Uitgeverij tijdstroom (3^{e} editie 2017)

M. Klimek:
Hersenen en zenuwstelsel
In: Noordzij, **Klimek**, Landman: Klinische Anesthesiologie
Uitgeverij tijdstroom (3^{e} editie 2017)

J. Landman, **M. Klimek**:
Veiligheid, communicatie en juridische aspecten
In: Noordzij, **Klimek**, Landman: Klinische Anesthesiologie
Uitgeverij tijdstroom (3^{e} editie 2017)

M. Klimek, P.G. Noordzij**:**
Bloedgasanalyse
In: Noordzij, **Klimek**, Landman: Klinische Anesthesiologie
Uitgeverij tijdstroom (3^e editie 2017)

J. Landman, **M. Klimek:**
Anesthesie bij interventies buiten het operatiekamercomplex
In: Noordzij, **Klimek**, Landman: Klinische Anesthesiologie
Uitgeverij tijdstroom (3^e editie 2017)

IV. Case Reports, Letters to the editor:

B. Hoogteijling, L. Chomrikh, S. Van Koeverden, **M. Klimek**.
Canulatie van de sinus coronarius bij een patiënt met een persisterende linkszijdige
vena cava superior.
Ned Tijdschr Anesthesiol 29;38-41 (2016)

M. Heesen, J. Hattler, **M. Klimek**, R. Rossaint.
In response on a letter to the editor.
Anesth & Analg 124;1015 (2017)

W. Droog, I.K. Haitsma, A. Andriessen, **M. Klimek**.
Een epidurale "blood patch" zonder bloed, gelatineoplossing als alternatief bij een
verhoogd infectierisico.
Ned Tijdschr Anesthesiol 30; 174-7 (2017)

M. Heesen, S. Weibel, P. Kranke, **M. Klimek**, R. Rossaint, LR Arends:
Epidural volume extension - a reply.
Letter
Anaesthesia 73;645-6 (2018)

M. Heesen, **M. Klimek**, G. Imberger, S.E. Hoeks, R. Rossaint, S. Straube:
On differences between systematic reviews.
Letter
Brit J Anaesth 120;1133-4 (2018)

P.M.L.A. van den Bemt, **M. Klimek**, T. van Gelder.
Medicatiefout door gebruik van de merknaam.
Ned Tijdschr Geneeskunde 162;D2542 (epub ahead 2018)

V. Invited lectures:

Lokale Anesthesie – wat de huisarts moet weten
Bijscholing voor huisartsen in dermatiologisch Chirurgie
Rotterdam, 12.01.2016

Een Incident – wat nu?
E-cursus van de NVA
Utrecht, 29.01.2016

Reanimaties op het witte doek – wat klopt in Film en TV?
Studio Erasmus ivm. Rotterdam Film-Festival
Rotterdam, 02.02.2016

Neurofysiologie
EDAIC-Cursus der NVA
Amersfoort, 08.03.2016

De patiënt met een hyper- of hypothyreoidie
CEEA-Cursus
Den Haag, 11.03.2016 en 18.03.2016

Anesthesie en het brein
50 jaar academische Anesthesiologie in Rotterdam
Rotterdam, 19.03.2016

Neuroanesthesie
D-Cursus / NVA-cursus
Doorwerth, 12.04.2016

Leadership and followership
7th NWAC (Networking World Anesthesia Convention)
New York, 21.04.2016

Cultural and sexual diversity in perioperative care (team and patients)
7th NWAC (Networking World Anesthesia Convention)
New York, 21.04.2016

The second victim – debriefing incidents and caring for the care provider
7th NWAC (Networking World Anesthesia Convention)
New York, 21.04.2016

Implementing change – how to do it.
7th NWAC (Networking World Anesthesia Convention)
New York, 21.04.2016

The patient with too much and too little blood in his brain in a general hospital without neurosurgeons.
7th NWAC (Networking World Anesthesia Convention)
New York, 22.04.2016

Best of literature in Neuroanesthesia from the last year
7th NWAC (Networking World Anesthesia Convention)
New York, 23.04.2016

Besser werden durch Fehler – Inzident-Analyse in der Praxis
1es CIRS-symposium des Universitäts-Klinikum Mannheim
Mannheim, 31.05.2016

Lokoregionale Anesthesie van Schedel en Gezicht
Face it – Operatiecursus voor Dermatologen
Rotterdam, 10.06.2016

The Patient with Increased ICP – What to do and what NOT to do?
11th Pan Arab Congress of Anaesthesia
Dubai, 10.11.2016

Anaesthesiological Management of Patients with Cervical Spine Injury
11th Pan Arab Congress of Anaesthesia
Dubai, 11.11.2016

Professionaliteit voor Geneeskundestudenten
Expert-meeting georganiseerd door "De Geneeskundestudent"
Bussum, 22.02.2017

Wat doet de anesthesioloog bij de wakkere craniotomie, waar ook de niet-neuroanesthesioloog iets aan heeft?
CEEA-cursus
Antwerpen, 03. & 10.03.2017

Bloed-Gas-Analyse
EDAIC-cursus van de NVA
Doorwerth, 07.03. & 12.09.2017

(Semi-)elective surgery at night – a risk for the patient and/or the doctor?
7th Erasmus Master Class in Anesthesia and Perioperative Care EMCAP
Rotterdam, 31.03.2017

Was kann der Anästhesist tun, um Wundinfektionen zu verhindern?
Vortragsabend im Klinikum Friedrichshafen
Friedrichshafen, 18.04.2017

Diversiteit en veiligheid
Workshop op de student-docent-dagen van het Erasmus MC
Rotterdam, 18.05.2017

Wir müssen reden… Zwischenfälle und Kommunikation
5. Kölner QM-Tag der Universitätskliniken Köln
Köln, 14.09.2017

Anesthesiologie – meer dan alleen slapen…
Proefcollege op de orientatiedag voor aankomende studenten
Rotterdam, 04.11.2017

Professional issues (Disruptive behaviour, drug dependency, distraction, burnout, resilience etc.)
10th Post-ASA-meeting
Amsterdam, 09.11.2017

Wat een gynaekoloog over anesthesie wil en moet weten, maar niet durft te vragen…
Landelijke opleidingsdagen Gynaekologie
Houten, 07. & 08.12.2017

Anesthesie - meer dan alleen maar slapen
Open dag Bacheloropleidingen Erasmus MC
Rotterdam, 07.04.2018

Neuroanesthesie
D-Cursus van de NVA
Doorwerth, 10.04.2018

Echte Helden melden - Fehler-Kultur und Inzidentenmanagement im Universitätsklinikum Rotterdam
SANA-Kliniken - Qualitätsforum
Ismaning 13.04.2018

Incident reporting - the Rotterdam approach
Experience Day Erasmus MC
IHI International Forum Quality & Safety in Healthcare
Rotterdam, 02.05.2018

VI. Organisation/Chairman of scientific meetings:

Dagvoorzitter en moderator
Jaarlijks congres van de NVAM
Ede, 16.01.2016

2 Workshops: EPA's – ook al in de co-schappen?
Onderwijsmiddag voor docenten van het Erasmus MC
Rotterdam, 10.03.2016

Coordinator wetenschappelijk programma:
50 jaar academische Anesthesiologie in Rotterdam
Rotterdam, 19.03.2016

EMCAP (7th International Erasmus Master Class on Anesthesia and Perioperative Care: Patient with organ failure)
Rotterdam, 31.03. & 01.04.2017

Dagvoorzitter
Inspiratiedag Patientveiligheid
Rotterdam, 14.11.2017

Chairman Site Visit & Chairman Workshop Incident Analysis
Experience Day Erasmus MC
IHI International Forum Quality & Safety in Healthcare
Rotterdam, 02.05.2018