TOTAL INTRAVENOUS ANESTHESIA: ADVANTAGES FOR INTRACRANIAL SURGERY

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OBJECTIVE: Although volatile anesthetics have been widely accepted in anesthetic management for neurosurgery, they reduce vascular resistance, resulting in increased cerebral blood flow and increased intracranial pressure (ICP). In patients with elevated ICP who undergo craniotomy, the increase in ICP during surgery from inhaled anesthetics can make the surgery more difficult, thereby increasing the risk of ischemic cerebral insults. Total intravenous anesthesia (TIVA) using propofol and analgesic drugs (remifentanil or fentanyl) and excluding simultaneous administration of any inhaled drugs is being used in patients undergoing craniotomy because of its potential to reduce ICP and ease access to the operative site.

METHODS: We reviewed the literature and describe our experience with TIVA, with emphasis on hemodynamic stability, effects on ICP, emergence from anesthesia, extubation times, and return of cognitive function in patients undergoing craniotomy for space-occupying lesions.

RESULTS: TIVA with propofol is similar to inhaled anesthetics with regard to hemodynamic stability, emergence times, extubation times, early cognitive function, and adverse events. In several prospective, randomized clinical trials, evidence suggests that ICP is decreased and cerebral perfusion pressure is increased in patients receiving TIVA when compared with those receiving volatile anesthetics during elective craniotomy procedures.

CONCLUSION: The impact of TIVA on ICP, brain swelling, and access to the operative site in patients with severely elevated ICP has yet to be evaluated and is the subject of a future study at our institution.

KEY WORDS: Anesthesia, Inhalants, Intravenous, Propofol

Anesthesia for neurosurgical patients undergoing intracranial procedures should provide hemodynamic stability, reduce cerebral metabolism, preserve cerebral autoregulation, avoid increases of intracranial pressure, and guarantee rapid recovery (36, 61, 69). In the last few years, volatile anesthetics (isoflurane, sevoflurane, and desflurane) combined with synthetic opioids (remifentanil and fentanyl) have been used most frequently for neurosurgical procedures because these combinations allow for rapid recovery and prompt neurological assessment (36, 61, 63). However, volatile anesthetics have been shown to affect cerebral autoregulation (38) and intracranial pressure (ICP) (36, 60), which can make the surgery more difficult and dangerous, increasing the risk of ischemic cerebral insults.

The benefits of total intravenous anesthesia (TIVA), which is defined as the combination of an intravenous hypnotic agent (e.g., propofol) and a synthetic opioid (e.g., fentanyl or remifentanil), excluding simultaneous administration of any inhaled drugs (7, 8, 50), are well recognized. TIVA with propofol-remifentanil is similar to inhaled anesthesia in that it has a short half-life, and therefore allows rapid recovery from surgery (5, 36). Because TIVA has a comparable influence on systemic hemodynamics to inhaled agents (61), the reduction in cerebral blood flow (CBF) with increase in cerebral vascular resistance seems to make TIVA the more advantageous anesthesia technique for patients with increased ICP (27, 36, 48, 63, 64). We performed a comprehensive literature review by searching PubMed using various combinations of the keywords "TIVA," "total intravenous anesthesia," "propofol," "neurosurgery," and "craniotomy," with emphasis on prospective trials, to evaluate the differences between TIVA and volatile anesthesia with regard to hemodynamic stability, maintenance of cerebral perfusion pressure (CPP), control of ICP, facilitation of a slack brain for surgical dissection, and

smooth, rapid emergence for early neurological assessment. We conclude with a discussion of our experience with TIVA for patients undergoing craniotomy.

History of Intravenous Anesthesia

Total intravenous anesthesia has a long history, beginning with the original report by Pierre-Cyprien in 1872 in which he described his use of chloral hydrate (44). Subsequently, the 1934 introduction of thiopentone into clinical practice popularized intravenous induction of anesthesia (6). In the 1960s, benzodiazepines were introduced; they ultimately proved useful as intravenous agents to relieve anxiety without producing the same degree of sedation as barbiturates. Concurrently, ketamine was introduced as a complete anesthetic in 1966 without the depressant cardiovascular effects previously noted (44). Despite these new uses of medications, intravenous anesthesia remained underutilized as a mode of complete anesthesia because of delayed emergence associated with the use of barbiturates or benzodiazepines during long procedures; additionally, delivery systems were complicated when compared with those for easy-to-administer volatile anesthetics (69).

Propofol, which was introduced in 1977 (30, 31, 67), eliminated most of the disadvantages of the other intravenous agents. As a consequence, and in particular because of its rapid recovery profile, propofol has achieved widespread use. It can provide all of the components (hypnosis, amnesia, and surgical immobility) of a true anesthetic, and when combined with an opioid, it is described as total intravenous anesthesia (TIVA). This combination offers excellent and predictable recovery conditions while minimizing postoperative side effects, especially nausea and vomiting (18).

Anesthetic Agents and General Effects on Increased Intracranial Pressure

The goal of neurosurgical anesthesia is to provide the patient with an adequate anesthetic (amnesia/sedation, hemodynamic stability, and immobility to surgical stimulation) that provides optimal operating conditions (e.g., low CBF, cerebral metabolic rate [CMR], ICP, and minimal brain bulk), neurological protection, and rapid emergence from anesthesia for neurological examination. An ideal agent for patients with intracranial hypertension would decrease ICP by a proportional reduction in both CBF and CMR (69). In general, anesthetic agents suppress CMR, although ketamine and N_2O are notable exceptions (*Table 1*). Increasing plasma concentrations of anesthetics, including barbiturates, isoflurane, sevoflurane, desflurane, and propofol, cause progressive suppression of electroencephalogram (EEG) activity and a concomitant reduction in CMR (44, 55). However, the CMR-CBF relationship is not the same for all anesthetics, so the anesthetic-induced changes in CBF and ICP are also likely a consequence of direct effects on cerebral vascular smooth muscle (e.g., vasodilation and alteration of autoregulatory function).

Minimum alveolar concentration (MAC) is a unit that describes the steady-state alveolar end-tidal concentration of volatile anesthetic that results in immobility in response to sur-

TABLE 1. Specific effects of selective anesthesia used in neuro-anesthesia

Drug	Affected parameter	
	Cerebral blood flow and intracranial pressure (reference no.)	Cerebral metabolic rate (reference no.)
Ketamine	Increase (28, 69)	Increase (28, 69)
Nitrous oxide	Increase (19, 47, 51)	Increase (21)
Halothane	Increase (1, 42)	Decrease (34)
Enflurane	Increase (33, 62)	Decrease (33, 62)
Isoflurane	Increase (1, 15)	Decrease (35)
Desflurane	Increase (33, 62)	Decrease (33, 62)
Sevoflurane	Increase (33, 62)	Decrease (4)
Thiopental	Decrease (69)	Decrease (69)
Etomidate	Decrease (69)	Decrease (69)
Propofol	Decrease (52, 66)	Decrease (16, 52, 66)

gical incision in 50% of patients. For example, 1.3 to 1.5 MAC provides "general anesthesia" to 99% of all adults. Although volatile anesthetic agents can provide complete general anesthesia, the dose-dependent uncoupling of the CMR-CBF relationship limits the use of more than 0.5 to 0.8 MAC of volatile anesthetic supplemented with the use of short-acting (fentanyl) and ultra-short-acting (remifentanil) synthetic opioids. During administration of 0.67 MAC of volatile anesthetic, the cerebral metabolism is decreased 56 to 74% while the CBF and cerebral blood volume are unchanged from that of an unanesthetized patient (26). In contrast, at an equal anesthetic depth, propofol produces a 50 to 68% decrease in cerebral metabolic rate, a 53 to 70% decrease in CBF, and a 25% decrease in cerebral blood volume (26). Thus, the combination of propofol-remifentanil may provide a more satisfactory result for patients with intracranial space-occupying lesions, mass-related cerebral edema, or intracranial bleeds than the combination of a low-dose volatile anesthetic with remifentanil.

Volatile or Inhaled Anesthetics

All volatile anesthetics suppress cerebral metabolism in a dose-related manner (33, 62) in addition to having a direct effect on vascular smooth muscle that results in vasodilation. The net effect is therefore a competition between a reduction in CBF caused by CMR suppression and augmentation of CBF as a result of direct cerebral vasodilation (44).

Halothane has been demonstrated to produce cerebrovasodilation that in turn is associated with an increase in ICP (2, 13, 23). Studies have demonstrated that isoflurane minimized CBF when compared with halothane (10, 62). Because it was assumed that the effect on ICP was directly a result of effects on CBF, isoflurane became a preferred volatile anesthetic for neurosurgical cases based on initial findings that it caused lesser changes in CBF (10). This dogma held until the first comparative studies on ICP effects of anesthetics

were reported. In 1987, Scheller et al. (57) examined the ICP effects of halothane and isoflurane given to morphine/N_2O-anesthetized rabbits with preexisting intracranial hypertension. Although isoflurane may have limited the increase in CBF as compared with halothane, no ICP differences between the groups were noted (57). Today, it is generally accepted that the order of vasodilating potency among the volatile anesthetics is approximately halothane > enflurane > desflurane ~ isoflurane > sevoflurane (*Table 1*) (10).

The addition of N_2O, which is a potent cerebral vasodilator, causes or exacerbates increases in CBF and ICP when given alone or in combination with a volatile agent (3, 9, 25). Although no uniform agreement regarding the effect of N_2O on CMR has been reached, evidence suggests that the vasodilatory action of N_2O can be clinically significant in neurosurgical patients with reduced intracranial compliance (21). In circumstances in which ICP is persistently elevated or the surgical field is persistently "tight," N_2O should be viewed as a potential contributing factor (*Table 1*) (44).

Barbiturates

Like other central nervous system depressants, barbiturates have potent effects on CMR. Several studies in the 1970s demonstrated the effect of barbiturates to be a dose-related depression in CMR, which produces progressive slowing of the EEG, a reduction in the rate of adenosine triphosphate (ATP) consumption, and protection from incomplete cerebral ischemia (40, 41). With reduction in CMR comes a parallel reduction in cerebral perfusion, which is seen as decreased CBF and ICP, but the long duration of action of thiopental has limited the use of this drug for purposes other than induction or when burst suppression is needed (*Table 1*).

Propofol

Propofol, on the other hand, clears more rapidly than barbiturates, yet it is also capable of reducing CBF and ICP (66). In patients with normal ICP, propofol has been shown to reduce CMR by 36% and ICP by 30% while minimally decreasing CPP by 10% (54). Normal cerebral reactivity to carbon dioxide and autoregulation are maintained during propofol infusion (22). It may also decrease blood pressure (and hence CPP) after bolus injections (*Table 1*). Although the use of propofol as a neuroprotectant for cerebral ischemia during certain neurosurgical procedures has been advocated, this may be limited to mild ischemic insults (11, 29). For moderate to severe insults with prolonged recovery periods, the neuroprotective effects of propofol fail and are not sustained to the same degree as seen with the use of barbiturates (29).

Opioids

For many years, opioids were assumed to have no important effects on ICP and CBF as long as ventilation was controlled (24). In general, opioids produce modest decreases in CMR and ICP, although the changes are influenced by the concomitant administration of other agents and anesthetics. Opioids decrease CBF when combined with N_2O (63).

Opioids usually have no influence or result in only a small increase in CBF (*Table 1*).

Comparison of Inhaled Anesthesia and TIVA on Hemodynamic Stability and Recovery for Neurosurgical Patients

Many anesthetics have been used during intracranial surgery, but it is impossible to determine whether a single agent or combination of agents is ideal for all situations. In the past few years, the anesthetic regimens of isoflurane with fentanyl, and more recently, of sevoflurane with fentanyl, have been the most frequently used for neurosurgical procedures because they allow for a rapid recovery, prompt neurological assessment and are considered acceptable in terms of short-term outcome (61, 63). However, because volatile anesthetics have been shown to affect cerebral autoregulation whereas propofol anesthesia preserves it, the best choice of anesthetics for neurosurgical patients remains controversial (60). Experimental and clinical studies of recovery time and cerebral hemodynamics including CBF, CMR, and ICP have been conducted during administration of isoflurane, sevoflurane, and propofol anesthesia. In some studies, an increase in ICP and CBF has been found during anesthesia with isoflurane and sevoflurane; however, in other studies of these agents, CBF and ICP were unchanged. In contrast, a dose-related decrease in CBF, CMR, and ICP has been found during propofol anesthesia. Only a few comparative studies demonstrating the effects on emergence time, hemodynamics, and ICP are available, and these are described below.

Van Hemelrijck et al. (65) compared the hemodynamics stability and length of recovery for thiopental-fentanyl-isoflurane-N_2O and propofol-alfentanil combinations. They found a decrease in blood pressure after induction with thiopental sodium was followed by a significant increase in blood pressure and heart rate during intubation. Conversely, blood pressure and heart rate did not change during the propofol-loading infusion. However, the administration of alfentanil was followed by a similar decrease in blood pressure with a return to baseline values during the intubation period. Return of normal orientation and concentration was shorter and more predictable for the patients treated with propofol-alfentanil than for those who were administered thiopental sodium (*Table 2*).

Talke et al. (61) also examined the recovery time from anesthesia by comparing anesthesia induced and maintained with propofol, anesthesia induced with thiopental and maintained with isoflurane, and anesthesia induced with propofol and maintained with isoflurane until the dura mater was closed and then reverted to propofol (during approximately the last 10 minutes of surgery). Background anesthesia using N_2O and fentanyl was carried out among all groups. These authors found all three approaches provided comparable heart rate and blood pressure readings throughout the procedures. Additionally, no significant differences in recovery time among the three groups were observed, although patients in the propofol group tended to have slower recoveries than those in the isoflurane and isoflurane-propofol groups (*Table 2*).

TABLE 2. Comparative trials of total intravenous anesthesia in neurosurgery[a, b]

Series (reference no.)	Study	Patients (no.)	Hemodynamics	Intracranial pressure or brain swelling	Immediate postoperative conditions
Van Hemel-rjick et al. 1991 (65)	Propofol-alfentanil vs. thiopental, isoflurane, fentanyl, and N_2O: open-label, randomized trial to evaluate blood pressure at time of intubation and emergence from anesthesia in patients undergoing brain tumor removal	40	Decrease in blood pressure after induction followed by increase in blood pressure and heart rate in thiopental group; no changes seen with propofol induction	Not available	Return of normal orientation and concentration was faster and more predictable for the propofol-alfentanil-treated patients than for the thiopental patients
Talke et al. 2002 (61)	Propofol vs. isoflurane vs. isoflurane followed by propofol: prospective randomized trial evaluating emergence time and early cognitive function in patients undergoing elective surgery for supratentorial mass lesions	60	No difference in intraoperative hemodynamic stability	Not available	No difference in emergence times, extubation times, or early cognitive function
Fábregas et al. 1995 (12)	Propofol-fentanyl vs. isoflurane-fentanyl: prospective randomized trial to evaluate hemodynamic stability and time to recovery of consciousness in patients scheduled for intracranial surgery who scored over 13 on the Glasgow Coma Scale	58	Propofol group had decreased hypertension in response to intubation	Not available	No difference in emergence times or early cognitive function, but a significantly shorter period to extubation for the isoflurane group for surgeries lasting longer than 3 hours
Magni et al. 2005 (36)	Sevoflurane-fentanyl vs. propofol-remifentanil: prospective randomized trial evaluating emergence time and early cognitive function in patients undergoing elective supratentorial craniotomy	120	Significantly more hypotension and hypertension in propofol patients	No significant difference in brain swelling, which was present in 7 patients with sevoflurane and 5 with propofol	No difference in emergence times, extubation times, or early cognitive function
Weninger et al. 2004 (70)	Propofol-remifentanil (target controlled infusion and manually administered) vs. sevoflurane-methohexitone: prospective single-blind study to compare hemodynamics, recovery time, and side effects in patients undergoing stereotactic biopsy of brain tumor	51	Target controlled infusion of total intravenous anesthesia required less hemodynamic intervention than manual administration of total intravenous anesthesia or administration of sevoflurane	Not available	No significant difference between groups to orientation
Todd et al. 1993 (63)[c]	Propofol-fentanyl vs. isoflurane-N_2O: prospective randomized trial to evaluate clinical differences in patients undergoing elective removal of supratentorial mass lesion	121	No significant differences	No clinically important differences in mean intracranial pressure measured via the first burr hole, but 9 patients in the isoflurane-N_2O group had intracranial pressure that measured 24 mmHg or higher, compared with 2 patients in the other group	No difference in emergence times or early cognitive function
Petersen et al. 2002 (48),[c] 2003 (49)	Propofol vs. isoflurane vs. sevoflurane (all with fentanyl): prospective randomized trial for evaluation of intracranial pressure for patients undergoing elective craniotomy for supratentorial tumors	117	Not available	After bone removal, decreased median intracranial pressure, increased median cerebral perfusion pressure, and decreased swelling after dural opening for propofol compared to others; no difference in PCO_2, temperature, tumor size, or midline shift between groups	Not available
Stilling et al. 2005 (58)[c]	Propofol-fentanyl vs. isoflurane-fentanyl: prospective randomized trial evaluating intracranial pressure, cerebral perfusion pressure, and cerebral swelling in children undergoing surgery for supra- and infratentorial mass lesions	48	Not available	No significant difference in mean intracranial pressure measured after bone removal, but cerebral perfusion pressure and mean arterial pressure decreased in the isoflurane group; no difference in PCO_2, temperature, tumor size, or midline shift between groups	Not available
Wong et al. 2006 (71)[d]	Propofol-remifentanil: prospective evaluation of postoperative complications for total intravenous anesthesia for elective neurosurgeries	145	Not available	Not available	Rapid return of consciousness and extubation without any respiratory complications

[a] PCO_2, partial pressure of carbon dioxide.
[b] Trials are listed in the order in which they appear in text.
[c] Actual intracranial pressure monitoring was performed.
[d] Included some patients who underwent neurosurgeries other than craniotomies.

Fàbregas et al. (12) analyzed hemodynamic stability and recovery time without the complicating effects of N_2O for patients who underwent resection of supratentorial masses. Patients in both treatment groups were induced with thiopental and given fentanyl for analgesia. Treatment groups were divided according to maintenance anesthesia using either propofol or isoflurane. The authors found that systolic and mean arterial pressures after induction decreased significantly in both groups compared with baseline values. In congruence with previously cited studies, emergence time and time to extubation were shorter for the patients administered isoflurane (Table 2).

Magni et al. (36) compared sevoflurane-fentanyl against propofol-remifentanil in patients undergoing craniotomy for supratentorial expanding lesions. The primary goal of this study was a comparison of early postoperative recovery and cognitive function between the two groups. In addition, hemodynamic events were analyzed and compared. The investigators found that mean recovery times and extubation times were similar between the two groups. The incidence of hypotension was greater in the propofol-remifentanil group, which is consistent with results published by Ozkose et al. (46). Heart rate and mean arterial blood pressure both decreased significantly after induction and during maintenance of anesthesia in the propofol group. In addition, no difference in early cognitive function during recovery of anesthesia was observed. The authors did find an excess of postoperative hypertensive episodes during recovery and in the postoperative period in those patients treated with propofol, which was consistent with the results from a previous study by Guy et al. (17).

Weninger et al. (70) analyzed whether the addition of a target-controlled infusion (or pharmokinetic model-driven, computer-controlled pump) system, which is purported to administer a smooth and controlled dosage of propofol anesthesia, had any effect on hemodynamics and the postoperative recovery period compared with either propofol administered by a manual technique or methohexitone-sevoflurane. In this study, remifentanil was used as a background analgesic component for all groups. The hemodynamic effects were found to be similar between all groups. All treatments decreased heart rate, systolic blood pressure, and diastolic blood pressure, although the need for intervention was slightly greater in the sevoflurane and manual propofol groups than in the target-controlled infusion propofol group (Table 2).

Wong et al. (71) analyzed postoperative hemodynamic and adverse effects associated with TIVA using propofol and remifentanil. They reviewed five different types of elective neurosurgical procedures (supratentorial craniotomy, posterior fossa craniotomy, intracranial vascular procedures, transsphenoidal hypophysectomy, and extracranial procedures). These investigators found a rapid return of consciousness and a low incidence of respiratory complications. In addition, they found that shivering, postoperative nausea and/or vomiting, and postoperative hypertension occurred in a significant percentage of all patients analyzed, with the overall most adverse effects identified in patients who underwent posterior fossa surgery or intracranial vascular surgery. The overall rate of these side effects was significantly related to the anesthetic time.

Comparison of the Effects of Inhaled Anesthesia and Total Intravenous Anesthesia on Intracranial Pressure

With a focus on the effects of ICP, Todd et al. (63) performed a prospective comparative trial of three anesthetics based on their widely differing cerebrovascular effects. One group of patients received isoflurane-N_2O (no intravenous drugs other than thiopental for induction), the second group received a pure intravenous anesthetic with propofol and fentanyl, and the third group received a fentanyl-N_2O-isoflurane combination. After the end-tidal carbon dioxide was adjusted to 30 mmHg, a burr hole was drilled into the cranium, an ICP transducer was placed into the epidural space, and readings were measured for 1 to 3 minutes. They showed no statistically significant intergroup differences for ICP measurements, even though more patients in the isoflurane-N_2O group had ICP that was higher (by 24 mmHg or more) than in the other two groups. In addition, the authors found that the fentanyl-N_2O group had the most rapid emergence time but also had a higher frequency of vomiting during this postoperative period. No differences in postoperative deficits, total hospital stay, or costs were appreciated (Table 2).

Petersen et al. (48) investigated possible differences in subdural ICP in patients treated with either propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. In this study, subdural ICP was measured after removal of the bone flap in patients undergoing elective craniotomy for cerebral supratentorial tumors. ICP alone was found to be significantly lower and CPP was found to be significantly higher in the propofol group than in the isoflurane and sevoflurane groups. Additionally, the arteriovenous difference of oxygen content was determined using a jugular-dwelling catheter and was found to be higher for the propofol group than for the isoflurane and sevoflurane groups. Through extrapolation of this data, cerebral blood volume and the vasodilatory effects of propofol were concluded to be less than those of either isoflurane or sevoflurane. In a follow-up article, Petersen et al. (49) showed that hyperventilation decreased ICP more in patients treated with isoflurane and sevoflurane than in patients treated with propofol. They surmised that carbon dioxide reactivity is maintained during administration of volatile agents but not with propofol. Their findings opposed the results of a previous experiment that showed carbon dioxide to be directly related to CPP (20).

Stilling et al. (58) examined the effects of TIVA on ICP, CPP, and cerebral swelling in children undergoing posterior craniotomy, in which the patient is placed in the prone position. Two forms of anesthesia were compared: isoflurane-N_2O-fentanyl and propofol-fentanyl. The authors found no significant difference in ICP when patients receiving isoflurane and propofol were compared; however, mean arterial pressure and CPP were found to be significantly lower in the isoflurane group. Furthermore, the tension on the dura mater and the degree of cerebral swelling were comparable between the two groups.

Utah Experience with Total Intravenous Anesthesia in Patients with Elevated Intracranial Pressure

In cranial base and neurovascular operations at the University of Utah, we have moved toward using TIVA (e.g., propofol-remifentanil) to minimize the brain bulk while providing an environment that is conducive to intraoperative neurophysiological monitoring. Using an eight-channel EEG (Cadwell Cascade; Cadwell Laboratories, Kennewick, WA) in a monopolar montage (F3, F4, C3, C4, P3,P4, T5, and T6, referred to as CZ) along with an esophageal-placed temperature probe (Mona-Therm; Mallinckrodt, St. Louis, MO), the depth of anesthesia along with cooling and/or warming of the patient are adjusted to optimize neuroprotection.

In most cases, a bolus injection of propofol (1–2 mg/kg) in combination with a remifentanil infusion (0.1–0.5 µg/kg/min) is used for induction of anesthesia. This is followed by a short period during which an infusion of remifentanil (0.05–0.15 µg/kg/min) is combined with a low dose of volatile anesthetic (0.5–0.8 MAC desflurane or isoflurane) along with hyperventilation to an arterial carbon dioxide tension of 28–32 mmHg while arterial and venous cannulae are placed and the patient is positioned. Soon after the skin incision is made, the volatile anesthetic is discontinued, and a propofol infusion (100–150 µg/kg/min) is added to a lower dose of remifentanil (0.05–0.1 µg/kg/min). With the concomitant administration of 50 g of mannitol and 20 mg of dexamethasone, most patients have a brain that is relaxed and amenable to dural opening and deep dissection with minimal retractor pressure. In those situations in which the brain is still full (e.g., subarachnoid hemorrhage, posterior fossa or middle fossa cranial base mass), the anesthetic is deepened by increasing the propofol infusion to a dose that produces a mild amount of EEG burst suppression (150–225 µg/kg/min) while decreasing the remifentanil infusion (≤0.1 µg/kg/min).

A few patients develop hypotension as a result of these higher propofol infusion rates (59). In these patients, an intravenous fluid bolus (5–7 ml/kg colloid) is administered to ensure euvolemia, and if this is unsuccessful in normalizing the blood pressure, a low-dose phenylephrine infusion is administered to maintain adequate cerebral perfusion and prevent hypotension-induced reflexive cerebral arterial dilation. If cerebrospinal fluid can be removed to slacken the brain, the high-dose propofol infusions are decreased to normal maintenance levels (100–150 µg/kg/min). On the other hand, in those patients in whom focal neurological injury is a concern, the mild amount of EEG burst suppression is continued until the surgical resection of the mass or the clip ligation of the aneurysm is completed.

To facilitate rapid emergence from anesthesia, as the dural closure is begun, the propofol infusion is often discontinued and a low dose of volatile anesthetic (0.5 MAC desflurane or isoflurane) is added to the remifentanil infusion (0.1–0.15 µg/kg/min). In the rare situation in which the brain is still full before dural closure and despite drainage of cerebrospinal fluid, the propofol infusion is continued at a lower infusion rate (80–100 µg/kg/min). In either case, the decreased infusion rate of propofol allows for more rapid clearance of propofol to subhypnotic concentrations. Upon removal of the Mayfield frame, the hypnotic agent (propofol or volatile anesthetic) and the remifentanil are both discontinued. In most situations, the patient emerges from anesthesia in less than 10 minutes.

We have found a substantial improvement in operating conditions in our patients with cranial base masses and intracranial hemorrhages, and therefore we have recently incorporated a similar technique with three other patient populations. Because of the lack of age-related cerebral atrophy, young patients (younger than 50 years) undergoing craniotomy for the placement of subdural grid electrodes for planning resection of medically refractory epileptic lesions seem to benefit from the switch to a TIVA from a traditional anesthetic. During posterior fossa craniotomies for the treatment of trigeminal neuralgia or cranial base tumor resection (vestibular schwannoma, meningioma), the improved brain relaxation may limit the retractor-related injury of normal brain. Finally, in patients with traumatic brain injury or intracerebral hemorrhage, TIVA may provide the optimal cerebral hemodynamic state for the injured brain by providing enhanced brain relaxation and preserving cerebral autoregulation to all the physiological determinants of CBF. The pharmacodynamics of propofol are akin to those of phenobarbital, whereas the pharmacokinetic profiles of propofol and remifentanil provide a significantly more rapid emergence and more hemodynamic stability than observed with phenobarbital comas.

We have observed improved brain relaxation with TIVA relative to that achieved with a balanced volatile-opioid anesthetic. This may be because we have used TIVA for cranial base mass lesions and vascular lesions, whereas most trials comparing anesthetics have been limited to the more common supratentorial tumors. Furthermore, trials that compare brain relaxation between anesthetic techniques generally include heterogeneous groups of patients with a variety of lesions. These patients are assigned to receive a single anesthetic and the resultant cerebral hemodynamic parameters are compared between groups. Because each of the groups contains a variety of lesion types, lesions with a wide range of cerebral edema, and lesions in a vast number of different locations (even if limited to supratentorial lesions), the variability in the baseline cerebral hemodynamic parameters makes these studies underpowered to determine whether a patient with a given lesion will have a small or large change in cerebral hemodynamics. To rigorously determine whether TIVA quantitatively or qualitatively improves cerebral hemodynamics, a cross-over study to determine those patient characteristics that predict an improvement with TIVA must be performed.

Potential Limitations of Total Intravenous Anesthesia

Our technique has several potential limitations. First, for anesthesiologists who are unfamiliar with the use of propofol-remifentanil anesthetics, there is a potential for either delayed emergence because of accumulation of propofol or intra-

operative awareness as a result of inadequate propofol plasma concentrations. Using a quantitative processed EEG (e.g., Bispectral Index, Auditory Evoked Potential Index, Specific Entropy, or Patient State Index) as a target for titration of the propofol infusion may limit the occurrences of excessive (14) or inadequate (45) propofol administration. Another potential problem with the use of a propofol infusion is the unpredictable development of propofol-related infusion syndrome (32). Characterized by the development of lactic acidosis, rhabdomyolysis, renal failure, and possibly cardiac failure, this potentially devastating syndrome, nevertheless, has no accurate predictors.

Another potential complication of TIVA is the potential for a large decrease in cerebral blood volume. This becomes significant during stereotactic-guided craniotomies, where brain shift may ensue. This problem may be easily overcome with the availability of intraoperative imaging. Additionally, a large decrease in cerebral blood volume may worsen epidural bleeds; however, the average decrease of the cerebral blood volume with a typical balanced propofol-remifentanil anesthetic is only 25% (26).

Propofol has been shown to have strong anticonvulsant properties and is now widely used in controlling refractory status epilepticus (53). Notwithstanding this, TIVA (propofol) has also been shown to induce seizure activity when used in the context of short-term anesthesia (37, 39, 56, 68).

Finally, despite the advantages of TIVA, there is a substantial cost differential for TIVA when it is compared with inhaled anesthesia. However, the pharmacoeconomic advantages of a drug are certainly not limited to minimizing the drug acquisition costs (43). Perioperative drug costs also depend on the need to use potentially expensive antiemetic agents to counteract the proemetic side effects of many anesthetics as well as on the ability to provide a predictable and fast awakening that facilitates neurological testing and minimizes the need for unplanned (and costly) radiological evaluation.

CONCLUSIONS

We have reviewed the literature to determine whether TIVA offers satisfactory hemodynamic stability, avoids increases of ICP, and ensures rapid recovery with emergence and extubation times and rapid return of cognitive function in patients undergoing craniotomy for space-occupying lesions. Overall, TIVA is similar to volatile anesthetics with regard to hemodynamic stability, emergence times, extubation times, early cognitive function, and adverse events. In several prospective, randomized clinical trials, evidence suggested that ICP is decreased and CPP is increased in patients receiving TIVA relative to those receiving volatile anesthetics in elective craniotomy procedures. Our institutional experience with TIVA in these patients has shown a subjective improvement in brain relaxation and surgical access to the operative site. The impact of TIVA on ICP, brain swelling, and access to the operative site in a study group with severely elevated ICP has yet to be evaluated.

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Acknowledgment

COMMENTS

Cole et al. review the effects of total intravenous anesthesia (TIVA) with propofol and opioids on physiological parameters such as cerebral blood flow (CBF), cerebral perfusion pressure, cerebral metabolic rate, intracranial pressure (ICP), and brain relaxation as noted by the neurosurgeon. The findings are compared with the effects of volatile anesthetic agents. This is a well-written article. The authors make a case for the use of TIVA when brain relaxation is needed, as well as present the disadvantages and complications of TIVA. This article will make many neurosurgeons think about a greater use of TIVA in their practice.

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This interesting review article describes management of the patient undergoing intracranial surgery with TIVA. In the past few years, a considerable number of studies have been performed to compare TIVA and administration of inhaled anesthetics to patients undergoing craniotomy.

There are certain implications in this review article with which we strongly agree. Although TIVA is similar to volatile anesthetics with regard to hemodynamic stability (awakening from anesthesia and adverse events), multiple clinical studies suggest that TIVA is a better alternative when it comes to a decrease in ICP and an increase in cerebral perfusion pressure in elective craniotomy procedures. The authors have observed improvements in operating conditions in their own patients by switching to TIVA; patients have shown improvement in cerebral hemodynamic state, enhancement of brain relaxation, and preservation of cerebral autoregulation. At our institution, we also see this new trend in moving toward TIVA during craniotomies. Patients tolerate intravenous anesthetics without acquiring nausea and vomiting postoperatively, and evoked potential monitoring has also improved secondary to TIVA.

It is important to know that TIVA has potential limitations. As described in the article, TIVA administration has the potential to induce a decrease in cerebral blood volume. Its use also creates a small possibility of development of propofol-related infusion syndrome. Cost-related concerns are mentioned as a controversial issue. As the authors said, "the pharmacoeconomic advantages of a drug are certainly not limited to minimizing the drug acquisition costs." Other factors include the potential decrease in use of anti-emetic agents secondary to counteracting the pro-emetic properties of inhaled anesthetics, and the fast awakening that the patient experiences when TIVA is used.

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In this article, Cole et al. try to respond to the question of which kind of anesthetic is the best choice when a patient's ICP is increased.

Scheller et al. (6) found no ICP differences between isoflurane and halothane administration with cryogenic brain injury in rabbits when ICP was increased to approximately 20 mmHg. In contrast, Fitch and McDowall (1) examined the effects of halothane on ICP using an intracranial expanded balloon. In their study, as ICP increased, so did the negative effects of halothane. On the other hand, Reinstrup et al. (5) identified differences in halothane and isoflurane distribution in human cerebrospinal fluid. Therefore, we think that the cerebral lesion size, the degree of lost compliance, and the localization of the lesion within the brain should be considered to compare halothane and isoflurane.

Guy et al. (2) found that when patients received remifentanil, they required analgesic administration earlier than patients who received fentanyl. Magni et al. (4) and Wong et al. (7) noticed that arterial hypertension was present postoperatively with use of TIVA. We try to treat postoperative hypertension while avoiding a lack of analgesia by administering small doses of fentanyl before the patient wakes up.

Although the neuroprotective effect of propofol is not identical to that of barbiturates. (3), the authors of this article, decided to deepen the anesthesia using propofol at electroencephalograph burst suppression. They believed that TIVA would provide better brain relaxation over the volatile agents. We agree with this, considering that TIVA is superior to volatile anesthetic agents in providing a slack brain, which translates to easier handling of the brain by the neurosurgeon, with only minor ischemia. The Utah experience with administering TIVA to patients with elevated ICP brings a "little light at the end of the tunnel" with respect to the controversies surrounding anesthetic choice for patients with increased ICP. Although there are limitations to using TIVA, they are manageable; otherwise, the authors are thinking academically when they say that at severely elevated ICP, some studies have to be evaluated.

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1. Fitch W, McDowall DG: Effect of halothane on intracranial pressure gradients in the presence of intracranial space-occupying lesions. **Br J Anaesth** 43:904–912, 1971.
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6. Scheller MS, Todd MM, Drummond JC, Zornow MH: The intracranial pressure effects of isoflurane and halothane administered following cryogenic brain injury in rabbits. **Anesthesiology** 67:507–512, 1987.

7. Wong AY, O'Regan AM, Irwin MG: Total intravenous anaesthesia with propofol and remifentanil for elective neurosurgical procedures: An audit of early postoperative complications. **Eur J Anaesthesiol** 23:586–590, 2006.

Cole et al. offer a review of the literature and description of their experience with TIVA in their department at the University of Utah. This is an interesting review, although the benefits of propofol-based anesthesia for craniotomy have been recognized for more than 20 years, and propofol-maintained anesthesia has been widely used for craniotomy in the United Kingdom, Europe, and Australia during that time. In these countries, computer-controlled infusion devices that target constant concentrations of propofol (i.e., Diprifusor; AstraZeneca Pharmaceuticals) have been available for more than 10 years, whereas these devices were not available in the United States. Enthusiasm for TIVA in Australia has also increased since the introduction of the ultra-short acting opioid remifentanil. In our experience, a combination of propofol and remifentanil provides excellent operating conditions with a rapid and smooth recovery from anesthesia, without the need for volatile anesthetics that may increase the risk of nausea and vomiting. It is of note that the authors' recommendation is not entirely "total intravenous anesthesia," as they recommend the use of volatile anesthetics after induction and toward the end of the procedure. Nevertheless, the authors provide an interesting review of the use of intravenous anesthesia in neurosurgical patients.

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The authors review the literature concerning the use of TIVA in patients undergoing craniotomy for neurosurgical problems. Their research is aimed to compare the most significant parameters related to anesthesia (among them ICP, CBF and its autoregulation, metabolism, time to awakening, and hemodynamic stability) in patients treated with TIVA and in patients treated with volatile anesthetics. According to the authors, TIVA seems to positively modify both ICP and CBF with no significant effects on the other parameters. They seem to be oriented toward a superiority of TIVA to other anesthetics.

This conclusion is not shared by most neuroanesthesiologists, and there are several reports in the literature, some of which are quoted also by the authors [1], concluding that there is no evidence of the superiority of one type of anesthetic over another (see, in addition, the recent work of Sneyd et al. [2]). Moreover, the personal experience quoted by the authors is reported only as a general feeling, not as proven evidence founded on numbers; therefore, there is no means of substantiating this opinion. This is particularly important because the authors do not really use "total intravenous anesthesia." In fact, they report that they use volatile anesthetics as well, for some patients and in some moments of anesthesia (not better defined).

I think that this article is an excellent starting point for a prospective study on patients undergoing craniotomies with different anesthesia. Certainly there will be the necessity to measure ICP, CBF, and other metabolic parameters, as well as the clinical results in terms of morbidity and length of hospital stay. This will be particularly interesting as it pertains to patients with increased ICP.

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1. Todd MM, Warner DS, Sokoll MD, Maktabi MA, Hindman BJ, Scamman FL, Kirschner J: A prospective comparative trial of three anaesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide and fentanyl/nitrous oxide. **Anesthesiology** 78:1005–1020, 1993.

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This article is a worthy recipe for a very good intravenous anesthetic; however, it lacks sufficient evidence to support its advantages compared with proven techniques. We agree that TIVA will lower the cerebral metabolic rate and thus improve the operative field. However, it does not improve cerebral protection. A rapidly emerging neurosurgical patient is a worthy goal, but it should not be a blind goal. We believe that the most appropriate anesthetic is the one that is tailored to each patient. This article seems to advocate the overall superiority of TIVA. The technique is useful, but it is only one of many anesthetics available for neurosurgical patients.

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