Safety of neuraxial anesthesia

Evaluation of complications

Bos, E.M.E.

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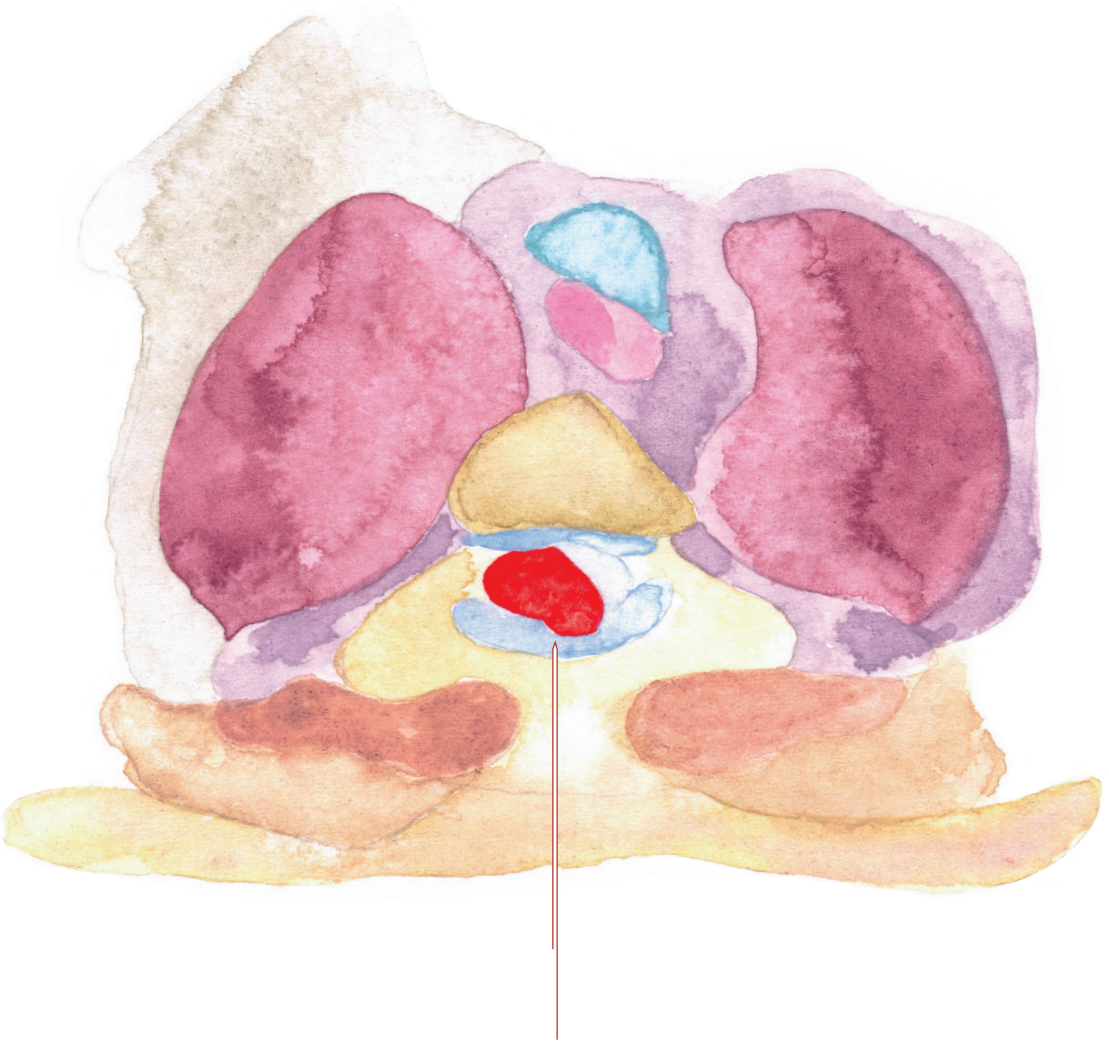

Elke Maria Elisabeth Bos

Safety of Neuraxial Anesthesia
Evaluation of Complications

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Chapter 1

Introduction and outline of the thesis

Introduction

Neuraxial anesthesia is commonly used in the perioperative, obstetric, acute and chronic pain setting. Neuraxial anesthetic techniques comprise epidural analgesia, spinal anesthesia, combined spinal-epidurals (CSE), epidural injection, spinal catheters, spinal cord stimulators, and caudal block. The most prevalent side effects and complications, such as hypotension, nausea or vomiting, pruritus, urine retention and post dural puncture headache, are mostly benign, and can be self-limiting or relatively easy to treat.[1] However, particularly in certain patient categories, there is the possibility of causing permanent and severe harm. Rare complications of neuraxial anesthesia that can lead to permanent neurological deficit are spinal hematoma or abscess,[2] intracranial hematoma or abscess, and meningitis.

Complications of neuraxial anesthesia

The incidence of major complications of neuraxial anesthesia is more common than estimated in past decades. In 1998, the rate of serious adverse events after epidural anesthesia was estimated at 1:150.000.[3] In the meantime, indications for neuraxial anesthesia have changed, patient characteristics have shifted,[4]

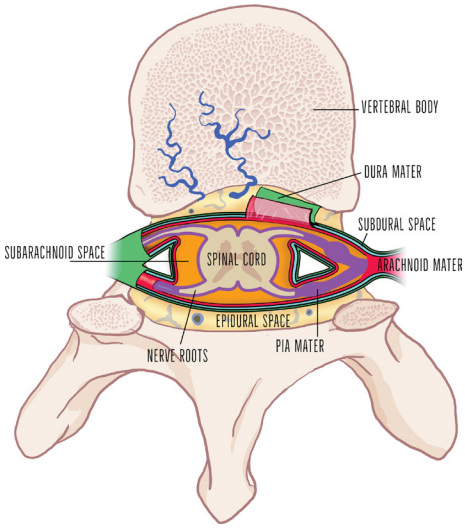

Figure 1. *The anatomy of the spinal canal.* "The epidural, subdural, and subarachnoid spaces are defined by the dura, arachnoid, and pia maters. The epidural space contains fat, the internal venous plexus, connective tissue, and exiting nerve roots. The arachnoid mater is subjacent to the dura mater, and the small subdural space is located between these two layers. The subarachnoid space, also known as the cerebrospinal fluid (CSF) space, is the large space where CSF surrounds the spinal cord, nerve roots, and small vessels. The pia mater closely invests the cord and nerve roots."[13] Reproduced, with permission, from Pierce JL, Donahue JH, Nacey NC, et al. Spinal Hematomas: What a Radiologist Needs to Know. *RadioGraphics* 2018;38:1516–1535.

and awareness has grown.[5] More recent large scale studies have proven that the incidence of severe complications in the perioperative setting may be as high as one per 1.000 – 6.000 epidural procedures, depending on the patient population under consideration.[6-11] With this incidence, the likelihood of encountering these complications is higher than previousy expected.

In a single-center database analysis of prospectively raised data between 1998 and 2006, the risk of a spinal hematoma was 1:4.741 (0.02%) and the risk of a spinal abscess was 1:7.142 (0.014%) in postoperative patients treated with epidural analgesia.[11] A nationwide study published by Rosero and Joshi in 2016, demonstrated that the incidence of spinal hematoma and abscess were one per 5.401 (18.5 per 100.000, 95% CI 16.3 – 20.9 x 10^{-5}) and one per 13.968 (7.2 per 100.000, 95% CI 5.8 – 8.7 x 10^{-5}) epidural catheterizations, respectively, in more than 1.3 million *non-obstetric* epidural analgesic procedures that were identified.[6] The incidence of major complications of neuraxial blocks is much lower in *obstetric* patients, with spinal hematoma estimated at 1:154.730 and spinal abscess too rare to calculate in the large trial of Rosero and Joshi.[6] Intracranial complications are even less prevalent, making it impossible to estimate the true incidences.

Besides the incidence of severe complications, also ultimate patient outcome is of importance. In the UK, the Third National Audit Project of the Royal College of Anesthetists found that permanent injury after neuraxial block caused by spinal hematoma or abscess, but also by meningitis, nerve injury, spinal cord ischemia, fatal cardiovascular collapse or wrong-route errors, was 1:23.810 cases (4.2 per 100.000), and the incidence of the two worst possible complications, paraplegia or death, was 1:55.556 cases (1.8 per 100.000).[5]

This thesis focuses mainly on hematoma, abscess and meningitis; spinal hematoma and abscess when complications occur below the level of C0, see Figure 1, and intracranial hematoma and abscess when complications occur above the level of C0. The space-occupying lesions may occur in the epidural space, subdural space, subarachnoid space or in the intramedular or intraparenchymal tissue. Even though hematoma, abscess and meningitis

are diverse pathophysiological entities, we focused on these complications as pro-active management may prevent or reduce the severity of unfavorable outcomes.[12]

Aims of this thesis

Severe complications of neuraxial anesthesia occur in a heterogeneous patient population, therefore, decision making is tailored to the individual patient and treatment of complications is based on expert-opinion. This thesis aims to provide evidence-based insight on patient characteristics, neuraxial block characteristics and treatment strategies of severe complications of neuraxial anesthesia. Furthermore, we aim to improve the clinical selection of appropriate patients for neuraxial anesthesia and to improve the diagnostic process in case complications of neuraxial anesthesia are suspected.

Studies in this thesis:

- Investigate the circumstances under which complications most likely occur.
- Investigate clinical factors that predict persistent neurological damage.
- Investigate the indication and timing of neurosurgical management.
- Investigate neuraxial anesthesia practice and the diagnostic process of complications in the Netherlands.

Hypotheses of this thesis

Hypotheses of this thesis are:

- The risk and consequences of spinal hematoma and abscess is related to patient characteristics, including age, medication use and comorbidities.
- Neurological outcome is dependent on the severity of neurological symptoms at the time of treatment.
- Neurological outcome is dependent on timely diagnosis and management of complications.

Outline of this thesis

PART 1 – SAFETY OF EPIDURAL ANALGESIA

The safety of epidural analgesia and the safety of drugs used for epidural analgesia are addressed in **Chapter 2** and **Chapter 3** of this thesis. **Chapter 2** is a narrative review critically acclaiming the risk-benefit ratio for epidural analgesia by discussing the literature that focuses on the use of epidural analgesia for acute, labor and chronic pain. **Chapter 3** is an expert opinion article discussing the safety of the most widely used epidural drugs. The article focuses on potential neurotoxicity, side effects, and complications in the adult, non-pregnant population.

PART 2 – COMPLICATIONS OF NEURAXIAL ANESTHESIA

The second part of this thesis addresses complications of neuraxial anesthesia. **Chapter 4** is a systematic review that summarizes patient characteristics, symptoms, treatment and outcome of patients with spinal hematoma and abscess associated with neuraxial blocks. Also, the optimal timing of surgical decompression of hematoma or abscess is explored and risk factors for post-operative morbidity as described in the literature are identified. In **Chapter 5** we describe a systematic review of intracranial complications for which a similar approach was used as for the analysis of spinal complications (**Chapter 4**). **Chapter 6** describes a closed claims analysis, that focused on claims of hematoma, abscess or meningitis after neuraxial anesthesia with the aim to identify potential preventable causes in patient-related, neuraxial procedure-related and treatment-related characteristics of these complications. Closed anesthesia malpractice claims from the USA and the Netherlands from 2007 until 2017 were examined. **Chapter 7** is a short commentary discussing the results of a technical analysis – simulating extreme forces – investigating the vulnerability of epidural needles by analyzing the force needed to deform or break an epidural needle.

PART 3 – TRENDS IN NEURAXIAL ANESTHESIA PRACTICE

In the final part of this thesis, **Chapter 8,** we describe the results of our survey that evaluated trends in neuraxial anesthesia practice, key indications, safety measures, safety reporting, and management of complications of epidural analgesia in the Netherlands.

Chapter 9 summarizes the findings of the studies bundled in this thesis and discusses future perspectives. **Chapter 10** includes the summary and future perspectives in Dutch.

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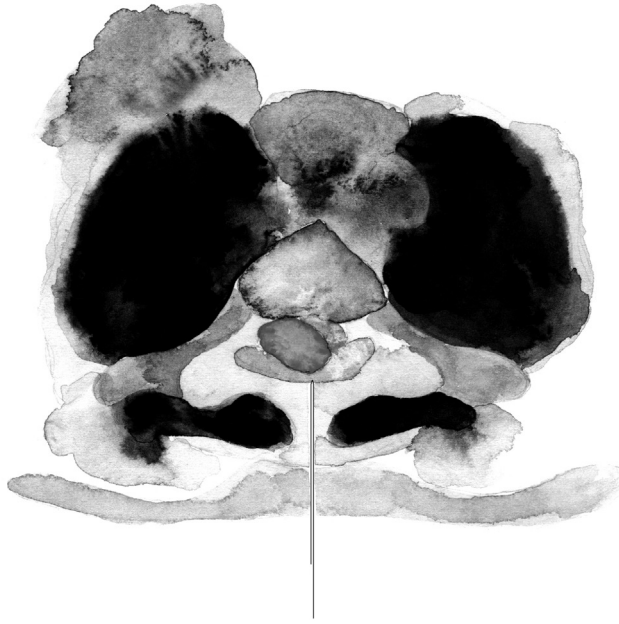
PART 1

Safety of Epidural Anesthesia



Chapter 2

Safety of Epidural Anesthesia

Elke M.E. Bos, Markus W. Hollmann, Philipp B. Lirk

Current Opinion in Anesthesiology

Abstract

Purpose of review – Epidural analgesia remains a widely used analgesic technique. This article aims to assess the safety of epidural analgesia by balancing efficacy and complications, of epidural analgesia for acute, labor and chronic pain.

Recent findings – Main indications for epidural analgesia include major open abdominal surgery, thoracotomy and labor analgesia. Past and current literature show that epidural analgesia leads to statistically significant, but possibly clinically less meaningful, reductions in pain scores compared with intravenous analgesia. The debate continues whether epidural analgesia leads to decreased complications and improved outcome. Non-inferiority of alternative regional analgesic approaches, that is continuous wound-infiltration, peripheral nerve blocks or surgical site infiltration, appears to be present and is promising for the future. Serious adverse events after epidural analgesia seem to occur more often than was previously thought and clinicians must realize that incidence rates differ in specific perioperative patient populations.

Summary – Epidural analgesia for obstetric analgesic purposes is considered to be well tolerated in young, healthy women, since efficacy has been proven and complications leading to permanent neurological damage seldomly occur. Safety of epidural analgesia for perioperative and chronic pain treatment is more difficult to balance; careful selection of appropriate patients cannot be over-emphasized.

Keywords – acute pain, chronic pain, efficacy, epidural analgesia, labor analgesia

Keypoints

- The risk-benefit ratio for epidural analgesia has been critically acclaimed, and overall, the number of solid indications has declined.
- Main indications for epidural anesthesia/analgesia are labor, major open abdominal surgery and thoracotomy.
- Epidural analgesia is still gold standard for labor analgesia, the main argument against remifentanil patient-controlled-analgesia being the high incidence of respiratory depression.
- In the chronic pain population, epidural anesthesia is chosen based on individual risk–benefit assessment and incidences of complications are difficult to assess due to the paucity of structured studies.

Introduction

Over the years, the use of epidural analgesia has been fluctuating with periods of major popularity and periods of increasing concern regarding possible severe complications of the anesthetic technique.[1] However, epidural analgesia is still considered superior to intravenous analgesia in several surgical settings and during labor[2-5,6**,7,8] and remains a widely practiced analgesic technique worldwide.

When assessing the safety of epidural analgesia, two important aspects can be evaluated; on the one hand, the presence of possible complications due to the technique and on the other hand the protective measures that has been established to prevent patients from the consequences of possible complications. This review is written to assess the safety of epidural analgesia and to give an update on the efficacy, complications, treatment and outcome of complications after epidural analgesia for acute, labor and chronic pain.

Acute Pain (perioperative and trauma)

Efficacy

The excellent analgesic effect of epidural analgesia is well established[4,6**,7,8,9*] and is not necessarily the focus of current literature. Main indications for epidural analgesia include major open abdominal surgery [4,5,6**,8,10] and open-chest surgery (thoracotomy).[11,12,13**,14**] In addition to its use in treating acute postoperative pain, epidural analgesia may be effective in reducing chronic post-thoracotomy pain, a critical endpoint for thoracotomy patients.[12] Epidural analgesia compared with general anesthesia with postoperative systemic opioid-based analgesia for adults undergoing elective abdominal aortic surgery reduced visual or verbal analogical scale (VAS) scores up to 3 days after surgery [mean difference -1.78 (95% confidence interval (CI) -2.32 to -1.25); I^2=0% for VAS scores on movement on postoperative day one].[15]

Possible additional benefits of epidural analgesia, for example accelerated recovery and decreased postoperative complications, remain a field of interest for those preferring epidural analgesia,[2-5,6**,7,8,10,11,16-21] even though opponents heavily debate the presence of these benefits and even consider an unfavorable influence of epidural analgesia on the perioperative course.[9*,13**,22-25,26**,27-30] Furthermore, effectiveness ranges from 82 to 91%[5], with an epidural failure rate of up to 30% in the perioperative setting.[31]

Keeping possible complications, side effects and failure rates in mind, current research focuses on alternatives for epidural analgesia with similar effects on perioperative pain control. For example, in laparoscopic colorectal surgical interventions and in major orthopedic procedures (total knee arthroplasty), epidural analgesia does not seem to offer additional clinical benefits compared with alternative analgesic techniques as intravenous analgesia, wound infusion catheter or nerve blocks.[32*,33,34] Moreover, even in certain major surgical procedures with a historical preference for epidural analgesia, that is open hepato-pancreato-biliary surgery,[9*] open liver resection[35] and thoracotomy,[14**, 36-38] continuous wound infiltration or paravertebral block (PVB) was found to be non-inferior to epidural analgesia within an enhanced recovery after surgery setting, in terms of pain scores, opioid side effects and patient satisfaction. Further large-scale trials are required to make a definitive assessment of true non-inferiority in effectiveness of pain control[9*,14**] and, most importantly, in immediate and mid-term patient outcome, such that a change in clinical practice is not to be expected immediately.

Concerning trauma patients, the main indication for epidural analgesia is the treatment of traumatic rib fractures. Patients who receive thoracic epidural analgesia are generally more severely injured and require longer treatments.[39] Malekpour *et al.*[40] retrospectively evaluated records of a National Trauma Data Bank. They found that less than 1.2% of patients with rib fractures received epidural analgesia or PVB for pain control. Significantly, mortality was higher in patients receiving neither epidural

analgesia nor PVB (Odds Ratio (OR) 2.25, *P*=0.002), despite the fact that patients receiving either of the procedures had more severe injuries, as evidenced by higher rates of pulmonary contusion, pneumothorax, hemothorax and a higher median number of fractured ribs.[40] Another study, confirmed similar duration of mechanical ventilation and development of pneumonia in patients treated with epidural analgesia compared with patients treated with continuous intercostal nerve blockade; however, no comparison was made with patients treated without nerve blockade.[41]

Complications

Although historically reported incidences of major complications of epidural analgesia, that is infection, hematoma or direct nerve trauma,[42] were relatively low, current large scale multicenter studies have proven that the incidence of these severe complications may be as high as one per 1.000 – 6.000 epidural procedures, depending on the population under consideration.[23,43,44] A recent nationwide study assessing the incidence of major complications after epidural analgesia is published by Rosero and Joshi.[26**] More than 1.3 million non-obstetric epidural analgesic procedures were identified and the incidence of spinal hematoma and abscess were one per 5.401 (18.5 per 100.000, 95% CI 16.3 – 20.9 x 10^{-5}) and one per 13.968 (7.2 per 100.000, 95% CI 5.8 – 8.7 x 10^{-5}) catheterizations, respectively.[26**] Wide ranges in incidences are commonly encountered when evaluating single center studies and specific patient populations; for example Kupersztych-Hagege *et al.*[45] reported one spinal hematoma in 2.907 patients (95% CI 0.06– 1.95) who underwent lung surgery during a study period of 8 years. The same study identified two cases of spinal abscesses (one per 1.454 catheterizations, 95% CI 0.19 – 2.5).[45] Other major complications that were encountered after epidural analgesia were postoperative neurological deficits in 57 patients (1.12%), post dural-puncture headache in seven patients (0.14%) and systemic local anesthetic toxicity in four patients (0.08%).[46] A fourth incidence study, identified seven serious adverse events after thoracic epidural analgesia

over a 10-year period; spinal abscess, persistent neurological damage and cardiac arrest were all seen in one patient per 7.273 catheterizations (0.01%, 95% CI 0 – 0.08%) and catheter breakage leaving a catheter fragment *in situ* was seen in four patients [one per 1.818 (0.06%), 95% CI 0.01 – 0.14%].[47]

Labor Pain

Efficacy

Epidural analgesia is considered the golden standard for labor analgesia and is recommended by the American Society of Anesthesiologists in patients without contraindications, which include coagulation disorders, infection at the puncture site or patient refusal.[48] Both epidural analgesia and combined spinal epidural (CSE) anesthesia are feasible techniques for labor analgesic purposes, with low failure rates of epidural analgesia and CSE in the obstetric population, 3.0– 4.3% and 2.1%, respectively.[49, 50] As emphasized by Bonnet *et al.*[51], the effectiveness of labor epidural analgesia is difficult to explore, as it includes the maternal satisfaction with analgesia as well as an overall childbirth experience.

Current research has focused on alternatives for epidural analgesia in patients with contraindications for epidural analgesia. An extensively studied topic is the use of remifentanil patient-controlled-analgesia (RPCA). A recent meta-analysis of randomized trials comparing RPCA to epidural analgesia, reported that the average VAS [weighted mean difference (WMD) 2.0 cm, 95% CI 1.72–2.29] and VAS at 1 h (WMD 1.33 cm, 95% CI 0.30–2.36) was higher in the RPCA group. Most importantly, hypoxemia was increased in the RPCA group (OR 7.48, 95% CI 3.42–16.36), which underlines the need for increased monitoring of patients treated with RPCA. No significant differences were detected for maternal satisfaction, and VAS at 2 or 3 h; however, the authors state that this meta-analysis remains underpowered to rule out clinically important differences due to the few existing randomized trials.[52] Two other trials, by Freeman *et al.*[53*] (which is included in the previous-mentioned meta-analysis) and Logtenberg *et al.*[54*] (not included in the meta-analysis), were able to detect

a higher satisfaction with pain relief in women who received epidural analgesia compared with RPCA. Notwithstanding these findings, safety and the preconditions for well tolerated use remain the main argument against RPCA.

Complications

Complications in young, healthy, obstetric patients occur less frequent than complications in other patient categories. The before-mentioned study from Rosero and Joshi[26**] studied epidural analgesia procedures in over 2.3 million obstetric patients; the incidence of spinal hematoma was one per 154.730 catheterizations (0.6 per 100.000, 95% CI 0.3 – 1.0 x 10^{-5}) and zero spinal abscesses were seen during the study period of 13 years. As the authors state, the risk of spinal hematoma depends, among other things, on patient comorbidities including coagulation defects, use of anticoagulant medications and thrombocytopenia. The young age and infrequency of comorbidities in obstetric patients has likely contributed to the low incidence rate of complications. Other studies have reported congruent incidence rates of spinal hematoma in this patient category.[55,56] Furthermore, the authors explain the low incidence of spinal abscess by the short duration of epidural catheterization in obstetric patients. They indicate that a case of epidural abscess would possibly be "*diagnosed after the patient is discharged to home and, therefore, could not be captured in the"* Nationwide Inpatient Sample, "*which lacks information about hospital readmissions*." Previous studies have reported incidences between 0.7 and 1.6 per 100.000 epidural catheterizations in the obstetric population.[26**,56-58]

A current development regarding complications of neuraxial anesthesia in obstetric patients is the focus on cranial complications next to spinal complications. Cranial hematoma is principally described after cerebrospinal leakage due to spinal anesthesia, CSE or after accidental dural puncture in epidural analgesia. The pathophysiology is grounded on intracranial hypotension with subsequent tearing of bridging veins. A literature review assessing characteristics of obstetric patients with cranial

hematoma following neuraxial anesthesia was published by Cuypers *et al.*[59*] Predisposing risk factors as coagulation disorders, arteriovenous malformations or multiple punctures were present in only a minority of patients. The authors conclude that vigilance is required whenever a headache becomes non-postural, prolonged, or whenever focal neurological signs occur, as the complication can easily be confused with postspinal-puncture headache.[59*]

A single-center case series, reported 11 obstetric patients with subdural hematoma (SDH) associated with labor epidural analgesia over 7 years at a tertiary care hospital, an observed rate of approximately one SDH per 3.900 catheterizations. A much higher rate of SDH was seen when a recognized dural puncture occurred during epidural catheter placement (one SDH per 87 catheterizations). "*Ten of 11 cases had a second hospital stay for a mean of 2.8 days (range, 2–4 days) for observation, without further requirement for neurosurgical intervention. One case had decompressive hemicraniectomy after becoming unresponsive.*" The authors conclude that SDH is rare but potentially more common than historically estimated.[60]

We must emphasize that more accuracy concerning clinical relevance and incidence rates could only be expected from multicenter registries with larger sample sizes. Further, we believe that increased awareness for potential SDH associated with epidural analgesia in obstetric patients with headache that is not typical for dural puncture or refractory in nature may improve diagnosis, ensure adequate monitoring of affected patients and avoid erroneous diagnoses (e.g. postspinal headache).

Chronic Pain

Efficacy

Epidural analgesia can be used in chronic pain syndromes caused by both non-cancer and cancer related morbidities. A current overview article concerning new treatment options in cancer pain highlights that 50% of cancer patients report inadequate pain control.[61] Interventional pain management procedures may be suitable for chronic pain refractory

to standard treatments and include peripheral neural blockade, neurodestructive techniques, neuromodulators and epidural or intrathecal drug delivery systems.[62*] Neuraxial analgesia has a longstanding proven history of providing outstanding pain relief to patients suffering from intractable chronic pain.[62*] A specific benefit of neuraxial analgesia is the avoidance of opioid toxicity; however, neuraxial approaches are mainly used in patients in whom pain control has failed using alternative methods. Depending on the population under consideration, central neuraxial blocks are suitable in around 2% of patients.[63] "*Consequently, there is limited high-quality controlled study evidence available, evaluating the"* effectiveness of neuraxial analgesia in treating chronic pain patients; therefore, it is difficult to draw conclusions on the efficacy and safety of epidural analgesia in this population. The few systematic reviews that are present, "*tend to include studies for epidural versus intrathecal routes under the umbrella term 'spinal' analgesia and data are often presented as combined for both approaches".*[64] A review of uncontrolled studies comparing epidural and intrathecal opioids in patients with chronic cancer-related pain reported excellent or good pain relief in 87% of patients treated with epidural analgesia and 84% of patients treated with intrathecal opioids.[64,65] Recent literature evaluating the efficacy of epidural analgesia in chronic pain patients, consisted of two case reports describing efficient pain treatment with epidural analgesia in a patient with malignant psoas syndrome[66] and in a pregnant patient with non-obstetric pain due to a progressively enlarging thoracoabdominal sarcoma.[67]

Even though interventional management has found a definite place in cancer pain, there is a lack of evidence-based practice guidelines for interventional therapies, due to paucity of good-quality randomized controlled trials evaluating the safety and efficacy in treatment of chronic pain.[68] Based on current literature, we cannot report reliable effectiveness of epidural analgesia, and furthermore we cannot give specific indications for epidural analgesia. We advocate that the decision for epidural analgesia in the chronic pain population should again be weighed against

patient-specific comorbidities, possible risk factors for complications, life expectation and the possibility of alternative analgesic regimens.

Complications

In addition to the previous mentioned complications, specific complications of chronic pain therapy are related to problems with mechanical devices used for long-term continuous infusion and the long-term effects of neuraxially administered drugs. An additional risk in chronic pain patients is infection because an immune-compromised status can be present in advanced cancer patients.[61] Complications may occur, but often can be managed without the need to remove the catheter or the implanted device.[64]

It must be said that many studies evaluating complications of epidural analgesia did not specifically focus on epidural analgesia for chronic pain treatment and reliable incidence rates of complications in chronic pain patients remains a field of further research.

Treatment and Outcome of Complications

Treatment of complications is based on the cause of the complication, the severity of symptoms and specific patient-related comorbidities and medication use. Mild postoperative neurological deficits, without the presence of hematoma or abscess, usually resolve spontaneously within months without intervention. Hematoma or abscess after central neuraxial block is often treated with urgent neurosurgical intervention, with a beneficial neurological outcome when performed within 12 h after symptom onset.[69] However, besides surgical treatment, there is a place for conservative treatment for certain patient categories with mild neurological injury due to epidural hematoma or abscess.[70]

Prognosis of patients with major complications after epidural analgesia is infrequently reported, nonetheless retrospective reviews indicate full recovery in 61–75% of patients, epidural hematoma accounting for two-thirds of the residual neurological deficits.[23,42,43] A comprehensive study

focusing on major complications of central neuraxial blocks performed by Cook and others, reported an incidence of permanent harm (including death) due to epidural abscess, hematoma, meningitis, nerve injury, spinal cord ischemia, fatal cardiovascular collapse and wrong route errors of one per 5.747 epidural catheterizations (17.4 per 100.000 cases, 95% CI 7.2 – 27.8) in the perioperative population, one per 166.667 epidural catheterizations (0.6 per 100.000 cases, 95% CI 0 – 3.4) in the obstetric population and 0 per 100.000 cases (95% CI 0 –10.7) in the chronic pain population. The outcome in chronic pain patients was based on 27.975 patients treated with epidural analgesia on an annual basis. However, if besides epidural analgesia, patients treated with caudal analgesia were incorporated, the incidence of permanent harm (including death) was 8.8 per 100.000 patients (95% CI 1.0 – 49.0) in the chronic pain population (based on a reported number of 11.375 caudal procedures performed per year). This study also confirmed that two-thirds of initially disabling injuries resolved fully.[23]

Conclusion

Major perioperative indications for epidural analgesia are open upper abdominal surgery and thoracotomy. Furthermore, epidural analgesia is the golden standard for analgesia in the obstetric setting and is considered as a well-tolerated technique in young, healthy women, as efficacy has been proven and complications with permanent neurological damage seldom occur. Safety of epidural analgesia for perioperative indications and for chronic pain treatment is more difficult to balance; a careful selection of appropriate patients cannot be over-emphasized.

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Conflicts of interest

None.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

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   * A prospective, randomized, controlled, open-label, noninferiority trial that in- cluded 105 eligible patients (55 received continuous wound infiltration and 47 received epidural analgesia) who underwent hepato-pancreato-biliary surgery. Mean Overall Benefit of Analgesic Score, a validated composite endpoint of pain scores, opioid side effects, and patient satisfaction, was 3.8 (SD 2.4) in the continuous wound infiltration group versus 4.4 (2.2) in the epidural group [mean difference 0.62, 95% confidence interval (CI) 1.54 to 0.30]. These data suggest that continuous wound infiltration might be noninferior to epidural analgesia in hepato-pancreato-biliary surgery within an enhanced recovery setting.
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** Systematic review comparing TEA and paravertebral block (PVB) in adults undergoing elective thoracotomy. The authors included 14 studies with a total of 698 participants undergoing thoracotomy. Overall, the authors state that the included studies have a moderate-to-high potential for bias, lacking details of randomization, group allocation concealment or arrangements to blind participants or outcome assessors. PVB reduced the risks of developing minor complications compared with TEA, was as effective as TEA in controlling acute pain. There was no difference in 30-day mortality, major complications or length of hospital stay. There was insufficient data on chronic pain and costs. Results from this review should be interpreted with caution due to the heterogeneity of the included studies and the lack of reliable evidence. Future studies in this area need well conducted, adequately powered randomized controlled trials that focus not only on acute pain but also on major complications, chronic pain, length of stay and costs.
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Chapter 3

Safety of Epidural Drugs: a Narrative Review

Mark L. van Zuylen, Werner ten Hoope, Elke M.E. Bos, Jeroen Hermanides, Markus F. Stevens, Markus W. Hollmann, Markus W. Hollmann, Philipp B. Lirk

Expert Opinion on Drug Safety

Abstract

Introduction – Epidural analgesia is a popular approach to postoperative and labor pain. Neurotoxicity and drug-specific systemic side effects can occur after epidural administration. As an increasing number of epidural drugs are studied and clinically applied, drug efficacy and safety evaluation are crucial.

Areas covered – In this narrative review, the authors provide a thorough overview on the safety of the most widely used epidural drugs, focusing on potential neurotoxicity, side effects, and complications in the adult, non-pregnant population. A combined text and MeSH heading search strategy was used to identify relevant publications.

Expert opinion – The search for the ideal epidural medication has resulted in a surplus of drug combinations with extensive heterogeneity amongst studies, while the value of investigating these is not always evident. Epidural drugs pose a potential threat of neurotoxicity and other side effects. Consequently, we should pursue safe epidural drug administration to patients and refrain from drugs with minimal proven benefit. Also, studies should compare epidural with systemic application. Because why use a drug epidurally, which can be safely used systemically? Future research should focus on providing solid evidence regarding efficacy of epidural analgesia compared to new and already existing modalities and optimizing presently used medicinal regimens.

Keywords – Epidural; Safety; Epidural drugs; Neurotoxicity; Systemic toxicity; Side effects; Drug efficacy; Safety evaluation; Neuraxial; Analgesia

Article Highlights

- Research regarding new epidural drugs and drug combinations is ever increasing.
- Clinically safe epidural usage of drugs should be pursued, reducing possible neurotoxicity and other side effects. In vitro and in vivo data can prescreen new drugs and drug combinations before administering them to patients, but only large-scale observational prospective studies looking for short- and long-term neurological change can demonstrate clinical safety.
- If there is no added benefit of administering drugs epidurally as compared to systemically, the systemic application should be preferred.
- The incidence of serious complications seems to be low, but the consequences can be devastating.
- Future research should focus on providing solid evidence regarding efficacy of epidural analgesia compared to new and existing modalities and optimizing established regimens.

Introduction

Epidural analgesia is a popular method for treating postoperative and labor pain, with over 3.7 million adult patients receiving epidural analgesia between 1998 and 2010 in the United States alone.[1] However, some concerns exist regarding epidural safety and efficacy. Observed severe complications, albeit rare, include epidural hematoma or abscess and neurological injury. Epidurally administered drugs have a higher potential for inducing neurotoxicity as compared to systemically. Hence, administering drugs systemically is the preferred route when efficacy is comparable to epidural application. In addition, drug-specific systemic side effects like hemodynamic instability or intoxication can also occur after epidural administration. In this narrative review, we aim to give a thorough overview on the safety of the most widely used epidural drugs, focusing on potential neurotoxicity, known side effects and possible complications of specific drug groups.

Search Strategy

The search strategy is summarized in Figure 1. We included studies on epidural drug safety for perioperative analgesia in the adult, non-pregnant population, excluding papers on epidural drug safety in chronic pain, pregnant and pediatric patients. In addition, we included studies regarding systemic versus epidural drug efficacy. Medical Subject Headings terms used were, among others, epidural analgesia, local anesthetics, glucocorticoids, steroids, dexamethasone, bupivacaine, mepivacaine, lidocaine, opioid analgesics, buprenorphine, morphine, fentanyl, sufentanil, adrenergic alpha-agonists, epinephrine, clonidine, dexmedetomidine, ketamine, drug-related side effects and adverse reactions, hypotension and synonyms. Titles and abstracts were screened and cross-referenced for possible inclusion by MvZ, while when in doubt discussing eligibility with other authors (WtH, JH, MFS). Selected articles were restricted to articles in English, German or Dutch. Full text articles were retrieved and reviewed for all studies that seemed relevant and were assessed for eligibility.

Local Anesthetic

Local anesthetics (LA) are the main component in most epidural mixtures used in daily clinical practice. LA main site of action is a specific intracellular portion of voltage-gated sodium channels, which they block reversibly. The onset of action of LA is related to their pKa. A high pKa indicates a slow onset of action. Potency and duration of action of a LA, on the other hand, depend mostly on lipid solubility and protein-binding capacity: the more lipophilic the LA, the easier it diffuses across nerve membranes, increasing its potency. Increased protein-binding ensures LA are more tightly bound to the receptor sites and therefore dissociate more slowly (see Table 1).[2]

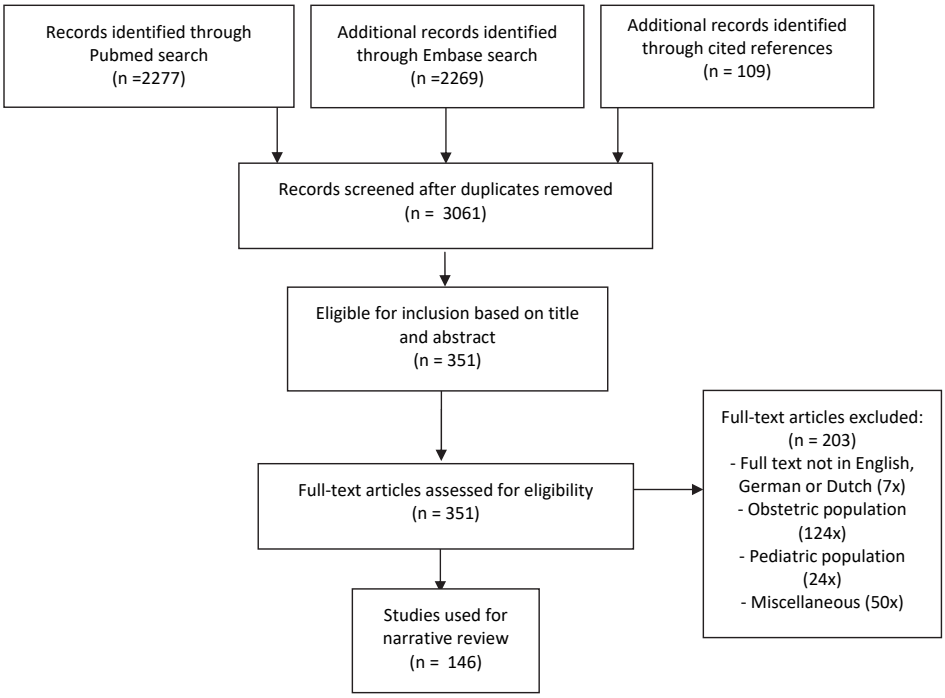

Figure 1. *Search strategy.*

Table 1. *Widely used local anesthetics.*

Local anesthetic	Neurotoxicity[6]*	Cardiotoxicity[3]**	pKa	Lipid solubility	Protein binding capacity
Lidocaine	++	++	7.8[4]	+[4,5]	++[4]
Bupivacaine	++	++	8.1[4,5]	+++[4,5]	+++[4,5]
Levobupivacaine	++	++	8.1[4,5]	+++[4,5]	+++[4,5]
Ropivacaine	++	++	8.1[5]	++[4,5]	+++[4,5]

* ++ = neurotoxic when increasing doses are administered.
**: – = no reported side effects; + = mild effect; ++ = moderate effect; +++ = profound effect.

Neurotoxicity

All LA have time- and dose-dependent neurotoxic properties[6,7] which correlate with their clinical potency.[8] Neurotoxicity is mediated through a variety of different mechanisms leading to apoptosis and necrosis.[7] Epidural neurotoxicity predominantly occurs after supraclinical LA doses and therefore has little clinical impact in daily practice. Transient neurological symptoms (TNS) have been described after intrathecal LA administration, specifically lidocaine.[9] However, only one case report described TNS after epidural administration of lidocaine, and this was after a high dose (≥600 mg) was administered over a short (20 min) period of time.[10]

Systemic Toxicity

LA toxicity after systemic absorption of high doses of LA can produce central nervous system excitation with seizures, central nervous system inhibition, loss of airway reflexes, respiratory arrest, hemodynamic instability, and in extreme cases, coma or cardiovascular collapse. Case reports have shown possible benefit from the use of intravenous lipid emulsions in case of LA overdose,[11] however its effect on lidocaine central nervous system toxicity has been debated.[12]

In the sixties[13] the antiarrhythmic properties of lidocaine were described, which has resulted in its intentional intravenous administration in case of ventricular arrhythmias. In recent years, more widespread use of systemically

administered lidocaine has been promoted as a possible alternative to epidural analgesia. Even high intravenous doses (up to 300 mg) of systemic lidocaine rarely give rise to problems like conduction disturbances or ventricular arrhythmias.[14,15]

At equipotent dosing, all LA have similar toxic properties, however systemic LA toxicity after epidural injection is rare.[16] It has been suggested that ropivacaine has a superior safety profile compared to racemic bupivacaine. When given systemically to healthy volunteers, the tolerated maximum dosage of ropivacaine before start of neurotoxic and cardiovascular effects was twice as high as that of racemic bupivacaine.[17,18] Ropivacaine has a lower potency than both levo-and racemic bupivacaine and is approximately 10 times less lipophilic. At equipotent dose,[19] it is uncertain whether there is really clinically relevant lower toxicity. Several cases in which intended epidural doses of ropivacaine were accidentally administered either intrathecally or intravenously resulted in severe complications.[20,21] Thus, whether ropivacaine actually has a safer clinical profile is questionable.

Finally, all LA can cause hypotension when administered epidurally. Increased hypotension after epidural LA administration, either with or without adjuvant opioids, was reported in two recent systematic reviews.[22,23] In both studies the incidence of hypotension was lower when a lower dose of LA was combined with an opioid, nonetheless it was still markedly higher than in the control group.

Opioids

Epidural opioids have been used for over three decades, after receiving their United States Food and Drugs Administrations (FDA) approval in 1984, with the first studies ranging back as far as 1979. Most epidural mixtures currently used combine a lipophilic opioid (fentanyl, sufentanil) with a long-acting LA (levo- or racemic bupivacaine, ropivacaine) because of their presumed synergism and the avoidance of delayed respiratory depression. A meta-analysis[22] suggested slightly better analgesic efficacy of epidural analgesia when compared with an intravenous pain regimen. A Cochrane systematic

review supports this limited superior analgesic effect of epidural analgesia over systemic opioid administration in patients undergoing open aortic surgery, reporting a mean difference in VAS scores on movement on postoperative day 1 of −1.78 (95% CI −2.32 to −1.25).[24] The clinical relevance of this difference is however debatable. According to the requirements for a clinically superior pain regimen of two points NRS reduction or 30% relative pain reduction from baseline recommended by the International Association for the Study of Pain (IASP), this difference cannot be seen as clinically superior.

Neurotoxicity

Nearly every opioid has shown at least some degree of neurotoxicity, including hydromorphone, tramadol, oxycodone, fentanyl, sufentanil and buprenorphine.[25-35] For neuraxial morphine, this is less consistent.[26,36] Researchers studying neurotoxicity of the DepoFoam technology, a lipid-based depot used for extended release morphine, deemed it safe (see Table 2).[37] Epidural nalbuphine[27] showed no neurotoxicity, but long-term clinical research regarding its safety is missing.

Table 2. *Widely used epidural opioids.*

Opioid	Neurotoxicity*	Notable side-effects as epidural adjuvant
Morphine	+[26,31]	Delayed respiratory depression +++[44,45], sedation +[38], hypotension +[38]
Morphine (extended-release)	+[26,31]	Delayed respiratory depression +++[47-52], sedation ++[54], hypotension ++[55]
Hydromorphone	+[25]	Delayed respiratory depression ++[59], sedation +[39], hypotension ++[39]
Fentanyl	+[35]	Sedation +[38,42,60], hypotension +[38]
Sufentanil	+[27]	Sedation ++[38,40], hypotension +[38]

*: – = no reported neurotoxicity; + = at least some reported neurotoxicity or inconclusive data; ++ = multiple reports, neurotoxicity probable; +++ = multiple reports, almost certainly neurotoxic

**: – = no reported side effects; + = mild effect; ++ = moderate effect; +++ = profound effect

It's worth noting that very little neurotoxicity is reported in daily clinical practice, thus it can be assumed that the most frequently used epidural opioids (i.e. morphine, fentanyl, sufentanil) are safe when epidurally administered doses are in accordance with the current standard of care.

Systemic response and respiratory depression – hydrophilic opioids

Since the introduction of epidural opioids, it is well-defined that they all share, to some extent, the adverse effects as known from their systemic administration. These include, but are not limited to, hypotension, sedation, nausea, vomiting, pruritus, urinary retention and respiratory depression, whereby pruritus occurs more often after epidural opioid administration.[41]

Morphine is one of the most frequently used opioids in epidural anesthesia. It has long-lasting analgesic effects, especially in combination with LA. Epidural morphine can produce delayed respiratory depression and it's an ongoing discussion whether the respiratory depression is a result of its active metabolite morphine-6-glucuronide or because of the rostral spread of morphine in the cerebrospinal fluid into the brainstem.[42] It is worth noting that the pharmacokinetics of morphine seems to differ depending on the injection site (i.e. lumbar vs. thoracic catheter placement). This could result in a concentration gradient in the cerebrospinal fluid with concurrent alterations in the rostral spread, resulting in increased systemic side effects if similar doses of morphine are used in a thoracic relative to lumbar epidural.[43] Late respiratory depression has been found to occur up to 24 h after an epidural dose.[44] The incidence for delayed respiratory depression was found to be 0–2.8%[45], however a clear definition of respiratory depression is missing in the literature.[45,46] Older studies used larger dosages of epidural morphine and excluding those would result in a lower incidence.

The recently introduced extended-release variant of morphine should guarantee sufficient analgesia for up to 48 h, whilst simultaneously decreasing total opioid consumption. The sterile suspension of multivesicular liposomes contains morphine sulfate and works as a depot, ensuring a controlled release. After FDA approval in 2004, a high incidence (>10%) of adverse events,

including respiratory depression, has been reported, especially after doses >15 mg,[47-52] leading to the current-advised dose of ≤15 mg. Interestingly, this decreased dose resulted in less adverse events, but consequently also reduced the duration of action.[53] It has been debated whether it should be combined with LA because of potential physicochemical interactions which could alter the release of the morphine,[54] triggering adverse effects like respiratory depression.[55]

Hydromorphone is a hydrophilic opioid similar to morphine, but significantly more potent (for systemic action 1.5 mg hydromorphone equals 10 mg morphine). Its analgesic efficacy is comparable to epidural fentanyl, sufentanil[56] and morphine.[57,58] Delayed respiratory depression up to 4,5 hours after epidural drug administration at even modest dosages is reported[59] but seems to have a lower incidence than with morphine. Similar to morphine, an extended release preparation is available.

Many risk factors for delayed respiratory depression, like usage of hydrophilic opioids, advanced age, morbid obesity or obstructive sleep apnea, have been identified.[45] Considering these risk factors, the lowest clinically effective dose and adequate monitoring are essential for safe epidural usage of hydrophilic opioids.

Systemic response and respiratory depression – lipophilic opioids

For lipophilic opioids, the distribution to, and clearance from, the spinal cord and epidural space are rapid as compared to hydrophilic opioids, decreasing the risk of delayed respiratory depression when given epidurally.[42] Indeed, lower sedation levels and less respiratory depression are reported when comparing fentanyl to morphine.[42,60] Buprenorphine is a lipophilic long-lasting mixed agonist-antagonist. Its specific site of action is still unclear, but seems to be predominantly supraspinal of nature.[61] The use of epidural buprenorphine showed no advantages over epidural morphine.[62] Naloxone-resistant respiratory depression has been reported for epidural buprenorphine,[63] but the incidence appears to be low.

Clinical implication

We suggest avoiding all widely used opioids that are proven neurotoxic and have no proven benefit when administered epidurally, being hydromorphone,[64] buprenorphine[62] and tramadol.[29,30] Individual patient risk stratification is advised when using morphine and especially extended release morphine considering late respiratory depression. Dosing needs to be done carefully as adjustments cannot be made after administering the drug.[51] Because of its long duration of action, continuous monitoring for 24–48 h is recommended. Whether the risks of (extended-release) morphine outweigh its benefits remains to be seen.

Even though multiple studies have shown no added benefit for epidural sufentanil compared to its intravenous administration,[65,66] it remains one of the most widely used adjuvants in epidural analgesia, presumably due to the LA sparing effect and thereby reducing the adverse effects of both drugs.[67] The use of epidural fentanyl and sufentanil appears safe when standard precautions for the use of opioids are taken. Because their mechanism of action is predominantly systemic,[43] equianalgesic doses of intravenous lipophilic opioids are similar to epidural doses,[65,66] compared to the much lower epidural doses of hydrophilic opioids necessary for equianalgesia.

In summary, none of the opioids reviewed show ideal epidural analgesic properties without any side effects. This does, however, not mean that there is no place for opiates in epidural anesthesia. The benefits of the synergistic LA/opioid mixture which result in less side effects are well established. Using the lowest effective dose and applying adequate monitoring should minimize complications.

Alpha-adrenergic receptor agonists

In recent years alpha-adrenergic receptor agonists have increasingly been used for epidural analgesia. Epinephrine as an adjuvant to LA is thought to decrease the clearance and distribution of LA from the epidural space. Intravenous clonidine and dexmedetomidine are known for their analgesic properties and, when administered epidurally, are thought to have an analgesic

and LA sparing effect. Clonidine can be administered systemically, epidurally or intrathecally, because alpha-2-adrenoceptors are localized throughout the central nervous system. Recent studies propose a predominantly spinal site of action suggesting neuraxial administration to be preferable over systemic clonidine for its analgesic effect.[68,69] When clonidine is administered epidurally, lower doses of LA and opioids can be used whilst still maintaining sufficient analgesia.[70-72] This dose-sparing effect could limit possible complications and adverse effects associated with the use of epidural LA and/or opioids. In contrast, oral clonidine similarly decreased epidural morphine dosages without any clonidine specific side effects.[73] This gives rise to the hypothesis that at least one extra pathway, apart from the spinal site of action, for clonidine's analgesic properties exist. Oral administration of clonidine may reduce the required doses of epidurally applied drugs and medication-associated side effects to a similar extent as epidural clonidine.

Neurotoxicity

Safety concerns were initially issued regarding possible spinal cord ischemia after epidural epinephrine administration, however since then, studies in both animals and humans have debunked this.[74] Neurotoxicity or spinal cord ischemia in epidural use of epinephrine seems to be highly unlikely. Ambiguity remains regarding the safety of epinephrine in patients with an already compromised spinal circulation, where epidural epinephrine may perhaps aggravate already present LA-induced neurotoxic injury (see Table 3).[74]

Clonidine has been thoroughly studied in both animals and humans as an epidural adjuvant. Neurotoxicity seems to be low and epidural administration safe.[76,77] There is no consensus regarding the epidural neurotoxicity of dexmedetomidine and it is therefore currently not approved by the FDA.[78]

Table 3. *Epidural alpha-adrenergic receptor agonists.*

Alpha-adrenergic receptor agonist	Neurotoxicity*	Notable side-effects as epidural adjuvant**
Clonidine	-	Sedation+++[79,80], hypotension++[68,71,82], bradycardia++[68]
Dexmedetomidine	+[78]	Sedation+++[75,81], hypotension++[75], bradycardia++[75,81]
Epinephrine	-	-

*: – = no reported neurotoxicity; + = at least some reported neurotoxicity or inconclusive data; ++ = multiple reports, neurotoxicity probable; +++ = multiple reports, almost certainly neurotoxic
**: – = no reported side effects; + = mild effect; ++ = moderate effect; +++ = profound effect

Side effects

Common side effects of alpha-adrenergic receptor agonists include sedation, hypotension, and bradycardia. This resulted in discussions regarding its safety and the risk–benefit ratio for epidural administration. The adverse events reported for clonidine are dose dependent.[79] Similar to morphine, the systemic side effects increase when clonidine is given via thoracic epidural catheter, perhaps as a reflection of rostral spread.[68] Dexmedetomidine shares most of clonidine's dose-dependent adverse effects,[80] but displays a significant higher incidence of bradycardia and clearly increases sedation scores.[81] Pooled data did, however, not show any statistically significant increase in hypotension. Similar to clonidine less systemic opioids were needed.

Clinical implications

A recent systematic review concluded that the possible impact of adding epinephrine to epidural local anesthetics remains uncertain due to insufficient evidence. In addition, the side effects of clonidine and dexmedetomidine should prompt caution before using them as adjuvants in epidural analgesia, because even a low epidural dose of approximately 50ug/h of clonidine can cause considerable hypotension.[68,71,82] Care should be taken to assess and maintain hemodynamic stability in patients receiving clonidine.

Finally, more data from large comprehensive trials assessing long-term safety and efficacy of dexmedetomidine used as an adjuvant in epidural analgesia are necessary before recommending dexmedetomidine for neuraxial use.

Other frequently used epidural adjuvants

Dexamethasone

In 2014 the FDA issued a warning concerning the use of epidural steroids after a series of serious neurological problems including loss of vision, stroke, paralysis, and death.[83,84] Dexamethasone is a water-soluble steroid known for its analgesic, anti-inflammatory and antiemetic properties.[85-87] It is thought that water-soluble steroids like dexamethasone are safer than the more lipid soluble steroids like triamcinolone when given epidurally.[88]

Multiple studies have emerged where dexamethasone has been used as an adjuvant to LA in epidural mixtures. The rationale for using dexamethasone epidurally was an assumed analgesic effect that was at least similar to other adjuvants, but with less side effects than other adjuvants like opioids or alpha-adrenergic receptor agonists.[89] To date, however, no studies assessed dexamethasone as the sole adjuvant to LA and comparing it to other LA/adjuvant mixtures.

Some researchers have deemed epidural dexamethasone safe. Nevertheless, safety issues still surround the use of epidural corticosteroids in general, and dexamethasone in particular (see Table 4).[90,91] For example, high (≥15 mg) doses of epidural dexamethasone were associated with transient adrenal suppression.[92]

Very little is known about neurotoxicity of dexamethasone. The potential for neurotoxicity was not actively sought in the majority of the studies performed.[96] Water-soluble steroids have been implicated in seizures when given intrathecally[97-99] and higher doses of intrathecal dexamethasone were associated with increased inflammation of the subarachnoid space in rats.[100]

In vitro, neurotoxicity was suggested when combining dexamethasone with ropivacaine.[101]

Table 4. *Other epidural medication.*

Other drugs	Neurotoxicity*	Notable side-effects as epidural adjuvant
Dexamethasone	+++[97-101]	-
Ketamine	+++[102-104]	Sedation, psychoto- and sympaticomimetic effects +[93,94]
MgSO4	++[113-116]	-
Midazolam	+++[119-121,123]	Sedation+[95,119,120], hypotension +[119,120]
Neostigmine	-	Sedation+[128]

*: – = no reported neurotoxicity; + = at least some reported neurotoxicity or inconclusive data; ++ = multiple reports, neurotoxicity probable; +++ = multiple reports, almost certainly neurotoxic;
**: – = no reported side-effects; + = mild effect; ++ = moderate effect; +++ = profound effect.

Ketamine

Ketamine is a selective, non-competitive NMDA-receptor antagonist with known analgesic and in particular anti-hyperalgesic action. Evidence suggests that ketamine has neurotoxic properties when administered intrathecally.[102,103] Epidural ketamine should also be used with caution, especially when ketamine with preservatives is used. Particularly the well-known neurotoxic preservative benzethonium could worsen ketamine's own neurotoxicity.[104] The added benefits of epidural ketamine over systemic ketamine are still debated,[105,106] even though a small potentiating effect was seen when epidural ketamine was given in combination with morphine.[107] Systemic adverse reactions include psychotomimetic side effects and a mild sympathomimetic action, whereby the latter only occurs at plasma levels of >243 ± 54 ng/mL.[93] Considering the above, epidural ketamine should be reserved for very specific individual cases, for example, in palliative care. Only a few human studies assessed neurological complications[108] associated with the neuraxial use of ketamine and more data on its safety should be gathered.

Interestingly, ketamine had been advocated as an adjuvant for pediatric caudal anesthesia[109,110] based on a meta-analysis of 13 randomized controlled trials demonstrating its effectiveness.[111] However, doses used in those studies make a predominantly systemic analgesic effect likely. Thus, there is no evidence suggesting superiority of epidural over systemic application. There

is considerable experimental data demonstrating neurotoxicity yet only one clinical study looked at permanent neurological damage. Therefore, neuraxial use of ketamine cannot be advocated.

Magnesium

Magnesium is a NMDA-receptor antagonist, similar to ketamine. The main reason for adding magnesium to an epidural drug-mixture is to reduce side effects of epidural LA and/or opioids, whilst assuring the same level of analgesia.[112] A high dose of magnesium intravenously (resulting in plasma levels >5 mmol/L) can produce flushing and hypotension that is not seen when applied via the epidural route, presumably due to a dose-dependent effect. Very high doses of magnesium resulting in plasma levels exceeding 6 mmol/L could lead to hypermagnesemia, a potentially lethal condition.

Similar to ketamine, the main concern regarding neuraxial magnesium pertains to its neurotoxic potential.[113,114] Case reports in the obstetric population describe patients suffering from disorientation[115] or burning pain[116] following supra-clinical doses of magnesium accidentally given neuraxially.

Midazolam

Midazolam is a benzodiazepine acting on GABA-A receptors thereby facilitating chloride influx into the cell resulting in neural inhibition. Midazolam showed some analgesic action when epidurally administered as an adjuvant to racemic bupivacaine.[117,118] Side effects for epidural midazolam are mainly sedation and hypotension, however, when using the lowest clinically effective dose of midazolam, those adverse events should be rare.

Neurotoxicity is a considerable concern and neurologic damage has been reported in animals when midazolam was given neuraxially.[119,120] Apoptosis induction is known to be mediated via the same mechanism as described for LA.[121] However, the quality of some animal studies reporting on neurotoxicity of midazolam has been questioned.[122] Therefore, no conclusive statement on the safety of neuraxial midazolam can be given. Worth mentioning, midazolam aggravated the neurotoxic properties of lidocaine.[123] Because all

LA are neurotoxic,[7] midazolam added to any mixture containing an LA could potentiate neurotoxicity.

Neostigmine

Neostigmine inhibits the enzyme acetylcholinesterase, thus interfering with the breakdown of acetylcholine in the synaptic cleft. Epidural neostigmine has shown, at best, doubtful efficacy. Some studies reported a dose-independent analgesic effect when combined with lidocaine.[124] Adding neostigmine to epidural morphine results in a longer time to first analgesic rescue medication, albeit, without a reduction in the total opioid consumption.[125]

The main clinically relevant side effect for epidural neostigmine was significant hypotension,[126] while nausea, vomiting, and sedation were also reported.[127] Epidural administration of neostigmine appears to be safe after extensive neurotoxicity research.[123,128-130]

Clinical implications

When searching for a clinically useful epidural adjuvant, safety of the drug should have been proven and the epidural administration should have a clear beneficial effect. With this in mind, all adjuvants mentioned in the latter part of our review do not meet the aforementioned criteria. Epidural dexamethasone, ketamine, and midazolam are possibly neurotoxic and the analgesic efficacy of neostigmine or dexamethasone has not been well established. Potentially neurotoxic drugs should not be given epidurally, especially when systemic administration seems to work equally well.

Other epidurally used drugs like prilocaine, calcitonin or haloperidol fall beyond the scope of this review, due to a lack of appropriate studies.

Conclusion

As presented above, the optimal mixture for epidural analgesia does not exist. Consequently, individual patient characteristics, safety of the chosen medication (see Table 5), and a risk–benefit analysis should be leading in deciding which epidural medications to choose. Specific hospital safety

Table 5. *Recommended safe doses* for commonly used epidural drugs in the adult non-obstetric population.*

Drug (stand-alone therapy)	Safe hourly dose (continued infusion)	Maximal safe dose in 24 hours	Safe bolus dose	Drug (as adjuvant)	Safe hourly dose (continued infusion)*
Lidocaine	1,5 mg/kg/h[131]	2 g/24h**	4,5 mg/kg[138] (LE max. 500 mg / TE max. 300mg)[131]	Lidocaine	Not applicable
Bupivacaine	Max. 0.5 mg/kg/h[132]	400 mg/24h[132,133]	2.5 mg/kg[133]	Bupivacaine	Not applicable
Levobupivacaine	Max. 0.3 mg/kg/h**	400 mg/24h[134,135**]	2.5 mg/kg (max. 150 mg)[134]	Levobupivacaine	Not applicable
Ropivacaine	Max. 0.4 mg/kg/h**	800 mg/24h[136, 137]	4 mg/kg (max. 250mg)[137]	Ropivacaine	Not applicable
Morphine	0.1-1.0 mg/h[139]	10 mg/24h[140]	2-5 mg[140**]	Morphine	0.1-0.2 mg/h[140]
Fentanyl	25-100 µg/h[139]	Variable	50-100 µg[141**]	Fentanyl	5-30 µg/h**
Sufentanil	X	Variable	10-30 µg**	Sufentanil	Max. 8 µg/h**
Hydromorphone	0.04-0.4 mg/h[142]	Variable	0.5-1.5 mg[142]	Hydromorphone	0.04-0.2 mg/h[60**]
Clonidine	0.1-0.4 µg/kg/h[143**] (max. 30-40ug)[143]	300 µg/24h**	0.1-0.4 µg/kg[143**] (max. 30-40ug)[143]	Clonidine	0.1-0.4 µg/kg/h[143**] (max. 30-40ug)[143]

* If multiple drugs are used in an epidural mixture all individual drugs should be dosed lower.
** Expert opinion: consensus by anesthesiologists in our University Hospital
LE: lumbar epidural; TE: thoracic epidural

measures should be in place before the application of epidural drugs in order to handle possible adverse events.

When deciding on epidural medication, patient safety is most important. Whenever medication is dispensed close to the central nervous system it poses a potential risk for neurotoxicity or other adverse effects. If questions regarding drug safety are still unanswered or high-quality long-term studies have not unequivocally shown the safety of an epidurally administered drug, they should not be used in routine clinical practice.

Where most local anesthetics and some opioids clearly have their advantages when used in an epidural mixture, most adjuvant drugs described in this review have no or minor benefits when administered epidurally compared to alternative routes (mainly systemic administration). Especially drugs without any proven benefit when applied epidurally compared to their systemic administration should be avoided. Therefore, adjuvants beyond morphine, sufentanil, fentanyl, and clonidine cannot be advocated unequivocally.

Several relevant factors other than epidural drug safety, such as doses and side effects of systemic drugs, or the impact of a chosen analgesic regimen on patient outcome, fall out-side the scope of this narrative review. However, in recent years many papers worth reading have been published addressing these issues.[23,24,43,144,145]

Expert opinion

The search for new epidural medication seems neverending and an abundance of research is dedicated to finding the optimal combination of drugs. This has resulted in an enormous amount of heterogeneous studies, which all study different mixtures in very specific groups of patients and procedures. Conclusive evidence regarding safety and efficacy is therefore difficult to interpret. There is a paucity of large randomized, multicenter, placebo-controlled studies for epidural drug usage. In particular, studies where the epidural adjuvant is compared to systemic administration are warranted. Furthermore, there are no large-scale prospective observational studies regarding the safety of frequently used epidural drugs.

In recent years regulatory oversight of clinical trials has greatly approved. It has become common practice to use multiple well-characterized animal models studying supra-clinical doses and concentrations of perineural drugs before administering them in humans. However, in rare cases, some epidural medications are still used experimentally without ensuring safety in humans. It sometimes seems minor advantages were weighed against perceivable, yet probably rare, deleterious neurologic outcomes.

Even if medication has thoroughly been tested, and no neurotoxicity has been shown in both animal and human studies, it still should be questioned whether it is necessary to administer these drugs epidurally. If a drug shows no added benefit when administered epidurally compared to intravenously, or when epidural efficacy is questioned, systemic administration should be preferred.

Our literature search focused on safety and efficacy of epidural drugs in non-pregnant adults. However, in vulnerable patient groups like pregnant women or children even more caution should be taken. The particularities of transplacental transport, teratogenic properties of drugs and increased neurotoxicity in a developing central nervous system should ensure even more precautions to be taken to avoid any possible harm.

Where in some fields, like obstetrics, the role of epidural analgesia is still widely accepted as the gold standard with regards to analgesic efficacy, the role of postsurgical epidural analgesia has somewhat diminished in recent years. Cumulative evidence supports the notion that there is no added benefit of epidural analgesia over a systemically administered pain regimen or peripheral/local nerve blocks (e.g. pre-peritoneal wound catheter[146]) for analgesic purposes for a growing number of perioperative indications.

Future research should focus on the risk–benefit analysis of epidural analgesia compared to new modalities and on optimizing presently used regimens rather than on fast-tracking the search for new epidural drugs. This is, in particular, true whenever basic safety issues have not been addressed properly.

This review has focused on the safety of epidural drugs. It is however important to keep in mind that other factors should be taken into account when using epidural analgesia. For instance, primary and secondary epidural failure rates are relatively high and minimally invasive surgical techniques, opiate sparing regimens and peripheral regional anesthesia, ranging from paravertebral blocks to pre-peritoneal or pre-pleural wound catheters, offer numerous options and alternatives to new experimental epidural drugs.

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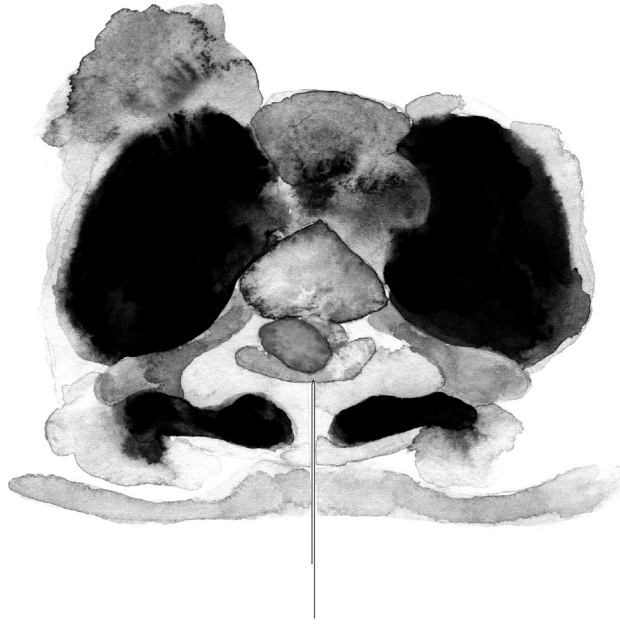
PART 2

Complications of neuraxial anesthesia



Chapter 4

Haematoma and abscess after neuraxial anaesthesia: a review of 647 cases

E. M. E. Bos, J. Haumann, M. de Quelerij, W. P. Vandertop,
C. J. Kalkman, M. W. Hollmann, P. Lirk

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Abstract

Although rare, spinal haematoma and abscess after central neuraxial blocks may cause severe permanent neurological injury. Optimal treatment and outcome remain unclear. In order to identify possible predisposing patient characteristics and describe the ensuing clinical course, we searched Medline, Embase, and the Cochrane Library for reports of spinal haematomas and abscesses associated with central neuraxial blocks. Extracted data included patient characteristics, symptoms, treatment, and outcome. We analysed 409 reports, including 647 patients (387 patients with spinal haematoma and 260 patients with spinal abscess). Spinal haematoma and abscess occurred predominantly after epidural anaesthesia (58% and 83%, respectively). Neurological recovery was correlated with the severity of initial neurological deficit. When decompression of spinal haematoma was delayed for >12 h after clinical diagnosis, neurological outcome was worse compared with earlier decompression (odds ratio 4.5, 95% confidence interval 2.1 – 9.9, P<0.001, n=163). After spinal haematoma, 47% of published patients had full recovery, 28% had partial recovery, and in 25% no recovery was observed. Good outcome after conservative management was observed in patients with mild symptoms or with spontaneous recovery during the diagnostic and therapeutic workup. After spinal abscess, 68% of reported patients recovered fully, 21% showed partial recovery, and no recovery was reported in 11%. Persistent neurological symptoms after spinal haematoma and abscess are common and correlate with the severity of initial neurological deficit. Neurological outcome seems worse when decompressive surgery of haematoma is delayed. Notwithstanding the considerable risk of selection bias and publication bias, conservative management may be feasible in patients with mild symptoms or spontaneous recovery.

Keywords – haematoma; abscess; complication; anaesthesia, epidural; anaesthesia, spinal

Editor's key points

- The authors reviewed reports of spinal haematoma and abscess after neuraxial block. A total of 647 instances of spinal haematoma or abscess were described.
- They found a clear association between the adversity of outcome and the severity of the initial presentation, and the delay in surgical decompression.
- Epidural anaesthesia (compared with spinal anaesthesia) was associated with a greater incidence of haematoma, and a much greater incidence of abscess.

Introduction

The incidence of major complications after neuraxial anaesthesia, such as spinal haematoma or abscess, is more common than estimated in past decades. In 1998, the rate of serious adverse events after epidural anaesthesia was estimated at 1:150.000.[1] In the meantime, indications for epidural anaesthesia have changed, patient characteristics have shifted,[2] and awareness has grown.[3] Nowadays, it is accepted that the incidence of major complications of central neuraxial anaesthesia in non-obstetric patients may range from 1:6.000 to as high as 1:1.000 epidural procedures.[4-9] A retrospective case note review across six years, identified three cases of spinal haematoma and six cases of spinal abscess in 8.100 perioperative epidural procedures.[9] The incidence of major complications of central neuraxial blocks (CNB) is much lower in obstetric patients, with spinal haematoma estimated at 1:154.730 and spinal abscess too rare to calculate in one major study.[4]

Not only is the incidence of severe complications of importance, but also ultimate patient outcome. In the UK, the Third National Audit Project of the Royal College of Anaesthetists found that permanent injury after CNB caused by spinal haematoma or abscess, but also by meningitis, nerve injury, spinal cord ischaemia, fatal cardiovascular collapse or wrong-route errors, was 1:23 810 cases (4.2 per 100.000), and the incidence of the two worst possible complications, paraplegia or death, was 1:55.556 cases (1.8 per 100.000).[3]

As a result of the rare occurrence of these severe complications, accurate data on risk factors and clinical course are not available and, consequently, there is no evidence on which to base recommendations for management strategies.[10] Three large literature reviews were previously reported, focusing on spinal haematomas or abscesses with diverse pathophysiological origin, including mainly non-iatrogenic spontaneous, idiopathic, traumatic, or tumorous spinal haematomas or abscesses, but also including complications of iatrogenic origin, i.e. after CNB.[11-13] As these reviews comprise haematomas and abscesses with different underlying pathology, the results are not directly applicable to the anaesthetic setting. A small review, specifically reporting

spinal haematomas related to epidural anaesthesia (51 cases), was published in 1996,[14] but major changes in clinical practice have occurred since then.

The aim of this review was to collect all cases reported in the literature concerning spinal haematomas or abscesses after CNB, in order to identify possible predisposing patient characteristics and describe the ensuing clinical course. Realising the limitations of interpreting case report series, we aimed to gain insight under which circumstances complications would be most likely to occur, whether particular clinical factors might predict persistent neurological damage, and whether indication or timing of neurosurgical management was correlated with outcome.

Methods

For this review we followed the Preferred Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[15]

Search strategy

An information specialist performed a systematic search in OVID MEDLINE, OVID EMBASE and Central (the Cochrane Central Register of Controlled Trials) from inception to August 24, 2017 to identify relevant studies. The search consisted of controlled vocabulary (i.e. MeSH in MEDLINE) and free text words for central neuraxial blocks and epidural/spinal haematomas and abscesses. Animal studies were safely excluded by double negation (not exp animals/ not humans/). No further language, date, or other restrictions were imposed. For entire MEDLINE search strategy see Appendix Table A1. We cross-checked the reference lists and the cited articles of the identified relevant papers for additional references. The bibliographic records retrieved were imported and de-duplicated in EndNote X7.5 (Thomson Reuters, USA).

Article selection

Titles, abstracts, and subsequently, full texts were independently screened for reports concerning haematomas and abscesses associated with CNB by two authors (E.B. and J.H. or P.L.). Inclusion criteria for eligibility were spinal

haematoma or abscess after CNB in humans. We defined spinal haematoma or abscess as any epidural, subdural, or subarachnoid haematoma or abscess below the level of C0. CNBs were classified as continuous epidural anaesthesia, spinal anaesthesia, combined spinal-epidurals (CSE), epidural injection, spinal catheters, spinal cord stimulators, caudal block, and facet joint block. Facet joint block is usually not referred to as CNB; however, if facet block resulted in spinal complications, it was included. Case reports, case series, prospective and retrospective cohort studies, systematic reviews and literature reviews (if containing original data) in English, Dutch, French, or German were included. When articles in other languages were encountered but an English abstract was found, we restricted data extraction to the abstract. We confirmed that no overlap was present between cases described in reviews or cohort studies and case reports. Cases where causality of the haematoma to CNB was uncertain were included; however, cases were excluded if the haematoma could clearly be explained by underlying disease. Regarding abscesses, all cases with CNB before the development of a spinal abscess were included; also cases where causality of the complication to CNB was uncertain or when abscess could be explained by underlying disease.

Quality assessment

We used the critical appraisal of a case study checklist, adapted from The Pocket Guide to Critical Appraisal by Crombie,[16] to assess the quality of the included studies. Two authors (E.B. and P.L.) independently assessed the quality of all publications reporting on more than one case. The quality of single case reports was not assessed because of likely selection and publication bias.

Data extraction

Three independent reviewers (E.B., J.H., and P.L.) extracted information from the selected articles. When available, extracted data included age, sex, body mass index, ASA physical status,[17] coagulation status, indication for CNB, type of CNB, report of complicated puncture, timeline from CNB to complication, moment of first symptoms (rounded to full hours), presenting symptoms,

type of treatment, timing of evacuation of haematoma or abscess (rounded to full hours), and neurological recovery. For patients reported to have spinal abscess, additional data were extracted – whenever possible – on fever, leucocytosis, C-reactive protein concentrations and presence of concomitant meningitis. For complete information on extracted data see Appendix Table A2.

To evaluate neurological recovery, clinical symptoms before treatment decision were scored, based on symptoms described in the reported cases. Globally, all patients were scored for the presence of pain, and sensory and motor deficit. Pain was determined as back pain or radicular pain. The extent of neurological deficit, as defined by the American Spinal Injury Association Impairment Scale,[18] was further classified as follows:

- Grade A, complete neurological injury: no motor or sensory function, even in the lowest sacral segment (S4-5);
- Grade B, incomplete neurological injury: no motor function below neurological level but with sensory function below neurological level and in S4-5;
- Grade C, incomplete neurological injury: motor function preserved below neurological level and more than half of the key muscle groups have a muscle grade <3 (antigravity strength);
- Grade D, incomplete neurological injury: preserved functional motor function below neurological level and at least half of the key muscle groups have a muscle grade ≥3
- Grade E, normal motor and sensory function below the level of the lesion, abnormal reflexes may persist.

Regarding type of treatment, a distinction was made between neurosurgical decompression, conservative management and percutaneous drainage. Neurosurgical decompression consisted of laminectomy or other neurosurgical treatment for decompression of spinal complications. If neurosurgical evacuation was performed, we classified timing of surgery as: intervention within 6 h, intervention between 7 and 12 h, and intervention >12 h after symptom onset. Conservative management was described to

comprise treatment with analgesics, corticosteroids (i.e. dexamethasone), antibiotics, physiotherapy, rehabilitation, or no treatment at all.

Neurological recovery after treatment was scored as: 'full recovery', 'delayed but full recovery' (full recovery after more than 1 month from symptom onset), 'partial recovery' (improvement of symptoms, but persistent neurological deficit or pain present after treatment), and 'no objectified recovery after treatment'.

Statistical analysis

SPSS 24 (Chicago, IL, USA) was used for data management and statistical analyses. Normally distributed continuous variables are presented as mean (SD) and were compared using independent samples t-tests, whereas non-normally distributed variables are presented as medians (interquartile range) and compared using Mann-Whitney U-tests. Categorical variables are presented as n (%) and were compared using Pearson χ^2 tests, Fisher exact test, or Fisher-Freeman-Halton exact test.

Patients treated with neurosurgical intervention were compared with conservative management regarding outcome, and a distinction was made between the three different time intervals of intervention. A subgroup of patients with neurological deficit before treatment was analysed (with either sensory deficit or motor deficit), to truly reflect the degree of neurological recovery after treatment.

The association of patient characteristics, CNB characteristics and symptomatology with neurological recovery after treatment was assessed using logistic regression. We dichotomized neurological recovery as 'full recovery' (immediate and delayed full recovery) or 'persistent neurological deficit' (partial or no recovery) and treated it as binary variable in the analyses. Again, only patients with neurological deficit before treatment were included in the logistic regression analyses. Univariate regression models were generated in original data and multivariate regression models were generated in multiple imputed data to account for missing values. In the univariate regression model all factors significantly associated with persistent

neurological deficit were determined. These factors were then entered as covariates into a multivariate regression model. Regarding multivariate regression analysis, 'management type' (conservative management or neurosurgical decompression) and 'timing of intervention' were entered individually into the model as all patients with data for 'timing of intervention' were managed with neurosurgical decompression.

Results are presented as odds ratios [OR, 95% confidence intervals (CI)] in the univariate model and as adjusted odds ratios (aOR, 95% CI) in the multivariate model. A two-sided P-value of 0.05 was considered statistically significant.

Results

Of the 3291 retrieved publications, we selected 575 records for assessment of eligibility, after which we included 409 records in this review. Spinal haematoma after CNB was reported in 387 patients (280 articles); four patients suffered from a combination of spinal and intracranial haematoma after CNB.[19-22] Spinal abscess, was reported in 260 patients (139 articles, of which 129 unique articles, as 10 articles described both haematoma and abscess); one patient suffered from both spinal and intracranial abscesses.[23] Data collection and selection of articles are described in Figure 1. Articles concerning patients with spinal haematoma included 38 case series/cohort studies reporting 145 patients and 242 patients in single case reports. Patients with spinal abscess were reported in 36 case series/cohort studies including 157 patients and 103 single case reports. Median number of patients per article was two (2 – 46 patients). Characteristics of patients with spinal haematoma and abscess are described in Table 1.

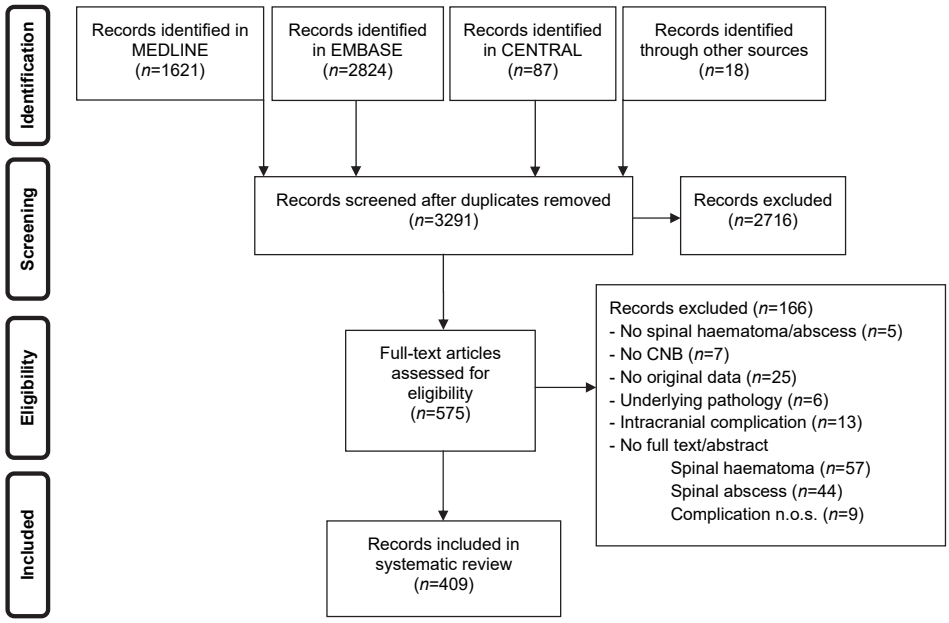

Figure 1. Flow chart of search and selection of records concerning spinal haematomas and abscesses after central neuraxial blocks from inception of databases until August 24 2017. CNB: central neuraxial block, n.o.s.: not otherwise specified.

Table 1. Characteristics of patients with spinal haematoma and spinal abscess after central neuraxial block. P: P-values are valid for comparison between patients with spinal haematoma and patients with spinal abscess. N: cases with available data on specific parameter. LMWH: low molecular weight heparin. NA: not applicable. *After spinal anaesthesia: after spinal anaesthesia or failed spinal anaesthesia. Spinal cord stimulator (SCS) and continuous spinal anaesthesia (spinal catheter) were included in the category 'during puncture' when symptoms were described during puncture, into the category 'during drugs administration' when drugs were administered through a catheter or treatment with SCS was ongoing and into the category 'after removal of catheter' if catheter or SCS was removed.

	Spinal Haematoma Total 387 (%)		n	Spinal Abscess Total 260 (%)		n	*P*-value
Age in years, median [IQR]	66.0	[48.5 – 76.0]	313	53.0	[38.0 – 66.0]	163	<0.001
Sex (male, female)	137 (39.8), 207 (60.2)		344	92 (50.0), 92 (50.0)		184	0.026
BMI, median [IQR]	25.9	[22.6 – 28.0]	52	30.2	[25.5 – 35.1]	6	0.054
ASA, N (%)			168			57	<0.001
Class 1	21	(12.5)		18	(31.6)		
Class 2	74	(44.0)		28	(49.1)		
Class 3	67	(39.9)		9	(15.3)		
Class 4	6	(3.6)		2	(3.5)		
Central neuraxial technique			374			247	<0.001
Epidural	215	(57.5)		205	(83.0)		
Spinal	62	(16.6)		14	(5.7)		
Combined spinal epidural	32	(8.6)		8	(3.2)		
Epidural injection	27	(7.2)		10	(4.0)		
Failed regional technique	19	(5.1)			-		
Spinal catheter	9	(2.4)		6	(2.4)		
Spinal cord stimulator	7	(1.9)		2	(0.8)		
Facet joint block	3	(0.8)		1	(0.4)		
Caudal block		-		1	(0.4)		
Report of complicated puncture			247			53	0.040
No difficult puncture	127	(51.4)		37	(69.8)		
Difficult/multiple punctures	77	(31.2)		14	(26.4)		
Bloody tap	28	(11.3)		1	(1.9)		
Accidental dural puncture	15	(6.1)		1	(1.9)		
Procedure			319			198	<0.001
Major orthopaedic	61	(19.1)		13	(6.6)		
Pain management	47	(14.7)		66	(33.3)		
Major digestive	40	(12.5)		25	(12.6)		
Peripheral vascular	36	(11.3)		6	(3.0)		
Minor digestive	22	(6.9)		2	(1.0)		
Obstetric: Labour analgesia	21	(6.6)		14	(7.1)		
Urologic	19	(6.0)		6	(3.0)		
Minor orthopaedic	14	(4.4)		4	(2.0)		
Obstetric: Caesarean section	12	(3.8)		20	(10.1)		
Aortic	11	(3.4)		4	(2.0)		
Thoracotomy	10	(3.1)		5	(2.5)		
Thoracoscopy	8	(2.5)		1	(0.5)		
Endovascular aneurysm repair	5	(1.6)			-		
Cardiac surgery	4	(1.3)			-		
Gynaecologic oncology/surgery	4	(1.3)		1	(0.5)		
Traumatology	2	(0.6)		23	(11.6)		
No Surgery	1	(0.3)		1	(0.5)		
Amputation (leg) / Extremities	1	(0.3)		7	(3.5)		
Neurosurgical	1	(0.3)			-		

	Spinal Haematoma Total 387 (%)		**n**	**Spinal Abscess** Total 260 (%)		**n**	***P*-value**
Coagulation status			262			27	0.018
No regular anticoagulants	76	(29.0)		4	(14.8)		
Aspirin	21	(8.0)		1	(3.7)		
Prophylactic LMWH	64	(24.4)		17	(63.0)		
Therapeutic LMWH	5	(1.9)			-		
Vitamin K antagonist	21	(8.0)			-		
Coagulation disorder	18	(6.9)		2	(7.4)		
Mistake in drug administration	4	(1.5)			-		
Unspecified anticoagulant therapy	5	(1.9)			-		
Heparin infusion	38	(14.5)		1	(3.7)		
Urokinase infusion	3	(1.1)		1	(3.7)		
LMWH and vitamin K antagonist	3	(1.1)			-		
Multi-therapy	4	(1.5)		1	(3.7)		
Time point of complication			299			152	<0.001
During puncture	49	(16.4)		11	(7.2)		
During drugs administration	70	(23.4)		56	(36.8)		
After removal of catheter	103	(34.4)		71	(46.7)		
After spinal anaesthesia*	77	(25.8)		14	(9.2)		
Symptom							
Pain (present, absent)	157 (64.3), 87 (35.7)		244	133 (92.4), 11 (7.6)		144	<0.001
Sensory deficit (present, absent)	230 (81.9), 51 (18.1)		281	55 (43.3), 72 (56.7)		127	<0.001
Motor deficit (present, absent)	266 (87.8), 37 (11.2)		303	83 (51.9), 77 (48.1)		160	<0.001
ASIA Impairment Scale			206			104	<0.001
Grade A	80	(38.8)		8	(7.7)		
Grade B	19	(9.2)		3	(2.9)		
Grade C	13	(6.3)		2	(1.9)		
Grade D	64	(31.1)		31	(29.8)		
Grade E	30	(14.6)		60	(57.7)		
Treatment			322			207	0.007
Conservative	96	(29.8)		62	(30.0)		
Neurosurgical decompression	226	(70.2)		139	(67.1)		
Percutaneous drainage		-		6	(2.9)		
Neurologic recovery after treatment	96	(30.2)	318	115	(60.5)	190	<0.001
Full recovery	53	(16.7)		14	(7.4)		
Delayed but full recovery	89	(28.0)		40	(21.1)		
Partial recovery	80	(25.2)		21	(11.1)		
No recovery							

Quality assessment

The risk of bias in the included studies was serious. Many variables of the checklist[16] were scored as negative or unclear. Information on quality of each of the case series or cohort studies is shown in Appendix Table A3. Among the 64 studies (28 articles reporting solely patients with spinal haematoma, 26 articles reporting solely patients with spinal abscess and 10 articles reporting both spinal haematoma and abscess), only three studies scored positive on all 11 required items of the checklist and another six studies scored positive on 10 items.

Clinical presentation

Spinal haematoma

Complete details on clinical presentation regarding pain, sensory and motor symptoms were present for 229 patients; the typical triad of pain, sensory and motor deficit, was present in 105 (46%) patients, overall clinical presentation was variable (Fig. 2). Pain as the sole isolated symptom, thus without neurological symptoms, was present in 23 (10%) patients.

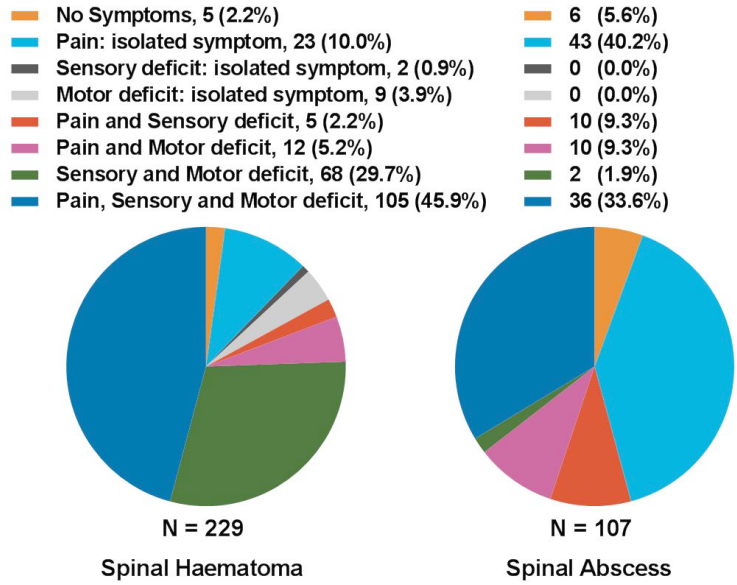

Figure 2. *Clinical presentation in patients with spinal haematoma and spinal abscess, N (%).*

Spinal abscess

Complete details on clinical presentation were present for 107 patients; a triad of pain, sensory and motor deficit was reported in 36 (34%) patients (Fig. 2). Pain as the sole isolated symptom, was present in 43 (40%) patients.

At the time of diagnosis, fever was present in 104 (74%) patients and described to be absent in 36 (26%) patients, while data on the presence or absence of fever were missing in 120 patients. The presence or absence of meningitis was explicitly reported in 15 patients; 14 patients had concomitant spinal abscess and meningitis and in one patient meningitis was absent; however, in the remaining patients, details were missing. Blood biomarkers for infection were only reported in few reports; mean leucocyte count was 15.7 x 10^9 litre^{-1} (5.4, n=30) and C-reactive protein was 37.0 mg litre^{-1} (16.5 – 126.0, n=27).

The clinical presentation of patients with spinal haematoma and spinal abscess is described in Table 1 and Figure 2. Overall, patients with spinal abscess presented with milder symptomatology compared with patients with spinal haematoma.

Development of symptoms

Spinal haematoma

The first symptoms suggestive of haematoma after epidural anaesthesia occurred in 11 (7%) patients during puncture, in 56 (36%) patients during treatment with an indwelling epidural catheter, and in 87 (56%) patients after epidural catheter removal (time point was missing in 61 patients treated with epidural anaesthesia). In patients treated with CSE, two (10%) patients developed first symptoms immediately after puncture, nine (45%) patients during treatment and nine (45%) patients after catheter removal (missing time point in 12 patients), and in patients treated with spinal catheter, one (17%) patient developed first symptoms directly after puncture, two (33%) patients during treatment, and three (50%) patients after catheter removal (missing time point in three patients). Median time to first symptoms was 24 h (5 – 48, n=264) after the predisposing event (i.e. central neuraxial procedure

or removal of catheter). Median duration of symptom progression was 12 h (5 – 48, n=78) and on average, neurosurgical decompression of the spinal haematoma after symptom onset was performed after 13 h (6 – 30, n=178). Patients with spinal haematoma had been treated with an indwelling catheter for a median duration of 48 h (11 – 72, n=124).

Spinal abscess

The first symptoms suggestive of an abscess occurred in 50 (43%) patients during treatment with an indwelling epidural catheter and in 65 (57%) patients after epidural catheter removal (time point was missing in 90 patients treated with epidural anaesthesia). In patients treated with CSE, one (14%) patient developed first symptoms during treatment and six (87%) patients after catheter removal (missing time point in one patient), and in patients treated with spinal catheter, three (100%) patients developed first symptoms during treatment (missing time point in three patients). The first symptoms suggestive for an abscess occurred 168 h (96 – 384, n=129) after the predisposing event (i.e. central neuraxial procedure). Median duration of symptom progression was 72 h (24 – 144, n=43) and neurosurgical decompression of the abscess after symptom onset was performed after 96 h (28 – 168, n=71). Patients with spinal abscess had been treated with an indwelling catheter for a median duration of 96 h (72 – 192, n=117). In the chronic pain population, the median duration of treatment was 180 h (72 – 696, n=28) vs 85 h (48 – 144, n=78) in the other patient categories (P=0.001).

The development of first symptoms, symptom progression, spinal decompression, and removal of the catheter were significantly accelerated in patients with spinal haematoma compared with patients with spinal abscess after CNB (all P<0.001).

Neurological recovery

Spinal haematoma

Treatment resulted in full recovery in 149 (47%), partial recovery in 89 (28%) and no recovery in 80 (25%) patients.

When focussing on patients with neurological deficit before treatment, conservative treatment was performed in 67 patients. In 37 of these patients, conservative treatment was explicitly chosen or the reason for conservative treatment was not documented, in five patients conservative treatment was

chosen because of a poor patient condition, and three patients refused surgery. In the remaining 22 patients, surgical decompression of the spinal haematoma was intended, or neurosurgical consultation was sought; however, as a result of spontaneous recovery a decision was made (often by the attending neurosurgeon) to defer surgery and follow a conservative approach. Excluding these patients with spontaneous recovery from consideration, the reports described full recovery in 25 (56%) patients and persistent neurological deficit in 20 (44%) patients after conservative treatment (n=45).

Neurosurgical decompression was selected for 202 patients with neurological deficit before treatment. The timing of neurosurgical decompression after symptom onset and the respective neurological outcome was reported in 163 patients; intervention within 6 h was performed in 48 (30%) patients, intervention from 7 to 12 h in 33 (20%) patients, and 82 (50%) patients were treated after >12 h. See Figure 3a for neurological outcome in patients treated with conservative management and neurosurgical intervention. Intervention after >12 h from symptom onset resulted in worse neurological outcome compared with conservative management and intervention within the first 12 h (Fig. 3a). However, patients treated with conservative management had milder neurological symptoms before treatment than patients treated with neurosurgical intervention (Fig. 3b).

Focussing on patients with pain as the sole isolated symptom, complete resolution of symptoms occurred over time in 21 out of 23 (91%) reports, while two patient reported persistent pain complaints at 6 months[24] and 9 months[25] of follow-up. Five (22%) of 23 patients had been treated with neurosurgical decompression, while the remaining patients had been treated conservatively. Both patients who reported pain after treatment had been treated conservatively.

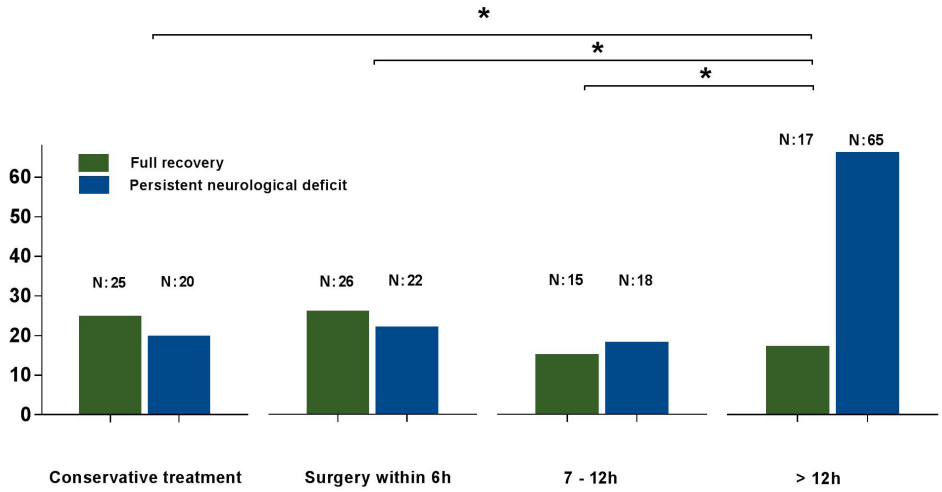

Figure 3a. Neurological recovery in patients with spinal haematoma managed with conservative treatment, neurosurgical decompression within 6 hours (h), decompression after 7 – 12h and decompression after more than 12h from symptom onset. Neurological recovery was significantly better in patients treated with conservative treatment (P<0.001), surgery within 6h (P<0.001), and surgery between 7 – 12h (P=0.007) compared with patients treated with surgery after more than 12h. No differences in outcome were present between patients managed with conservative treatment compared with neurosurgical evacuation within 6h after symptom onset (P=0.893), and compared to surgery at 7 – 12h (P=0.378). Also, no difference in outcome was present between intervention within 6h and intervention at 7 – 12h (P=0.645). Details on neurological outcome were missing in 2/50 cases treated with intervention within 6h, in 1/34 patients treated with surgery within 7 – 12h and in 2/84 cases treated after more than 12h from symptom onset.

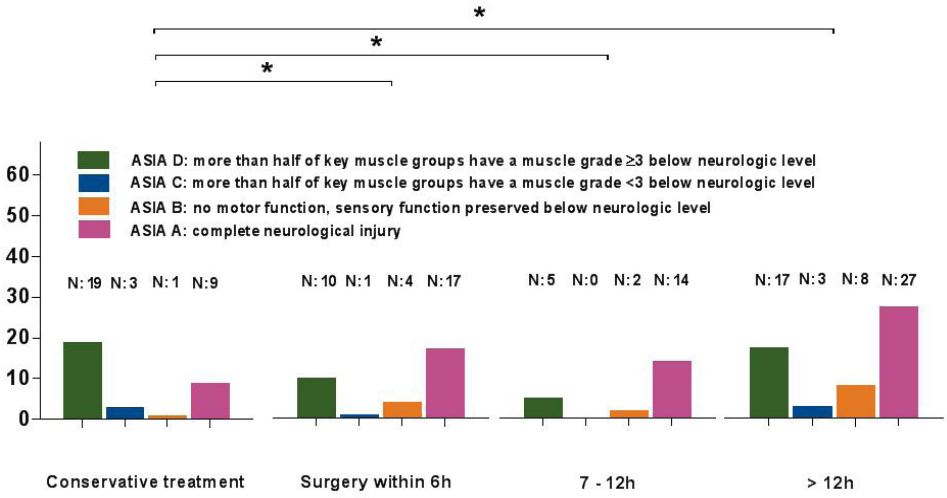

Figure 3b. ASIA impairment scale before treatment in patients with spinal haematoma managed with conservative treatment, neurosurgical decompression within 6 h, decompression after 7 – 12 h and decompression after more than 12 h from symptom onset. ASIA impairment scale was significantly better in patients treated with conservative treatment compared with patients treated with surgery within 6 h (P=0.036), compared with patients treated with surgery within 7 – 12h (P=0.007), and patients treated with surgery after more than 12h (P=0.024). Details on ASIA impairment scale prior to treatment were missing in 13/45 patients treated with conservative management (patients with spontaneous recovery excluded) and in 55/163 patients treated with neurosurgical decompression and a reported neurological outcome.

Spinal abscess

Full recovery was seen in 129 (68%) patients, 40 (21%) had partial recovery, and 21 (11%) had persistent complaints. Conservative treatment was performed in seven patients with neurological deficit before treatment. Conservative treatment was explicitly chosen in four patients, was chosen because of a poor patient condition in one patient, one patient refused surgery, and spinal surgery was considered in one patient, however, as a result of spontaneous recovery, surgery was deferred and a conservative approach was followed. Conservative treatment resulted in full recovery in six of seven patients with neurological deficit before treatment.

Neurosurgical decompression was selected in 84 patients with neurological deficit before treatment and one patient was treated with percutaneous drainage. Neurological recovery was not related to the timing of neurosurgical decompression after symptom onset (P=0.361, n=57). No differences were seen in the severity of neurological symptoms before treatment between patients treated with conservative management and with neurosurgical intervention (P=0.245, n=44).

Forty-three (40%) patients presented with pain as the sole isolated symptom; data on neurological recovery were missing in six patients with this clinical presentation, 36 of the remaining 37 patients had full recovery, and one patient[23] had persistent pain after treatment of the spinal abscess. Seventeen of 43 (40%) patients were treated with neurosurgical decompression, three (7%) were treated with percutaneous drainage, and 23 (53%) were treated conservatively.

Neurological recovery in patients with spinal haematoma and abscess is described in Table 1.

Univariate regression

Spinal haematoma

Older age, higher ASA physical status, a bloody tap during puncture, and severe neurological deficit before treatment were associated with persistent neurological deficit. Specifically, neurosurgical decompression was associated

with persistent neurological deficit after treatment compared with conservative management (OR 3.9, 95% CI 2.2 – 7.0, *P*<0.001, *n*=262), also when patients with spontaneous recovery were excluded (OR 2.4, 95% CI 1.2 – 4.6, *P*=0.010, *n*=240). However, as mentioned above, patients who underwent surgery had, on average, worse clinical symptoms than those treated conservatively. In the published patients treated with neurosurgical decompression, neurological outcome was similar in patients treated within 6 h, and between 7 and 12 h. Intervention after >12 h from symptom onset was associated with worse neurological outcome compared with intervention within 6 h (OR 4.5, 95% CI 2.1 – 9.9, *P*<0.001, *n*=163). Factors contributing to persistent neurological deficit after treatment in patients with spinal haematoma are listed in Figure 4.

Spinal abscess

Age, sex, and severe motor deficit before treatment were associated with persistent neurological deficit [age 40 – 64 yr (reference: 0 – 39 yr): OR 10.4, 95% CI 3.0 – 36.4, *P*<0.001, *n*=83, male (reference: female): OR 3.0, 95% CI 1.2 – 7.3, *P*=0.016, *n*=86, severe motor deficit (reference: no/mild deficit): OR 3.9, 95 % CI 1.2 – 12.4, *P*=0.021, *n*=87]. Furthermore, neurological recovery was favourable in seven patients treated conservatively compared with surgically treated patients (neurosurgical evacuation: OR 9.5, 95% CI 1.1 – 82.6, *P*=0.042, *n*=88). However, a wide confidence interval, as is consistent with a small number of patients treated conservatively, is present. When we excluded the patient with spontaneous recovery, neurological outcome was similar between management strategies (neurosurgical evacuation: OR 7.9, 95% CI 0.9 – 70.9, *P*=0.065, *n*=87; six patients treated conservatively). We found no association between neurological outcome and timing of neurosurgical intervention (timing of neurosurgical decompression >12 h from symptom onset: OR 0.3, 95% CI 0.0 – 3.2, *P*=0.336, *n*=57).

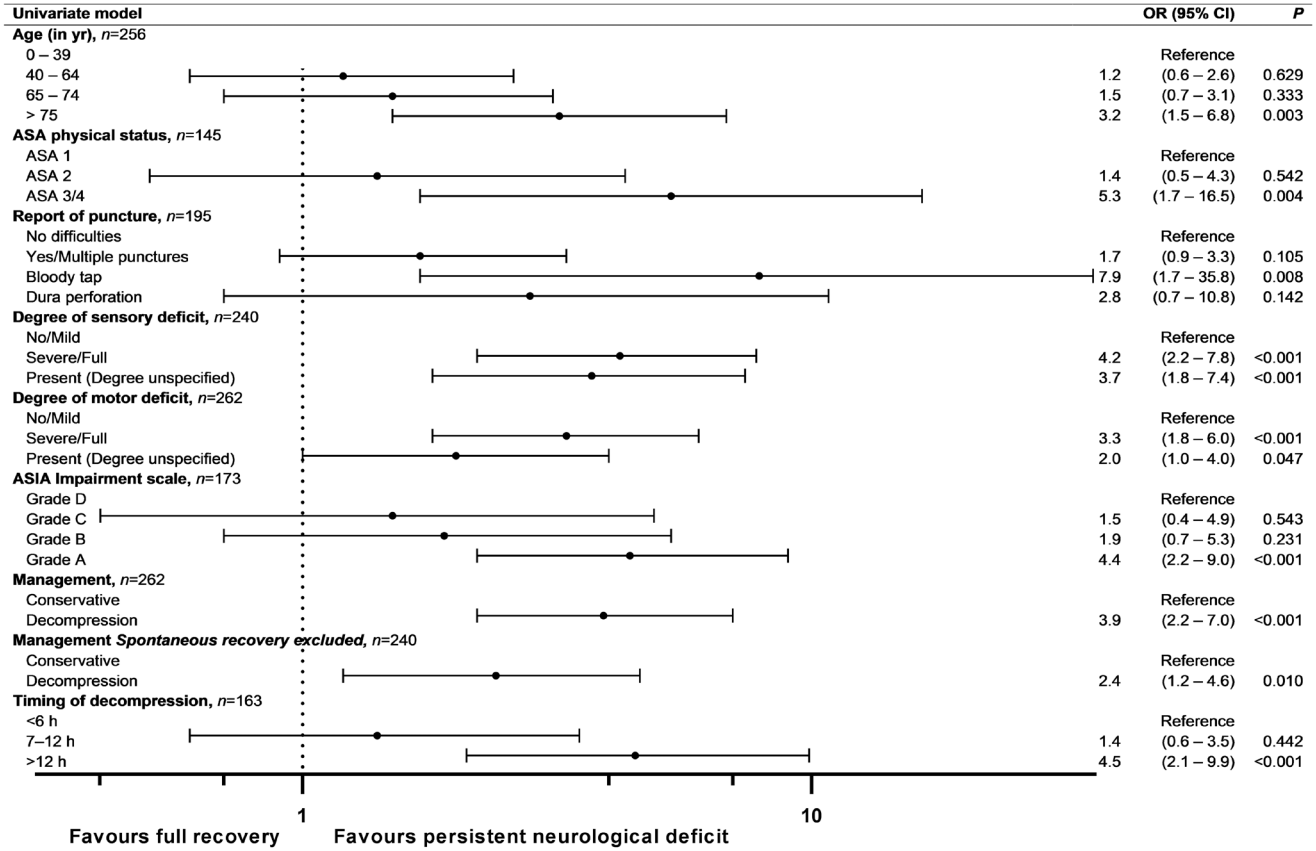

Figure 4. Odds ratios for persistent neurological deficit in patients with spinal haematoma with neurological deficit before treatment. Odds ratios [OR (95% confidence intervals)] are presented for univariate analysis of original data. N, patients with available data on specific parameter and outcome.

Multivariate regression

Spinal haematoma

Factors individually associated with persistent neurological deficit after treatment were a higher ASA physical status, bloody tap during puncture, sensory deficit, and management strategy. In detail, in the reports on spinal haematoma, neurosurgical decompression, when corrected for age, ASA physical status, bloody tap, and degree of sensory and motor deficit, was associated with persistent neurological deficit after treatment (aOR 3.5, 95% CI 1.9 – 6.4, $P<0.001$) compared with conservative management, as is consistent with the univariate analysis. However, when patients with spontaneous recovery were excluded from analysis, neurological outcome was similar between management strategies (neurosurgical decompression: aOR 1.9, 95% CI 0.9 – 4.0, $P=0.110$). Intervention after >12 h after symptom onset was associated with worse neurological outcome compared with intervention within 6 h when corrected for the above-mentioned contributing factors (aOR 3.1, 95% CI 1.2 – 7.4, $P=0.014$). When summarising published reports, neurological outcome was similar in patients treated within 6 h, and between 7 and 12 h.

Factors individually associated with persistent neurological deficit after treatment in patients with spinal haematoma are listed in Figure 5.

Spinal abscess

Severe motor deficit before treatment was individually associated with persistent neurological deficit after treatment, when corrected for sex and age (aOR 3.9, 95% CI 1.3 – 11.1, P=0.012). Sex and age were not individually associated with neurological outcome when corrected for age, sex, and degree of motor deficit.

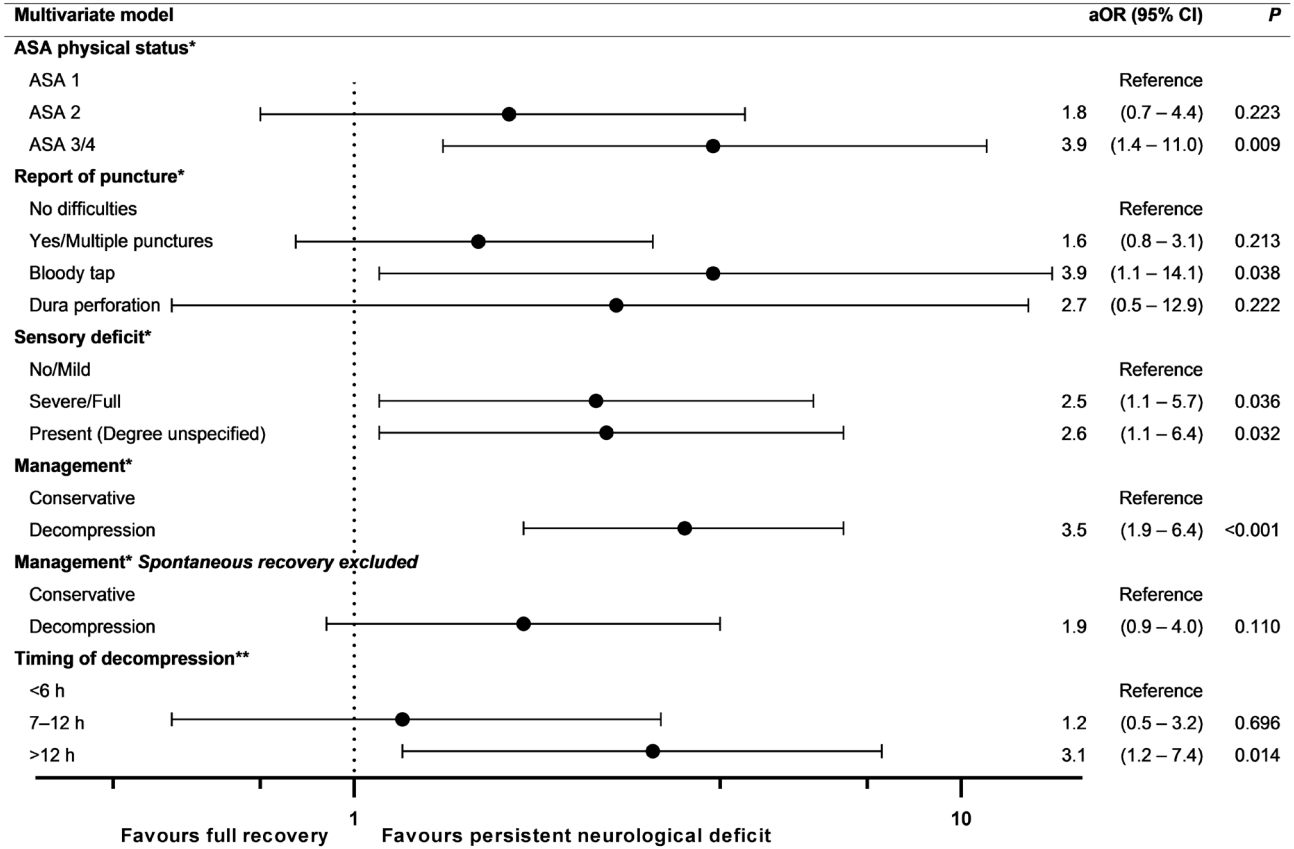

Figure 5. Adjusted Odds ratios (aOR) for persistent neurological deficit in patients with spinal haematoma with neurological deficit before treatment. aOR (95% confidence intervals, CI) are presented for multivariate regression analysis of multiple imputed data. *Adjusted for age, ASA physical status, report of complicated puncture, degree of sensory deficit, degree of motor deficit and management **Adjusted for age, ASA physical status, report of complicated puncture, degree of sensory deficit, degree of motor deficit and timing of decompression.

Discussion

We analysed all available case reports and case report series of spinal haematomas and abscesses after CNB. We identified 387 cases of spinal haematoma and 260 cases of spinal abscess.

Our main findings are that the clinical course and pathophysiology for spinal haematoma and abscess after CNB are distinct. Spinal haematomas are most likely to occur in older patients after epidural anaesthesia, and most often first symptoms appeared after catheter removal. Patients with higher ASA physical status, a 'bloody tap' during puncture, and with sensory deficit before treatment, appear to be most at risk for persistent neurological deficit. Furthermore, in patients with mild neurological symptoms, favourable neurological outcome was reported more often after conservative treatment than after surgical decompression. Patients with milder symptomatology are both more likely to recover fully, and more likely to be treated conservatively.[26] Furthermore, some patients had spontaneous recovery, that is, during the diagnostic process or while waiting for decompressive surgery. Consequently, after correcting for the severity of neurological deficit by the time of diagnosis and when excluding patients with spontaneous recovery, neurological outcome was similar in reports using each of the two different treatment strategies. Besides the type of management, also the time interval from symptom onset to intervention was associated with outcome. First, in the analysed cases we could find no difference in outcome between patients treated within 6 h and 7 – 12 h after first symptoms, and secondly, our analysis indicated that neurological outcome was favourable in patients treated within the first 12 h from symptoms onset compared with delayed intervention (after >12 h). We would like to emphasize that these findings should not be taken as a treatment recommendation, as we are aware that we cannot explicitly determine the most appropriate timing of surgery based on the results and quality of the data. Close monitoring, with frequent neurological examinations, is of utmost importance to select patients suitable for conservative treatment, and those patients in whom surgery should be

performed to prevent a potential worsening of symptoms. On average, delay to neurosurgical treatment was surprisingly long.

Spinal abscess occurred mainly after treatment with continuous epidural anaesthesia, and again, first symptoms often became apparent after removal of a spinal or epidural catheter. Overall, the reported symptomatology was milder and neurological outcome was better in patients with spinal abscess than in patients with spinal haematoma, which is probably because of the more rapid progression of symptoms in haematoma. Moreover, the severity to which the neurological deficit had progressed by the time of diagnosis was a strong predictor of outcome in spinal complications associated with CNB. Together with the data suggesting that neurosurgical treatment of spinal haematoma is often delayed substantially, this finding can be taken to re-emphasize the importance of education of patients and non-anaesthesia personnel to recognize and report potential symptoms that may indicate the development of a spinal haematoma or abscess.

Treatment considerations

The majority of patients with spinal haematoma and spinal abscess were surgically managed, which is congruent with the literature.[12] Furthermore, critical factors for recovery are the extent of preoperative neurological deficit and the operative interval, as is reported by other authors.[11] Although we are aware that we cannot advocate certain treatment strategies based on the results of this research, a possibility for conservative treatment seems to be present in certain patients. Other authors have previously stated that surgical decompression is the treatment of choice for progressive neurological deficits, but an initial conservative approach for patients with minimal neurological manifestations can be defended, for example in idiopathic, spontaneous and traumatic spinal haematomas.[26-31]

An extensive study of spinal haematomas described in literature between 1826 and 1996 by Kreppel,[11] reported only few patients (6%) treated with conservative management. This is much less than the proportion of patients treated conservatively in our analysis. It is conceivable that there has been a

shift towards conservative management especially in patients without or with mild neurological symptoms. Concerning patients with severe neurological symptoms, no recommendations on treatment strategy can be made as only a minority of patients with severe neurological injury were treated with conservative treatment in our analysis.

Pathophysiology

Spinal haematoma

Spinal haematoma is caused by injury to posterior spinal and epidural veins, or even arteries, which can occur during puncture, during drug administration or after catheter removal. It has been suggested that catheter placement may lead to a small haematoma and blood clot that is dislodged during catheter removal, which may explain at least some instances of (re)bleeding.[32] Of note, the volume of the haematoma is not the only factor that determines the degree of neurological deficit.

Retrospective series of patients after spinal surgery identified asymptomatic spinal haematoma in 33% of patients using magnetic resonance investigations. A substantial disparity was present between a large incidence of haematoma formation and a small rate of symptom development.[33] The location and, moreover, the degree of thecal sac compression correlates with the degree of neurological symptoms. Therefore, depending on the local diameter of the spinal canal, even a small haematoma volume can result in substantial compression of the spinal cord causing severe symptoms.[34] Of interest is that epidural blood patches, in order to treat post-spinal puncture headache, are frequently performed by anaesthetists without a specific fear for thecal sac compression and consequent neurological deficits, even though the volume of autologous blood that is administered in the epidural space, can often be up to 30 ml, and even volumes >50 ml have been reported.[35] However, it should be noted that these injections are performed under continuous monitoring of patient symptoms.

Spinal abscess

The pathophysiology of spinal abscesses is grounded on infection of the epidural, subdural, or subarachnoid space. Infection can occur at the time of CNB, through contamination of the skin site, through subsequent spread along a spinal or epidural catheter, by haematological spread, or by intraluminal contamination via a contaminated syringe or local anaesthetic solution.[7] It has also been suggested that an abscess can occur as a result of infection of a haematoma.[36]

Bacterial colonization of the skin insertion site increases significantly after 48 h and the risk of superficial infection increases with the duration of catheterization.[37] In keeping with the underlying diagnosis, a longer duration of catheterization was seen in chronic pain patients than in postoperative or postdelivery patients.[38] In the present review, a considerable proportion [66 (33%) patients] of the reported abscesses occurred in the chronic pain population.

Clinical course

In our analysis, many patients developed symptoms of spinal haematoma or abscess after removal of a spinal or epidural catheter, after spinal anaesthesia or after failed regional techniques. With respect to routine follow-up after CNB, it is of note that symptoms typically occur when patients are no longer followed-up by the anaesthetist. Also, patients with a failed technique are usually not included in follow-up rounds. Moreover, patients with spinal complications after CNB are seldom monitored on a ward with neurological or neurosurgical expertise, resulting in delayed recognition of symptoms, imaging and evacuation.

Future reporting and registration

During data collection for this review we noted that many reports described widely diverse aspects of the clinical course of spinal haematoma and abscess. Apparently, no consensus exists on the most important aspects of these severe complications. The irregular patterns in the reporting of complications

hamper thorough analysis, which could lead to underestimation of risk factors. Uniform registries are needed to reduce the risk of publication bias, to allow for a more accurate identification of relevant risk factors for serious complications after CNB, and to formulate treatment recommendations. We refer in particular to the effort by Christie and McCabe who registered sequelae of epidural anaesthesia over a period of six years and recorded detailed patient characteristics and procedure-related data.[9] We suggest that registration of complications after CNB and the reporting of cases should be compliant with a predefined format. This will allow collection of complete data, more accurate estimates of incidence rates, prognostic factors, response to therapy and assist in quality improvement efforts. We would like to encourage other authors to use a format as is described in this review when reporting rare complications of CNB such as spinal haematomas or abscesses (see Appendix Table A2).

Limitations

The quality of the included studies was low with high risk of publication bias, selection bias and underreporting of complications. For example, specific outcomes after selected treatments could be less or more likely to be reported than others, such as favourable recovery after conservative treatment vs devastating paraplegia. Also, we report the aggregated time point at which symptoms occurred after the previous event most likely to blame for the complication; puncture, during treatment or after catheter removal. However, because of the nature of the case reports, we cannot exclude that other factors may have precipitated or contributed to bleeding as well. Nevertheless, we would like to emphasize that symptoms of spinal haematoma frequently occur after catheter removal, at a time point when anaesthetists usually do not follow the patient on a routine basis.

The retrospective character and selective reporting of case reports and case series has resulted in other limitations; some cohort studies or reviews reported multiple cases, but details were not available for each separate case and led to missing data. Although we attempted to correct for missing data by using multiple imputation, lack of detail in the reports was a major limitation.

While acknowledging these caveats, we feel that the present analyses of aggregated reported cases can improve our understanding of these rare severe complications of CNB.

Conclusions

The severity to which the neurological deficit has progressed by the time of diagnosis is a strong predictor of outcome in spinal complications associated with CNB. Neurological deficit at the time of diagnosis is present in the absolute majority of patients with spinal haematoma, but individual presentation is highly variable and the classic triad of pain, sensory and motor deficit was present in just under half of patients. In our collective analysis of reported cases, with all inherent risks of bias, persistent neurological deficit was more likely when surgery was delayed. A less obvious 'new' insight is that in selected cases – those without or with mild neurological symptoms or those who show spontaneous recovery during the diagnostic process – one might consider a strategy of conservative management combined with frequent monitoring of neurological function.

Authors' contributions

Study design, literature search, data collection: E.B., J.H., P.L.
Data analysis: E.B., J.H., P.L.
Interpretation of data: all authors.
Drafting the article: E.B.
Revising the draft critically for important intellectual content: all authors.
Final approval of the version to be published; and agreement to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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Declaration of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2017.11.105.

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Appendix

Table A1. Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present. Search Strategy: 2017-08-24

#	Searches	Results
1	exp anesthesia, epidural/ or anesthesia, spinal/ or anesthesia, obstetrical/ or analgesia, epidural/	36746
2	*nerve block/ae or *autonomic nerve block/ae	1416
3	spinal cord stimulation/	594
4	epidur*.tw,kf. and an?esthe*.mp,jw.	21298
5	(epidurals or spinals).tw,kf.	656
6	(((regional or spinal* or caudal or neurax* or neuroax* or extradur* or peridur* or dural or intrathec*) adj6 an?esth*) or ((subarach* or sub-arach*) adj an?esth*)).tw,kf.	27125
7	((regional or spinal* or neurax* or neuroax* or epidural or extradur* or peridur* or dural or intrathec*) adj3 analg*).tw,kf.	11380
8	(exp injections, spinal/ or (((epidur* or neurax* or neuroax* or extradur* or peridur* or intrathec*) adj2 (cathet* or inject* or punct* or technique*)).tw,kf. or ((catheters, indwelling/ae or catheterization/ae) and epidural space/))) and (an?est* or analg* or neuralg* or palliat* or pain or adrenal cortex horm* or steroid* or corticoster* or gl#cocortic* or hydrocort* or methylpredn* or predniso* or dexamet* or opioid* or morphin* or morpholin* or fentanyl).mp,jw.	17712
9	((epidur* or neurax* or neuroax* or extradur* or peridur* or intrathec* or central nerv*) adj3 block*).tw,kf.	4017
10	((obstetric* or labo?r) adj an?est*).tw,kf.	2258
11	spinal cord stimulat*.tw,kf.	2738
12	**or/1-11 [epidural anesthesia]**	**74260**
13	hematoma, epidural, spinal/ or hematoma, subdural/ or hematoma, subdural, acute/ or hematoma, subdural, chronic/ or hematoma, subdural, spinal/ or subarachnoid hemorrhage/	27788
14	epidural abscess/	1093
15	(abscess/ or surgical wound infection/ or hematoma/ or infection/et) and (spinal diseases/ or spinal cord diseases/ or spinal cord injuries/ or exp spine/ or subarachnoid space/ or dura mater/)	2855
16	((epidur* or peridur* or extradur* or subdur* or intradur* or spin* or intraspin* or interspin* or paraspin* or neurax* or neuroax* or intrathec* or subarachnoid* or sub-arachnoid* or vertebra* or interverteb*) adj9 h?ematom*).tw,kf.	13173

17	((epidur* or peridur* or extradur* or subdur* or intradur* or spin* or intraspin* or interspin* or paraspin* or neurax* or neuroax* or intrathec* or subarachnoid* or sub-arachnoid* or vertebra* or interverteb*) adj3 h?emorrhag*).ti.	11960
18	(h?emorrh* adj2 l?esion*).tw,kf.	2585
19	((epidur* or peridur* or extradur* or subdur* or intradur* or spin* or intraspin* or interspin* or paraspin* or neurax* or neuroax* or intrathec* or subarachnoid* or sub-arachnoid* or vertebra* or interverteb*) adj (h?emorrhag* or bleed* or infect*)).tw,kf.	25359
20	((epidur* or peridur* or extradur* or subdur* or intradur* or spin* or intraspin* or interspin* or paraspin* or neurax* or neuroax* or intrathec* or subarachnoid* or sub-arachnoid* or vertebra* or interverteb*) adj3 ab?cess*).tw,kf.	3220
21	**or/13-20 [spinal hematomas and abscesses]**	**51446**
22	**12 and 21 [epidurals and spinal hematomas and abscesses]**	**1684**
23	exp animals/ not humans/ [animal filter]	4526855
24	**22 not 23 [epidurals and spinal hematomas and abscesses in humans]**	**1652**
25	**remove duplicates from 24 [epidurals and spinal hematomas and abscesses in humans - deduplicated]**	**1621**

Table A2. Extracted data in reports of spinal haematoma or abscess after central neuraxial blocks. ASA: American Society of Anesthesiologists. CNB: central neuraxial block, ASIA: American Spinal Injury Association Impairment Scale

Extracted data	
Age	In years (integer)
Sex	Male / Female
BMI	Weight in kilograms/(Height in meters)^2, 1 decimal
ASA physical status[1]	As reported by author or based on comorbidities reported by author
Type of regional technique	Continuous epidural anaesthesia, spinal anaesthesia, combined spinal epidural anaesthesia, spinal catheter, spinal cord stimulator, epidural injection, caudal block and facet joint block, or: 'other', describe
Report of complicated puncture	Easy/uncomplicated puncture, difficult/multiple punctures, 'bloody tap', inadvertent dural puncture
Number of attempts for CNB	Integer
Number of levels spinal cord attempted	Integer
Experience of anaesthesiologist performing CNB	Resident (≤5 years of experience) / anaesthesiologist (>5 years of experience)
Level of regional technique	Cervical, thoracic, lumbar or sacral/caudal
Puncture height	Between two vertebras; upper vertebra noted
Type of procedure	Major orthopaedic, Chronic pain management, Major digestive, Peripheral vascular, Minor digestive, Obstetric: Labour analgesia, Obstetric: Caesarean section, Urologic, Minor orthopaedic, Aortic, Thoracotomy, Thoracoscopy, Gynaecologic oncology/surgery, EVAR, Cardiac surgery, Trauma, Amputation (leg) / Extremities, Neurosurgical, or: 'other', describe
Hours to removal of catheter from time point 0	Time point 0 is first attempt CNB, rounded to full hours
Hours to symptoms from time point 0	Time point 0 is first attempt CNB, rounded to full hours
Hours to evacuation of complication from time point 0	Time point 0 is first attempt CNB, rounded to full hours
Hours progression of symptoms	From onset of first symptoms to worst symptoms evaluated, rounded to full hours
Hours to symptom onset after predisposing causative event	Causative event is defined as: i.e. CNB onset, removal of catheter or dose of anticoagulant, rounded to full hours
Hours to evacuation of complication from symptoms onset	Duration of first symptoms to evacuation of haematoma/abscess, rounded to full hours
Time point of complication as suspected by author	During puncture, during drug administration, after removal of catheter, after spinal anaesthesia

Symptoms	Pain: scored as partial/mild, full/severe, present; degree not further specified Sensory deficit: scored as partial/mild, full/severe, present; degree not further specified Motor deficit: scored as partial/mild, full/severe, present; degree not further specified
ASIA Impairment Scale	Grade A, complete neurological injury Grade B, no motor function present, but preserved sensation may be present Grade C, preserved non-functional motor function Grade D, preserved functional motor function Grade E, normal motor and sensory function, but abnormal reflexes may persist
Surgical evacuation	Yes / No / Percutaneous drainage
Neurological recovery	Full recovery, delayed but full recovery (recovery after more than 1 month from symptom onset), persistent weakness/partial recovery, persistent paralysis/no recovery
Type of haematoma/abscess	Spinal, spinal and intracranial
Coagulation status	No regular anticoagulant drugs, aspirin, prophylactic low molecular weight heparin (LMWH), therapeutic LMWH, vitamin K antagonist, heparin infusion, urokinase infusion, LMWH and vitamin K antagonist, multi-therapy (≥ 2 different anticoagulant drugs), coagulation disorder, mistake in drug administration, unspecified anticoagulant therapy
Practice consistent with current guideline	Consistent with most recent guideline Neuraxial Block and Anticoagulant Drugs – Dutch Society of Anaesthesiology[2]
Exclusively for Abscesses	
Immunosuppression	Yes / No
Diabetes	Yes / No
Prophylactic antibiotics	Yes / No
Fever	Yes / No, defined as temperature > 38 degree Celsius
Leucocytosis	Yes / No, > 11.0 x 10^9 per litre
Leucocytes	Exact number x 10^9 per litre
CRP	Exact number
Concomitant meningitis	Yes : No

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Table A3. *n*: number of patients reported. 1. Did the study address a clearly focused question / issue? 2. Is the research method (study design) appropriate for answering the research question? 3. Are both the setting and the subjects representative with regard to the population to which the findings will be referred? 4. Is the researcher's perspective clearly described and taken into account? 5. Are the methods for collecting data clearly described? 6a. Are the methods for analyzing the data likely to be valid and reliable? 6b. Are quality control measures used? 7. Was the analysis repeated by more than one researcher to ensure reliability? 8. Are the results credible, and if so, are they relevant for practice? 9. Are the conclusions drawn justified by the results? 10. Are the findings of the study transferable to other settings?

First author	Year	*n* Spinal Haematoma	*n* Spinal Abscess	1	2	3	4	5	6a	6b	7	8	9	10
Aldrete	1998	-	2	Yes	Yes	Yes	No	Yes	Yes	CT	CT	Yes	Yes	Yes
Barontini	1995	1	1	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Bateman	2013	7	-	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes
Bulow	1999	-	4	No	No	No	No	No	CT	CT	CT	Yes	Yes	Yes
Cameron	2007	2	6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CT	Yes	Yes	Yes
Christie	2007	3	6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CT	Yes	Yes	Yes
Cohen	2003	-	12	Yes	No	Yes	No	No	CT	CT	CT	CT	No	No
Cook	2009	6	15	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cullen	2004	7	-	Yes	No	Yes	Yes	No	CT	No	No	Yes	Yes	Yes
Dahlgren	1995	3	-	Yes	Yes	Yes	Yes	Yes	CT	CT	CT	Yes	Yes	Yes
Dawkins	1969	2	-	Yes	CT	Yes	Yes	No	No	No	CT	Yes	Yes	Yes
de Lima e souza	2011	2	-	No	No	Yes	Yes	No	No	CT	CT	Yes	Yes	Yes
de Seze	2007	3	-	Yes	No	Yes	Yes	Yes	No	CT	CT	CT	CT	Yes
Desai	2016	-	2	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Dickman	1990	2	-	Yes	No	Yes	Yes	No	No	No	CT	Yes	Yes	Yes
Dupeyrat	1990	2	-	Yes	No	Yes	Yes	No	No	No	CT	Yes	Yes	Yes
Ehrenfeld	2013	6	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Elwood	2009	2	-	Yes	No	Yes	Yes	No	No	No	CT	Yes	Yes	Yes
Flisberg	2007	1	1	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Gaul	2005	-	2	Yes	Yes	Yes	Yes	No	CT	CT	CT	Yes	Yes	Yes
Giberson	2013	2	-	No	CT	CT	No	No	No	No	No	Yes	Yes	Yes
Gosavi	2004	-	2	Yes	No	Yes	No	No	No	CT	CT	Yes	Yes	yes
Green	2010	-	2	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes
Gulur	2015	2	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CT	Yes	Yes	Yes
Hearn	2003	-	3	No	No	Yes	No	No	No	CT	CT	CT	Yes	Yes
Holt	1995	-	2	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes
Jeffreys	2006	-	4	Yes	CT	Yes	Yes	No	CT	CT	CT	Yes	Yes	Yes
Jones	2002	-	3	Yes	Yes	Yes	No	Yes	Yes	CT	CT	Yes	Yes	Yes

First author	Year	*n* Spinal Haematoma	*n* Spinal Abscess	1	2	3	4	5	6a	6b	7	8	9	10
Kamiyama	2006	-	2	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Kerdraon	1993	3	-	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Kupersztych	2017	1	2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kvalsvik	1998	-	2	Yes	No	Yes	Yes	No	CT	CT	CT	CT	Yes	Yes
LaBan	2007	2	-	No	No	Yes	No	No	No	No	CT	Yes	Yes	Yes
Li	2010	3	-	Yes	Yes	Yes	Yes	C	Yes	CT	CT	Yes	Yes	Yes
Lin	2005	-	2	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Linneman	1993	-	2	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Mamourian	1993	-	3	No	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Moen	2004	33	13	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes
Nam	2010	4	-	Yes	No	Yes	No	No	No	No	CT	Yes	Yes	Yes
North	1979	-	2	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Oda	2000	2	-	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Pandazi	2010	2	-	No	No	Yes	No	No	No	No	CT	Yes	Yes	Yes
Pedraza Gutierrez	1999	2	-	Yes	No	Yes	No	No	No	CT	CT	Yes	Yes	Yes
Phillips	2002	-	3	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Pitkanen	2013	13	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CT	Yes	Yes	Yes
Popping	2008	3	2	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes
Pumberger	2013	4	-	Yes	Yes	Yes	Yes	Yes	Yes	No	CT	Yes	Yes	Yes
Riley	2009	2	-	Yes	No	Yes	No	No	No	No	CT	Yes	Yes	Yes
Royakkers	2002	-	3	Yes	No	Yes	Yes	No	CT	CT	CT	Yes	Yes	Yes
Scott	1995	2	-	Yes	Yes	Yes	Yes	No	No	No	CT	Yes	Yes	Yes
Sillevis Smitt	1999	-	11	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes
Simpson	1999	-	3	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Sollmann	1987	1	1	No	No	CT	CT	CT	CT	CT	CT	Yes	Yes	Yes
Strong	1991	-	2	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Stroud	2000	2	-	Yes	No	Yes	Yes	No	No	No	CT	Yes	Yes	Yes
Tabo	1994	-	2	Yes	No	Yes	No	No	CT	CT	CT	Yes	Yes	Yes
Thiex	2005	2	-	Yes	Yes	Yes	No	No	Yes	Yes	CT	Yes	Yes	Yes
Volk	2012	5	-	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes
Wallace	2010	-	2	Yes	Yes	Yes	Yes	Yes	CT	CT	CT	Yes	Yes	Yes
Wang	2013	2	-	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Wang	2001	-	19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CT	Yes	Yes	Yes
Wang	1999	-	9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CT	Yes	Yes	Yes
Weis	1994	2	-	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Wille-J	1991	2	-	Yes	No	Yes	Yes	No	No	No	CT	Yes	Yes	Yes

Chapter 5

Intracranial Hematoma and Abscess after Neuraxial Analgesia and Anesthesia: a Review of the Literature describing 297 cases

Elke M.E. Bos, Koen van der Lee, Johan Haumann, Marcel de Quelerij, W. Peter , Vandertop, Cor J. Kalkman, Markus W. Hollmann, Philipp Lirk

Regional Anesthesia and Pain Medicine

Abstract

Background – Besides spinal complications, intracranial hematoma or abscess may occur after neuraxial block. Risk factors and outcome remain unclear.

Objective – This review evaluates characteristics, treatment and recovery of patients with intracranial complications after neuraxial block.

Evidence Review – We systematically searched Medline, Embase and the Cochrane Library from their inception to May 2020 for case reports/series, cohort studies and reviews of intracranial hematoma or abscess associated with neuraxial block. Quality of evidence was assessed using the critical appraisal of a case study checklist by Crombie.

Findings – We analyzed 232 reports, including 291 patients with hematoma and six with abscess/empyema. Major part of included studies comprised single case reports with a high risk of bias. Of the hematoma patients, 48% concerned obstetric patients, the remainder received neuraxial block for various perioperative indications or pain management. Prior dural puncture was reported in 81%, either intended (e.g. spinal anesthesia) or unintended (e.g. complicated epidural catheter placement). Headache was described in 217 patients, in 101 patients symptoms resembled post-dural puncture headache (PDPH). After treatment, 11% had partial/no recovery and 8% died, indicating the severity of this complication. Intracranial abscess after neuraxial block is seldom reported; six reports were found.

Conclusions – The diagnosis intracranial hematoma is often missed initially, as headache is assumed to be caused by cerebrospinal hypotension due to cerebrospinal fluid leakage, known as PDPH. Prolonged headache without improvement, worsening symptoms despite treatment or epidural blood patch, change of headache from postural to non-postural, or new neurological signs, should alert physicians to alternative diagnoses.

Introduction

Neuraxial administration of local anesthetics is widely used to provide analgesia or anesthesia. The most frequently reported side effects of neuraxial block, such as peri-procedural hypotension, urine retention and post-dural puncture headache (PDPH), are usually self-limiting or relatively easy to treat. More serious complications, such as spinal hematoma or abscess, although rare, feature prominently in the anesthesia literature as they may result in permanent neurological injury.[1–5] Intracranial complications, such as hematoma or abscess, may not be instantly recognized as complications of neuraxial analgesia, even though the consequences can be significant as well, with a possibility of permanent neurological deficit despite treatment.

Literature reviews focusing on the development of intracranial hematomas following neuraxial anesthesia are scarce and have mainly focused on obstetric patients as the incidence seems highest in this population.[6–9] The few reviews that are present in other populations, for example perioperative patients, are small and non-systematic.[10,11]

Previously, we systematically reviewed spinal complications after neuraxial block.[5] Using a similar approach, we aimed to collect all cases reported in the literature concerning intracranial hematomas or abscesses following neuraxial block, in order to identify possible predisposing patient characteristics, to describe the ensuing clinical course and to gain insight under which circumstances complications would be most likely to occur. [5]

Methods

Search Strategy

A systematic search in Medline, Embase and the Cochrane Central Register of Controlled Trials from inception of databases to May 11, 2020 was performed to identify relevant studies. The search consisted of controlled vocabulary (i.e. MeSH in Medline) and free text words for neuraxial blocks and intracranial hematomas and abscesses. Animal studies were safely excluded by double negation (not exp animals/ not humans/). No further language, date or other restrictions were imposed. For the entire Medline search strategy see Supplementary File 1. We cross-checked the reference lists and the citing articles of the identified relevant papers for additional references. The bibliographic records retrieved were imported and de-duplicated in EndNote X9.3.3 (Clarivate Analytics, USA).[5]

Article Selection

Titles, abstracts and subsequently full texts were independently screened for reports concerning intracranial hematomas and abscesses associated with neuraxial block by two authors (E.B. and K.v.d.L). Inclusion criteria for eligibility were intracranial hematoma or abscess after neuraxial block in humans. We defined intracranial hematoma or abscess as any epidural, subdural, subarachnoid or intraparenchymal hematoma or abscess above the level of C0. Neuraxial blocks were classified as continuous epidural analgesia, spinal anesthesia, a combined spinal-epidural (CSE), epidural injection, spinal catheters and spinal cord stimulators. Case reports, case series, prospective and retrospective cohort studies, systematic reviews and literature reviews (if containing original data) in English, Dutch, French or German were included. When articles in other languages were encountered but an English abstract was found, we restricted data extraction to the abstract. We confirmed that no overlap was present between cases described in reviews or cohort studies and case reports, by screening data of patients with for instance identical age, comorbidities, author names and clinical affiliations. When all variables

were identical and the presence of a double citation was confirmed, one of the identical citations was excluded (see Figure 1, Double citation). All cases with neuraxial block prior to the development of intracranial hematoma or abscess were included; also cases where causality of the complication to neuraxial block was uncertain and may be explained by underlying disease (i.e. vascular malformations as aneurysms and arteriovenous malformations) were included.[5]

Quality Assessment

We used the critical appraisal of a case study checklist, adapted from The Pocket Guide to Critical Appraisal by Crombie, to assess the quality of the included studies.[12] Two authors (E.B. and K.v.d.L.) independently assessed the quality of all publications reporting more than one case. The quality of single case reports was not assessed because of likely selection and publication bias.[5]

Data Extraction

Two independent reviewers (E.B. and K.v.d.L.) extracted information from the selected articles. When available, extracted data included space of complication (epidural, subdural, subarachnoid or intraparenchymal), location of complication (unilateral/bilateral; unilateral hematoma/abscess describes a complication located in one hemisphere, while bilateral hematomas/abscesses describe complications located in both hemispheres of the brain), age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status,[13] coagulation status, indication for neuraxial block, type of neuraxial procedure, needle size, report of complicated puncture, presenting symptoms, timeline from onset of neuraxial block to complication, moment of first symptoms (rounded to full hours), moment of first neurological symptoms (rounded to full hours), type of treatment, timing of evacuation of hematoma or abscess if performed (rounded to full hours), and recovery after treatment. For complete information on extracted data see Supplementary File 2.

Clinical symptoms prior to treatment decision were scored, based on symptoms described in the reported cases. Globally, all patients were scored

for the presence of pain (i.e. headache/neck pain), seizures, nausea/vomiting/dizziness, aphasia/dysarthria, visual disturbance, drowsiness/disorientation and neurological deficits (motor and sensory disturbances). We classified the extent of neurological deficit further using the Glasgow Coma Scale[14] (GCS); a GCS score < 13 was considered to be disturbed. Neurological symptoms, as indicated in the variable 'moment of first neurological symptoms' comprised motor, sensory or GCS disturbances. When first presenting symptoms comprised neurological deficits, the variables 'moment of first symptoms' and 'moment of first neurological symptoms' were scored identical, when first presenting symptoms comprised symptoms other than motor/sensory/GCS disturbances (e.g. headache), the moment of first symptoms was scored different than the moment of first neurological symptoms (if any).

Regarding type of treatment, a distinction was made between neurosurgical decompression and conservative management. Neurosurgical decompression consisted of burr holes, craniotomy, or other neurosurgical decompressive intervention. Conservative management was described to comprise treatment with analgesics, corticosteroids (i.e. dexamethasone), antibiotics, physiotherapy, rehabilitation, or no treatment at all.[5]

Recovery after treatment was scored as: 'full recovery', 'delayed but full recovery' (full recovery after more than one month from symptom onset), 'partial recovery' (improvement of symptoms, but persistent neurological deficit or pain present after treatment) and 'no objective recovery after treatment'.

Statistical Analysis

SPSS 26.0 (Chicago, IL, USA) was used for statistical analyses. Normally distributed continuous variables are presented as mean (SD) and were compared using independent samples t-tests, whereas non-normally distributed variables are presented as medians (interquartile range) and compared using Mann–Whitney tests. Categorical variables are presented as n (%) and were compared using Pearson χ^2 tests, Fisher exact test, or Fisher–Freeman–Halton exact test. A 2-sided p-value of 0.05 was considered statistically significant.[5]

Results

The search retrieved 3.276 publications, of which we selected 338 records for assessment of eligibility. Finally, we included 232 records in this review. Intracranial hematoma after neuraxial block was reported in 291 patients (226 articles); nine patients suffered from a combination of spinal and intracranial hematoma.[15–23] Intracranial abscess, was reported in six patients (six articles); one patient suffered from both spinal and intracranial abscesses.[24] Data collection and selection of articles is described in Figure 1. Articles concerning patients with intracranial hematoma included 14 case series/cohort studies, reporting 79 patients, and 212 patients in single case reports. Patients with abscess/empyema were reported in five single case reports and in one closed claims analysis also describing other serious complications after neuraxial anesthesia, including spinal hematoma and abscess.

Quality Assessment

A large proportion of included studies comprise single case reports, therefore, the risk of bias in the included studies is high. Furthermore, the quality of the case series and cohort studies is questionable, as many variables of the checklist[12] were scored 'unclear' or 'negative'. Information on the quality of each of the case series and cohort studies is shown in Supplementary File 3. Among the 14 studies (13 articles reporting solely patients with intracranial hematoma and one article reporting intracranial abscess, but also reporting spinal hematoma and abscess, which are not included in this analysis), only one study scored positive on nine of 11 required items of the checklist. None of the case series or cohort studies scored positive on all items of the checklist.

Intracranial Hematoma

Characteristics of patients with intracranial hematoma are described in Table 1. Patients were generally young and healthy, with a median age of 34 (28 – 50) years and ASA physical status 2 in 119 of 146 cases with data on ASA physical status; data were missing in 145 cases (50%). Approximately half of

patients comprise obstetric patients either undergoing caesarean section or receiving neuraxial labor analgesia (141 of 291 patients, 48%).

Most intracranial hematomas occurred after intended dural punctures, i.e. spinal anesthesia, spinal catheter or CSE procedures (if intending spinal anesthesia). Unintended dural puncture (e.g. spinal tap when attempting to place an epidural catheter for epidural analgesia or CSE) occurred in 51 patients; in 32 of 77 patients (42%) treated with epidural analgesia, in seven patients who experienced a failed regional technique, in three patients during epidural injection, in one patient treated with a CSE procedure and in one patient who received a spinal cord stimulator; furthermore, it was decided to place a spinal catheter after unintended dural puncture while attempting different neuraxial blocks in an additional seven patients (epidural analgesia was intended in five of these patients and CSE in two patients). In this series, 237 of 291 patients (81%) experienced a dural puncture, either intended or unintended.

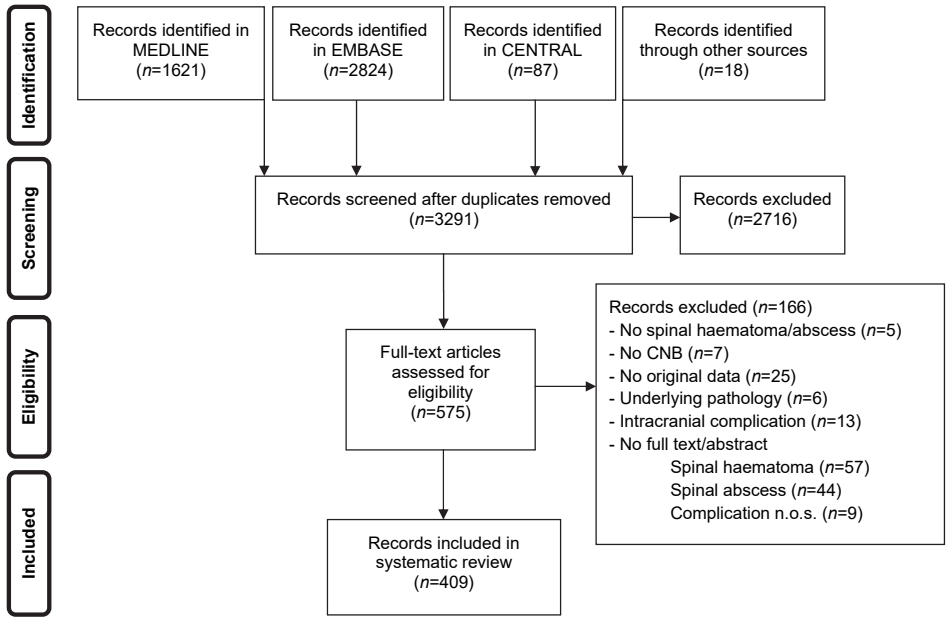

Figure 1: Flow chart of search and selection of records concerning intracranial hematomas and abscesses after neuraxial block from inception of databases until the 11th of May 2020. n: number of articles, n.o.s.: not otherwise specified.

No interference with the coagulation system (i.e. medication or underlying disease) was noticed in 74 patients, 25 patients used prophylactic low molecular weight heparin (LMWH), Aspirin/Clopidogrel, direct oral anticoagulants, a combination of anticoagulants, had heparin infusion or a coagulation disorder, or anticoagulant therapy was unspecified (see Table 1); interference with the coagulation system was unreported in 192 cases (66%).

Clinical Presentation

Virtually all patients reported pain (217 of 220 patients with information on the presence or absence of pain), i.e. headache and/or neck pain. In 101 of 217 patients with pain, the headache complied with criteria for (or was initially confused with) PDPH[25], in 16 patients the headache did not adhere to the criteria for PDPH and an alternative diagnosis was considered, and in the remaining 100 of 217 patients with pain, detailed information was missing. Sensory disturbances or motor deficit were present in 17% and 27%, respectively. Sensory and motor symptoms were diverse and could comprise mild neurological symptoms, i.e. numbness or mild muscle weakness in the face or extremities[17,26–30] or severe neurological deficit such as hemiparesis[31], tetraparesis due to bilateral parietal subdural hematomas[32] or a comatose state.[33] The GCS score was abnormal in 60 patients.

Concerning the 16 patients for which the clinician considered diagnoses different from PDPH, symptoms that were considered to be less suggestive for PDPH were the presence of a constant headache, position independent headache, headache that intensified in lying position or diminished in sitting position, or headache occurring during/immediately after puncture or after more than 14 days after neuraxial block. GCS was disturbed in five of these 16 patients, motor disturbances and sensory disturbances were reported in seven and five patients, respectively. Seven patients reported to have nausea/vomiting/dizziness, in six patients drowsiness/disorientation was described, three patients were described to have seizures, three patients had visual disturbances, and two of these patients presented with aphasia/dysarthria.

Intracranial hematoma: patient characteristics	**Total 291**	n
Age in years, median (IQR)	34.0 (28.0 – 50.0)	240
Sex (male, female, missing), n (%)	60 (20.6), 187 (64.3), 44 (15.1)	247
Body Mass Index, kg/m², median [IQR]	25.5 (23.5 – 29.8)	30
ASA physical status, n (%)		146
Class 1	13 (4.5)	
Class 2	119 (40.9)	
Class 3	12 (4.1)	
Class 4	2 (0.7)	
Missing	145 (49.8)	
Neuraxial technique		290
Spinal anesthesia	123 (42.3)	
Epidural catheter	77 (26.5)	
Spinal catheter	57 (19.6)	
Combined spinal-epidural procedure	14 (4.8)	
Failed regional technique	12 (4.1)	
Epidural injection	6 (2.1)	
Spinal cord stimulator	1 (0.3)	
Missing	1 (0.3)	
Needle size, in Gauge		118
<18	20 (6.9)	
18 – 21	25 (8.6)	
22 – 24	23 (7.9)	
25 – 27	50 (17.2)	
Missing	173 (59.5)	
Report of complicated puncture		150
No difficult puncture	71 (24.4)	
Difficult/multiple punctures	27 (9.3)	
Bloody tap	1 (0.3)	
Unintended dural puncture	51 (17.5)	
Missing	141 (48.5)	
Procedure		270
Obstetric: Cesarean section	76 (26.1)	
Obstetric: Labor analgesia	65 (22.3)	
Aneurysm repair (open or endovascular)	42 (14.4)	
Minor digestive	24 (8.2)	
Pain management	14 (4.8)	
Urological	13 (4.5)	
Major orthopedic	12 (4.1)	
Gynecologic oncology/surgery	8 (2.7)	

Intracranial hematoma: patient characteristics	**Total 291**	n
Minor orthopedic	6 (2.1)	
Peripheral vascular	4 (1.4)	
Major digestive	3 (1.0)	
Thoracic (Thoracotomy/Thoracoscopy)	2 (0.7)	
Amputation (leg) / Extremities	1 (0.3)	
Missing	21 (7.2)	
Coagulation status		99
No regular anticoagulants	74 (25.4)	
Prophylactic LMWH	10 (3.4)	
Aspirin/Clopidogrel	6 (2.1)	
Coagulation disorder	4 (1.4)	
Heparin infusion	2 (0.7)	
DOAC	1 (0.3)	
Unspecified anticoagulant therapy	1 (0.3)	
LMWH and vitamin K antagonist	1 (0.3)	
Missing	192 (66.0)	
Time point of complication*		228
During puncture	27 (9.3)	
During treatment	19 (6.5)	
After removal of catheter	58 (19.9)	
After spinal anesthesia	124 (42.6)	
Missing	63 (21.6)	
Space		237
Subdural	200 (68.7)	
Subarachnoidal	18 (6.2)	
Intraparenchymal	12 (4.1)	
Epidural	3 (1.0)	
Subdural and subarachnoidal	4 (1.4)	
Missing	54 (18.6)	
Unilateral, bilateral, missing, n (%)	119 (40.9), 46 (15.8), 126 (43.3)	165
Symptoms		
Pain (headache/neck pain) (present, absent, missing)	217 (74.6), 3 (1.0), 71 (24.4)	220
Sensory deficit (present, absent, missing)	50 (17.2), 128 (44.0), 113 (38.8)	178
Motor deficit (present, absent, missing)	79 (27.1), 131 (45.0), 81 (27.8)	210
PDPH (present, absent, missing)	101 (34.7), 16 (5.5), 174 (59.8)	117
Seizures (present, absent, missing)	27 (9.3), 27 (9.3), 237 (81.4)	54
Aphasia/Dysarthria (present, absent, missing)	19 (6.5), 26 (8.9), 246 (84.5)	45
Visual disturbance (present, absent, missing)	37 (12.7), 23 (7.9), 231 (79.4)	60

Intracranial hematoma: patient characteristics	**Total 291**	n
Vomiting/Nausea/Dizziness (present, absent, missing)	74 (25.4), 15 (5.2), 202 (69.4)	89
Drowsy/Disorientation (present, absent, missing)	49 (16.8), 24 (8.2), 218 (74.9)	73
GCS disturbed, e.g. <13 (present, absent, missing)	60 (20.6), 33 (11.3), 198 (68.0)	93
GCS count if GCS disturbed, median (IQR)	5.0 [3.0 – 7.0]	24
Treatment, n (%)		256
Conservative	144 (49.5)	
Neurosurgical decompression	112 (38.5)	
Missing	35 (12.0)	
EBP (yes, no, missing), n (%)	57 (19.6), 24 (8.2), 210 (72.2)	81
Recovery after treatment, n (%)		216
Full recovery	117 (40.2)	
Delayed but full recovery	45 (15.5)	
Partial recovery	19 (6.5)	
No recovery	13 (4.5)	
Death	22 (7.6)	
Missing	75 (25.8)	

Table 1. Characteristics of patients with intracranial hematoma associated with neuraxial block. n: cases with available data on specific parameter. IQR: interquartile range, BMI: body mass index, ASA: American Society of Anesthesiologists, LMWH: low molecular weight heparin, DOAC: direct oral anticoagulants, PDPH: post-dural puncture headache, GCS: Glasgow Coma Scale, EBP: epidural blood patch. * 'During puncture': symptoms during/directly after puncture, including epidural analgesia, spinal cord stimulator (SCS), continuous spinal anesthesia (spinal catheter), and failed regional techniques. 'During drugs administration': when drugs were administered through a catheter or treatment with SCS was ongoing. 'After removal of catheter': if catheter or SCS was removed.

Development of Symptoms (Timeline)

The median time to symptom onset after neuraxial block (i.e. all symptoms, for instance pain, nausea/vomiting, or neurological deficits such as motor/sensory/GCS disturbances) was 36 hours ([10 – 72], n=204), the first neurological symptoms (comprising motor/sensory/GCS disturbances) occurred after 120 hours ([48 – 276], n=112), the median time of symptom progression was 120 hours ([24 – 427], n=160). The time between start of first symptoms (often headache) and evacuation of hematoma, if performed, was 197 hours ([7 – 518], n=85), the time between development of neurological symptoms to evacuation was shorter, 4 hours ([3 – 24], n=63) and the time between diagnosis and evacuation, if performed, was 2 hours ([1 – 4], n=79).

Treatment and Recovery

After intracranial hematoma was diagnosed, 112 patients were treated with neurosurgical drainage and 144 patients were treated conservatively; this information was missing in the remaining 35 patients. Overall, the majority of patients had full recovery (162 of 291 patients, 56%), 32 patients (11%) had permanent sequelae after treatment, 22 patients died (8%) and information regarding recovery was missing in 75 patients (26%).

Patients with permanent sequelae after treatment remained with a variability of symptoms, ranging from ptosis, epilepsy, persistent paralysis or a remaining comatose state after symptom progression. Regarding the 22 patients who died due to the complication, many of these patients presented initially with or without mild neurological symptoms, however, after a period of vague complaints, a sudden and rapid progression to unconsciousness occurred, finally leading to brain herniation and death (median hours of symptom progression 72 hours [13 – 236], n=17). Patients who died were generally older than survivors; median age 66 (38 – 70) years (n=21) versus 34 (28 – 42) years (n=186), respectively ($p<0.001$), and were more often male; 52% (n=21) versus 20% (n=191), respectively ($p<0.01$).

Fifty-five of 101 patients diagnosed with PDPH were treated with an epidural blood patch (EBP) to alleviate the headache, 10 patients were treated

without EBP, and this information was missing in the remaining patients. One patient without PDPH-symptoms but with confirmed bilateral SDHs was treated with an EBP to stop ongoing cerebrospinal fluid (CSF) leakage[34] and one patient that was already treated twice with craniotomy for recurrent intracranial hematoma received an EBP because of ongoing CSF leakage from a lumbar drain site,[35] both cases resulted in complete recovery. In the limited number of patients with reported data regarding the performance of an EBP and outcome, no differences were seen in terms of recovery (n=73, p=0.13).

Intracranial Abscess/Empyema

Characteristics of six patients with intracranial abscess after neuraxial anesthesia previously reported in the literature are described in Table 2. Most patients were relatively young, with a median age of 32 (24 – 65) years, five were female, and the indication for neuraxial block was a Caesarean section in four cases. Most patients reported headache and/or neck pain (five patients). The median time to symptom onset after neuraxial block was 228 hours ([48 – 4170], n=6). Four cases were treated with neurosurgical decompression of abscess(es) combined with antibiotic treatment and two cases were treated conservatively, including antibiotic treatment. Cultures (blood cultures or culture of the surgical specimen) resulted in *Mycoplasma hominis* in two cases, *Streptococcus anginosus* in one case, *Aspergillus* in one case, and cultures remained negative in the two remaining cases. Overall, four patients recovered fully, while two patients died from the complication.

In one of the reported cases, a brain abscess developed 17 months after implantation of an intrathecal drug delivery device for severe cancer-related rectal and perineal pain in a male in his mid-seventies with metastatic anal cancer, after abdominoperineal resection, chemotherapy and radiation therapy.[36] The implanted device may have been contaminated and thereby may have contributed to the development of the abscess, however, a possible other cause include hematogenous spread of infection in a patient with chemotherapy-induced low immune response, indicating an uncertain causality between the neuraxial procedure and the development of a brain abscess.

Intracranial abscess: patient characteristics	Total 6	n
Age in years, median (IQR)	32.0 (24.3 – 65.3)	6
Sex (male, female), n (%)	1 (16.7), 5 (83.3)	6
ASA physical status, n (%)		4
Class 1	0 (0.0)	
Class 2	3 (50.0)	
Class 3	0 (0.0)	
Class 4	1 (16.7)	
Missing	2 (33.3)	
Neuraxial technique		6
Spinal anesthesia	4 (66.7)	
Epidural catheter	1 (16.7)	
Spinal catheter	1 (16.7)	
Report of complicated puncture		2
No difficult puncture	2 (33.3)	
Missing	4 (66.7)	
Procedure		6
Obstetric: Cesarean section	4 (66.7)	
Pain management	1 (16.7)	
Minor orthopedic	1 (16.7)	
Time point of complication*		6
During puncture	0 (0.0)	
During treatment	1 (16.7)	
After removal of catheter	1 (16.7)	
After spinal anesthesia	4 (66.7)	
Symptoms		
Pain (headache/neck pain) (present, absent, missing)	5 (83.3), 1 (16.7), 0 (0.0)	6
PDPH (present, absent, missing)	2 (33.3), 1 (16.7), 3 (50.0)	3
Seizures (present, absent, missing)	1 (16.7), 2 (33.3), 3 (50.0)	3
Aphasia/Dysarthria (present, absent, missing)	1 (16.7), 1 (16.7), 4 (66.7)	2
Visual disturbance (present, absent, missing)	1 (16.7), 2 (33.3, 3 (50.0)	3
Vomiting/Nausea/Dizziness (present, absent, missing)	0 (0.0), 2 (33.3), 4 (66.7)	2
Drowsy/Disorientation (present, absent, missing)	1 (16.7), 1 (16.7), 4 (66.7)	2
Fever (present, absent, missing)	5 (83.3), 0 (0.0), 1 (16.7)	5
Treatment, n (%)		6
Conservative	2 (33.3)	
Neurosurgical decompression	4 (66.7)	
Recovery after treatment, n (%)		6
Full recovery	4 (66.7)	
Delayed but full recovery	0 (0.0)	
Partial recovery	0 (0.0)	
No recovery	0 (0.0)	
Death	2 (33.3)	

Table 2. Characteristics of patients with intracranial abscess associated with neuraxial block. n: cases with available data on specific parameter. IQR: interquartile range, ASA: American Society of Anesthesiologists, PDPH: post-dural puncture headache. * 'During puncture': symptoms during/directly after puncture, including epidural analgesia, spinal cord stimulator (SCS), continuous spinal anesthesia (spinal catheter), and failed regional techniques. 'During drugs administration': when drugs were administered through a catheter or treatment with SCS was ongoing. 'After removal of catheter': if catheter or SCS was removed.

Discussion

We analyzed the literature of intracranial hematomas and abscesses after neuraxial block and identified 291 cases of hematoma and six cases of abscess or empyema.

Intracranial hematomas were reported predominantly after puncture of the dura mater, in relatively young and healthy females receiving neuraxial block for obstetric indications. Besides obstetric patients, intracranial hematoma was reported in diverse patient populations, including patients treated with a spinal catheter for aneurysm repair, or with neuraxial block for surgical indications or pain management.

Virtually every patient with an intracranial hematoma reported headache. In the majority of patients in this series, a dural puncture had taken place, either intended (e.g. spinal anesthesia) or unintended (e.g. spinal tap when attempting to place an epidural catheter). Within this review, many patients reported symptoms compatible with PDPH. Typical characteristics of PDPH, described by the International Classification of Headache disorders,[25] are headache occurring within five days of a lumbar puncture, remitting spontaneously within two weeks, or after sealing of the leak with an autologous epidural lumbar patch, and usually (but not invariably) the headache is orthostatic. Studies that evaluated the time course of PDPH demonstrated that in approximately 72-95% of cases the symptoms subsided within five to seven days.[11,37] Our analysis of the literature showed a median time lapse between neuraxial block and first neurological symptoms of five days, indicating that a diagnosis of PDPH is unlikely at that point in time or that ongoing CSF leakage may have led to secondary complications such as intracranial bleeding. Thus, when PDPH is prolonged for more than five days (and especially for more than two weeks), does not improve, or worsens, with clinical treatment or after an epidural blood patch, if changes in pain occur from postural to non-postural, or if neurological signs or symptoms develop besides the headache, the occurrence of other causes of headache, e.g. intracranial hematoma, should be considered.[11,29] Neurological consultation

and imaging studies are indicated at this point in the clinical course of falsely presumed PDPH, ideally before neurological symptoms occur, to prevent progression of underlying disease and delayed treatment. These findings are in line with previous studies assessing characteristics of patients with intracranial hematoma and PDPH after neuraxial procedures in the obstetric population.[6,9,33] Cuypers et al., accentuate that patients who develop a persistent headache after neuraxial procedures require careful follow-up, even in the absence of predisposing risk factors or an obvious dural puncture.[6] Also Lim et al., emphasize the need for close monitoring of patients who have PDPH after neuraxial anesthesia for signs that could signal the evolution of intracranial hematoma, based on their case series of 11 patients with subdural hematomas associated with the use of labor epidural analgesia over seven years at a tertiary care hospital.[33] Interestingly, in their series, most cases of subdural hematoma did not manifest with significant additional neurological changes beyond typical clinical symptoms of PDPH (10 of 11 patients), which differs from our results describing sensory disturbances or motor deficit in 17% and 27%, respectively, and a disturbed GCS in 21% of patients. A possible explanation for the higher number of patients presenting with neurological deficits in our literature review could be reporting bias; it may be more interesting to report severe complications as opposed to patients with mild symptoms and positive outcome. In general, PDPH may be associated with substantially increased risks of major neurologic complications and other maternal complications in obstetric patients, underscoring the need for early recognition, treatment, and follow-up of patients with PDPH.[9] Intracranial abscess after neuraxial block seems to be very seldom and is hardly ever reported in literature. It is impossible to yield any conclusion based on the limited data.

Pathophysiology

The pathophysiology of intracranial hematoma is based on craniospinal hypotension due to CSF leakage from the dural puncture site, which – if severe – may lead to a caudal shift of the brain, causing bridging veins to tear.[6] As is

discussed above, ongoing CSF leakage without sealing of the leak with an autologous epidural lumbar blood patch, may lead to intracranial hematoma. Furthermore, another possibility is that intracranial bleeding occurred regardless of CSF leakage or the diagnosis PDPH was falsely presumed and intracranial hematoma was present in the first place. The use of an epidural blood patch for suspected ongoing CSF leakage can be effective, however in the presence of confirmed intracranial hematoma, this may lead to increased intracranial pressure with further deterioration as a result. Epidural blood patching in the presence of confirmed cranial hematomas should therefore be used cautiously and only after consultation with a neurologist or neurosurgeon.

Of note, the incidence of unrecognized dural puncture at the time of epidural procedures is considerable, with reported rates of occurrence between 10-36%.[38,39] CSF leakage and subsequent PDPH or intracranial hematoma can occur after puncture with larger needles used for placement of epidural or spinal catheters, but also after puncture with smaller/thin needles used for spinal anesthesia. Other factors that may increase bleeding risk are pre-existing cranial vascular anomalies such as aneurysms or arterial venous malformations,[16,40] cerebral venous thrombosis, hypertension, brain tumors, coagulation disorders, hematologic disorders, or anticoagulant and thrombolytic therapy.[41]

In general, intracranial hematoma seems to be more common in pregnancy and during the direct postpartum period than in non-pregnant women of comparable age.[42,43] This may be related to an increased circulating volume, presence of pre-existing cranial vascular anomalies, coagulopathy or hypertensive disorders such as preexisting hypertension and preeclampsia/eclampsia.[42–44] The effect of a neuraxial block on the risk of intracranial bleeding in pregnant or direct postpartum women is unknown.

The pathophysiology of intracranial abscesses or empyema after neuraxial block seems to originate from meningitis which progresses to (mostly subdural) empyema or brain abscesses, or an infected hematoma that develops into an abscess. The infection can occur at the time of neuraxial procedure, or

through contamination of the skin site and subsequent spread along a spinal or epidural catheter (by skin flora of the patient or in exceptional cases skin flora of a treating physician), by hematological spread or by intraluminal contamination via a polluted syringe or local anesthetic solution.[45]

Overall, a high level of suspicion for the potential relationship between symptoms indicative of a complication and the previous neuraxial block should be present, as first symptoms may resemble alternative diagnoses (such as typical PDPH) and occur when patients are no longer under the care of an anesthesiologist or acute pain service physician.[5]

Limitations

The retrospective character and selective reporting of case reports and case series resulted in multiple limitations. For instance, lack of detail in the reports was a major limitation, the quality of the included studies was low, and, as is in accordance with retrospective research, a high risk of publication bias, selection bias and underreporting of complications is present. While acknowledging these limitations, we feel that the present analyses of aggregated reported cases can improve our understanding of the development of these rare but severe complications of neuraxial block.[5]

Specifically, we noted that many reports described widely diverse aspects of the clinical course, treatment and outcome of intracranial hematoma or abscess leading to large quantities of missing data. This is in congruence with the findings of our previous literature review analyzing spinal hematoma and abscess after neuraxial block.[5] No consensus appears to exist on the most important aspects of these severe complications. Again we want to suggest that registration of complications after neuraxial block and the reporting of cases should be compliant with a pre-defined format (see Supplementary File 2), to collect complete data allowing more accurate estimates of incidence rates, prognostic factors and response to therapy.[5]

Conclusion

Intracranial hematoma is a rare but possible complication after neuraxial block and mainly occurs after puncture of the dura mater. The diagnosis intracranial hematoma is often missed initially, as the headache is presumed to be caused by the much more common cerebrospinal hypotension syndrome after dural CSF leakage. When the headache is prolonged for more than five days, does not improve, or worsens, with clinical treatment or after epidural blood patch, changes from postural to non-postural, or if neurological symptoms develop besides the headache, alternative diagnoses should be considered warranting neurological consultation and imaging studies.

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Conflict of Interest:

EB: No interest declared.
KvdL: No interest declared.
JH: No interest declared.
MdQ: received payments for lectures from Johnson & Johnson Medical Devices Companies.
WPV: No interest declared.
CK: No interest declared.
MWH: is Executive Section Editor Pharmacology with Anesthesia & Analgesia and Section Editor Anesthesiology with Journal of Clinical Medicine. Furthermore he served as consultant for Eurocept BV and received honoraria for lectures from CSL Behring in the past.
PL: No interest declared.

Authors' contributions

All authors: Study concept and design.

EB, KvdL, JH: Literature search, data collection.

EB, KvdL, JH, PL: Data analysis.

All authors: Interpretation of data.

EB: Drafting the article.

All authors: Revising the draft critically for important intellectual content.

All authors: Final approval of the version to be published; and agreement to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Appendices

Supplementary File 1. Search strategy.

Supplementary File 2. Extracted data.

Supplementary File 3. Quality of case series and cohort studies.

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Supplementary File 1

Supplementary File Table 1. Search strategy. Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present.
Search Strategy: 2020-05-11

#	Searches	Results
1	exp anesthesia, epidural/ or anesthesia, spinal/ or anesthesia, obstetrical/ or analgesia, epidural/	38154
2	*nerve block/ae or *autonomic nerve block/ae	1511
3	spinal cord stimulation/	980
4	epidur*.tw,kf. and an?esthe*.mp,jw.	22814
5	(epidurals or spinals).tw,kf.	741
6	(((regional or spinal* or caudal or neurax* or neuroax* or extradur* or peridur* or dural or intrathec*) adj6 an?esth*) or ((subarach* or sub-arach*) adj an?esth*)).tw,kf.	30074
7	((regional or spinal* or neurax* or neuroax* or epidural or extradur* or peridur* or dural or intrathec*) adj3 analg*).tw,kf.	12481
8	(exp injections, spinal/ or spinal puncture/ or post-dural puncture headache/ or (((epidur* or neurax* or neuroax* or extradur* or peridur* or dural or postdural or intrathec*) adj2 (cathet* or inject* or punct* or technique*)).tw,kf. or ((catheters, indwelling/ae or catheterization/ae) and epidural space/))) and (an?est* or analg* or neuralg* or palliat* or pain or adrenal cortex horm* or steroid* or corticoster* or gl#cocortic* or hydrocort* or methylpredn* or predniso* or dexamet* or opioid* or morphin* or morpholin* or fentanyl).mp,jw.	21410
9	((epidur* or neurax* or neuroax* or extradur* or peridur* or intrathec* or central nerv*) adj3 block*).tw,kf.	4413
10	((obstetric* or labo?r) adj an?est*).tw,kf.	2493
11	spinal cord stimulat*.tw,kf.	3307
12	**or/1-11 [epidural anesthesia]**	**81584**
13	intracranial hemorrhages/ or hematoma, epidural, cranial/ or hematoma, subdural, intracranial/ or cerebral hemorrhage/ or cerebral hemorrhage, traumatic/ or intracranial hemorrhage, traumatic/	43255
14	brain abscess/	7705
15	(abscess/ or hematoma/) and (dura mater/ or brain/ or brain diseases/ or cerebellar diseases/)	1967

16	(hematoma, subdural/ or hematoma, subdural, acute/ or hematoma, subdural, chronic/ or epidural abscess/ or subarachnoid hemorrhage/) not ((((spinal or intraspinal or interspin* or paraspin* or vertebra* or interverteb* or lumbar or sacral or caudal or cervical) adj (h?ematom* or absces* or bleed* or h?emorrhag*)) or ((spinal or intraspinal or interspin* or paraspin* or vertebra* or interverteb* or lumbar or sacral or caudal or cervical) adj (epidur* or peridur* or extradur* or subdur* or intradur* or subarachnoid* or sub-arachnoid*) adj1 (h?ematom* or absces* or bleed* or h?emorrhag*))). tw. not (intracrani* or crani* or cerebra* or cerebel* or cerebrovascul* or cerebro-vascul* or brain* or intracereb* or hemispher* or interhemisph* or pariet*occipit* or front*parietal or occipital or temp*pariet* or parietal or posterior fossa or corpus callosum or intracortic* or periventricul* or intraventricul*).mp.)	29570
17	(encephalor?hag* or h?ematencephalo* or ((intracrani* or crani* or cerebra* or cerebel* or cerebrovascul* or cerebro-vascul* or brain* or intracereb* or hemispher* or interhemisph* or pariet*occipit* or front*parietal or occipital or temp*pariet* or parietal or posterior fossa or corpus callosum or intracortic* or periventricul* or intraventricul*) adj5 (h?ematom* or h?emorrhag* or microh?emorrhag* or bleed* or microbleed* or absces*))). tw,kf.	72069
18	((epidur* or peridur* or extradur* or subdur* or intradur* or subarachnoid* or sub-arachnoid*) adj1 (h?ematom* or h?emorrhag* or bleed* or absces*)). tw,kf. not (((spinal or intraspinal or interspin* or paraspin* or vertebra* or interverteb* or lumbar or sacral or caudal or cervical) adj (epidur* or peridur* or extradur* or subdur* or intradur* or subarachnoid* or sub-arachnoid*) adj1 (h?ematom* or h?emorrhag* or bleed* or absces*)). tw,kf. not (intracrani* or crani* or cerebra* or cerebel* or cerebrovascul* or cerebro-vascul* or brain* or intracereb* or hemispher* or interhemisph* or pariet*occipit* or front*parietal or occipital or temp*pariet* or parietal or posterior fossa or corpus callosum or intracortic* or periventricul* or intraventricul*).mp.)	39633
19	**or/13-18** [cranial hematomas & abscesses]	**120084**
20	**12 and 19** [epidurals and cranial hematomas & abscesses]	**1498**
21	**exp animals/ not humans/** [animal filter]	**4696997**
22	**20 not 21** [epidurals and cranial hematomas & abscesses in humans]	**1455**
23	**remove duplicates from 22** [epidurals and cranial hematomas & abscesses in humans - deduplicated]	**1449**

Supplementary File 2

Supplementary File Table 2. Extracted data in reports of intracranial hematoma or abscess after neuraxial block. BMI: body mass index, ASA: American Society of Anesthesiologists, LMWH: low molecular weight heparin, DOAC: direct oral anticoagulants (DOAC), NB: neuraxial block, EVAR: endovascular aneurysm repair, GCS: Glasgow Coma Scale, CT: computed tomography, MRI: magnetic resonance imaging, SCS: spinal cord stimulator.

Extracted data	
Age	In years (integer)
Sex	Male / Female
BMI	Weight in kilograms/(Height in meters)^2, 1 decimal
ASA physical status[1]	As reported by author or based on comorbidities reported by author
Coagulation status	No regular anticoagulant drugs, antiplatelet (e.g. aspirin/clopidogrel), prophylactic low molecular weight heparin (LMWH), therapeutic LMWH, vitamin K antagonist, direct oral anticoagulants (DOAC), heparin infusion, urokinase infusion, multi-therapy (≥ 2 different anticoagulant drugs), coagulation disorder, mistake in drug administration, unspecified anticoagulant therapy, or: 'other', describe
Type of neuraxial technique	Continuous epidural anaesthesia, spinal anaesthesia, combined spinal-epidural procedure, spinal catheter, spinal cord stimulator, epidural injection, caudal block, or: 'other', describe
Needle size	In Gauge
Report of complicated puncture	Easy/uncomplicated puncture, difficult/multiple punctures, 'bloody tap', inadvertent dural puncture
Number of attempts for neuraxial block (NB)	Integer
Number of levels spinal cord attempted	Integer
Experience of anesthesiologist performing NB	Resident (≤5 years of experience) / anesthesiologist (>5 years of experience)
Level of regional technique	Cervical, thoracic, lumbar or sacral/caudal
Puncture height	Between two vertebras; upper vertebra noted
Indication for neuraxial block/Type of procedure	Minor orthopedic, Major orthopedic, Chronic pain management, Minor digestive, Major digestive, Peripheral vascular, Obstetric: Labor analgesia, Obstetric: Caesarean section, Urologic, Aortic, Thoracotomy, Thoracoscopy, Gynecologic oncology/surgery, EVAR, Cardiac surgery, Trauma, Amputation (leg) / Extremities, Neurosurgical, or: 'other', describe

Hours to removal of catheter from time point 0	Time point 0 is first attempt NB, rounded to full hours. Variable only applicable for cases treated with a catheter.
Hours to symptom onset from time point 0	Time point 0 is first attempt NB, rounded to full hours. All symptoms, including among others pain, seizures, disorientation, nausea/vomiting, neurological deficits (motor and sensory disturbances) and Glasgow Coma Scale (GCS) disturbances. See variable 'Symptoms' below.
Hours to onset neurological symptoms from time point 0	Time point 0 is first attempt NB, rounded to full hours. First neurological symptoms describe motor/sensory disturbances and disturbed GCS.
Hours to evacuation of hematoma/abscess from time point 0	Time point 0 is first attempt NB, rounded to full hours
Hours to diagnosis from time point 0	Time point 0 is first attempt NB, rounded to full hours. Diagnosis by CT/MRI-scan.
Hours progression of symptoms	From onset of first symptoms to worst symptoms evaluated, rounded to full hours
Hours to symptom onset after predisposing causative event	Causative event is defined as: i.e. NB onset, removal of catheter or dose of anticoagulant, rounded to full hours
Hours to evacuation of complication from symptoms onset	Duration of first symptoms to evacuation of hematoma/abscess, rounded to full hours
Time point of complication as suspected by author	'During puncture': symptoms during/directly after puncture, including epidural analgesia, spinal cord stimulator (SCS), continuous spinal anaesthesia (spinal catheter), and failed regional techniques. 'During drugs administration': when drugs were administered through a catheter or treatment with SCS was ongoing. 'After removal of catheter': if catheter or SCS was removed, or 'After spinal anesthesia'
Symptoms	Pain: scored as partial/mild, full/severe, present; degree not further specified Sensory deficit: scored as partial/mild, full/severe, present; degree not further specified Motor deficit: scored as partial/mild, full/severe, present; degree not further specified Post-dural puncture headache (present : absent) Seizures (present : absent) Aphasia/Dysarthria (present : absent) Visual disturbance (present : absent) Vomiting/Nausea/Dizziness (present : absent) Drowsy/Disorientation (present : absent) GCS disturbed (present : absent), a disturbed GCS is defined as a GCS < 13 GCS count if GCS disturbed, median [IQR]

Surgical evacuation	Yes / No
Epidural Blood Patch (EBP)	Yes / No
Neurological recovery	Full recovery, delayed but full recovery (recovery after more than 1 month from symptom onset), partial recovery, no recovery, death
Type of hematoma/abscess	Intracranial, spinal and intracranial
Space	Epidural / Subdural / Subarachnoidal / Intraparenchymal Unilateral / Bilateral / Midline
Practice consistent with current guideline	Consistent with most recent guideline Neuraxial Block and Anticoagulant Drugs – Dutch Society of Anaesthesiology[2]

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Supplementary File 3

Supplementary File Table 3. Critical appraisal of a case study checklist, adapted from The Pocket Guide to Critical Appraisal by Crombie. n: number of patients with complication reported. CT: cannot tell. 1. Did the study address a clearly focused question / issue? 2. Is the research method (study design) appropriate for answering the research question? 3. Are both the setting and the subjects representative with regard to the population to which the findings will be referred? 4. Is the researcher's perspective clearly described and taken into account? 5. Are the methods for collecting data clearly described? 6a. Are the methods for analyzing the data likely to be valid and reliable? 6b. Are quality control measures used? 7. Was the analysis repeated by more than one researcher to ensure reliability? 8. Are the results credible, and if so, are they relevant for practice? 9. Are the conclusions drawn justified by the results? 10. Are the findings of the study transferable to other settings?

First author	Year	n Intracranial Hematoma	n Intracranial Abscess	1	2	3	4	5	6a	6b	7	8	9	10
Amorim	2010	2	-	Yes	Yes	Yes	Yes	CT	CT	CT	CT	Yes	Yes	Yes
Arseni	1970	6	-	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Elshanawany	2020	6	-	CT	CT	Yes	Yes	No	CT	CT	CT	Yes	Yes	Yes
Gago	2019	2	-	Yes	No	Yes	Yes	No	CT	CT	CT	Yes	Yes	Yes
Kale	2015	2	-	Yes	No	Yes	Yes	CT	CT	CT	CT	Yes	Yes	Yes
Lim	2016	11	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CT	Yes	Yes	Yes
McDougall	2015	2	-	Yes	CT	Yes	Yes	No	CT	CT	CT	Yes	Yes	Yes
Moradi	2012	2	-	Yes	CT	Yes	Yes	No	CT	CT	CT	Yes	Yes	Yes
Newrick	1982	2	-	Yes	CT	Yes	Yes	CT	CT	CT	CT	Yes	Yes	Yes
Pavlin	1979	2	-	Yes	CT	Yes	Yes	CT	CT	CT	CT	Yes	Yes	Yes
Pitkanen	2013	-	1	Yes	No	Yes	Yes	No	CT	No	No	Yes	Yes	Yes
Vilaca	2015	2	-	Yes	CT	Yes	Yes	CT	CT	CT	CT	Yes	Yes	Yes
Welch	1959	2	-	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Wynn	2015	38	-	Yes	Yes	Yes	Yes	Yes	Yes	CT	CT	Yes	Yes	Yes

Chapter 6

Haematoma, abscess or meningitis after neuraxial anaesthesia in the USA and the Netherlands

A closed claims analysis

Elke M.E. Bos, Karen L. Posner, Karen B. Domino, Marcel de Quelerij, Cor J. Kalkman, Markus W. Hollmann, Philipp Lirk

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Abstract

Background – Severe complications after neuraxial anaesthesia are rare but potentially devastating.

Objective – We aimed to identify characteristics and preventable causes of haematoma, abscess or meningitis after neuraxial anaesthesia.

Design – Observational study, closed claims analysis.

Setting – Closed anaesthesia malpractice claims from the USA and the Netherlands were examined from 2007 until 2017.

Patients – Claims of patients with haematoma (*n*=41), abscess (*n*=18) or meningitis (*n*=14) associated with neuraxial anaesthesia for labour, acute and chronic pain that initiated and closed between 2007 and 2017 were included. There were no exclusions.

Main outcome measures – We analysed potential preventable causes in patient-related, neuraxial procedure related, treatment-related and legal characteristics of these complications.

Results – Patients experiencing spinal haematoma were predominantly above 60 years of age and using antihaemostatic medication, whereas patients with abscess or meningitis were middle-aged, relatively healthy and more often involved in emergency interventions. Potential preventable causes of unfavourable sequelae constituted errors in timing/prescription of antihaemostatic medication (10 claims, 14%), unsterile procedures (*n*=10, 14%) and delay in diagnosis/treatment of the complication (*n*=18, 25%). The number of claims resulting in payment was similar between countries (USA *n*=15, 38% vs. the Netherlands *n*=17, 52%; *P*=0.25). The median indemnity payment, which the patient received varied widely between the USA (€285.488, *n*=14) and the Netherlands (€31.031, *n*=17) (*P*=0.004). However, the considerable differences in legal systems and administration of expenses between countries may make meaningful comparison of indemnity payments inappropriate.

Conclusions – Claims of spinal haematoma were often related to errors in antihaemostatic medication and delay in diagnosis and/or treatment. Spinal

abscess claims were related to emergency interventions and lack of sterility. We wish to highlight these potential preventable causes, both when performing the neuraxial procedure and during postprocedural care of patients.

Introduction

Neuraxial anaesthetic techniques, such as spinal anaesthesia or epidural analgesia, remain a cornerstone of current anaesthesia practice. Spinal anaesthesia is the leading technique for caesarean section and is regularly used for regional surgery on the lower half of the body.[1–4] Epidural analgesia remains the preferred analgesic technique in labouring patients and for surgical interventions, such as major open abdominal surgery and thoracotomy.[5] Furthermore, epidural injections, spinal cord stimulators and intrathecal drug delivery systems are used on a regular basis to treat chronic pain.[6–10]

Injury to the spinal cord by haematoma or abscess belongs to the most feared complications of neuraxial anaesthesia, and is often in the foreground of any risk–benefit analysis,[6] with reported incidences of up to 1 in 1.000 to 1 in 6.000 patients, depending on the population under consideration.[11–13] Other complications of neuraxial anaesthesia include errors in perineural medication, direct nerve injury during puncture and meningitis. The incidence of major complications after neuraxial anaesthesia is higher than historically reported, but because of the low incidence of these complications in single centres, it is challenging to obtain data concerning patient characteristics, treatment strategies and neurological outcome. Previously, we performed an extensive literature review to obtain more knowledge about haematoma or abscess after neuraxial anaesthesia,[14] but long-term outcomes may be missing in literature reports.

By using the Anaesthesia Closed Claims Project database from the USA and the databases of the two largest medical insurance companies in the Netherlands, this study aims to identify possible preventable causes and long-term outcomes by analysing specific patient-related, neuraxial procedure-related, treatment-related and legal characteristics. Even though haematoma, abscess and meningitis are diverse pathophysiological entities, we focused on these complications as severity of sequelae may be reduced or prevented with pro-active management of these complications.

Methods

For this closed claims analysis, we followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.
We conducted an analysis of closed claims from medical insurance companies available in the US Anaesthesia Closed Claims Project database and the databases of two major medical liability insurance companies from the Netherlands, Centramed and MediRisk.

Ethical approval for the American Society of Anesthesiologists' (ASA) Anaesthesia Closed Claims Project (#43939) was provided by the University of Washington Institutional Review Board (IRB), Washington DC, USA, with yearly renewed approval since 1985, the latest approval date being 25 October 2019 (Chairperson J Purcell). The IRB of the Amsterdam UMC, the Netherlands (Secretary Dr van der Wilt), waived the requirement to obtain informed consent for this study (W17_267 #17.316) on 13 April 2018.

Inclusion criteria were claims for haematoma, abscess or meningitis after neuraxial anaesthesia for labour, acute and chronic pain that initiated and closed between 2007 and 2017. Inclusions were closed in July 2018, because more recent data (up until 2018) were not yet available in the ASA Anaesthesia Closed Claims Project Database. There were no exclusions. Data from the USA and the Netherlands were combined and an 11-year inclusion period was chosen to balance between claims that reflect current practice and to achieve a substantial number of cases. Differences in legal and clinical systems were expected between the countries. Multiple consultations were performed between countries to reduce differences as far as possible, for example, equal variables and scoring systems were used to gather data. If differences in methodology between countries were inevitable, these differences are stated in the manuscript.

The ASA Anaesthesia Closed Claims Project is a structured database that identifies patterns of injury obtained from closed malpractice claims in the USA. The professional liability insurance companies that are affiliated to the Closed Claims Project together insured between one-third and one-half of

practising anaesthesiologists throughout the USA between 2007 and 2017. Information in the database is collected from medical records, medical evaluations, expert witness reports, claims manager summaries and legal summaries.[15] The Closed Claims Project methodology is described in detail in previous reports.[15,16]

The Closed Claims databases from the Netherlands constitute archives of the two largest medical liability insurance companies that together insured approximately 90% of Dutch hospitals in 2018 and the corresponding anaesthesiologists working in those hospitals.[17] One author (EMEB) and one insurance company employee (Centramed – AH and MediRisk – OD) searched anonymised claims, and subsequently data were extracted and analysed case-by-case by one author (EMEB). The extracted data were referenced against computer-based searches of the databases to ensure that datasets were complete, and that data found in the databases were accurately represented in our study dataset.

Data collected included patient characteristics, neuraxial technique characteristics, timing of events, symptoms, clinical outcomes and medicolegal outcomes. For complete information on extracted data, see the Supplemental Data File, http://links.lww.com/EJA/A324.

We defined spinal haematoma/abscess as any complication in the paraspinal muscles, epidural, subdural or subarachnoid space below the level of C0 (occipital condyles) and cranial haematoma/abscess as any complication in the epidural, subdural or subarachnoid space above C0. Neuraxial anaesthesia was classified as epidural analgesia, spinal anaesthesia, combined-spinal-epidurals, epidural injection and spinal catheter insertion performed by anaesthesiologists.

The extent of neurological deficit caused by spinal haematoma or abscess was scored using the American Spinal Injury Association (ASIA) Impairment Scale,[18] which ranges from Grade A (complete neurological injury) to Grade E (normal motor and sensory function below the level of the lesion, with/without abnormal reflexes). In addition, recovery after treatment of the complication was scored as full recovery, delayed but full recovery (full recovery after

more than 1 month from symptom onset), partial recovery (improvement of symptoms, but persistent neurological deficit, cognitive deficit or pain present after treatment) and no objectified recovery after treatment.

Medicolegal variables

The overall severity of injury in each claim was scored using the National Association of Insurance Commissioners' 10-point scale,[19] which ranges from 0 (no apparent injury) to 9 (death). This scale was collapsed into three severity outcomes: death, permanent disabling injury (6 to 8) and temporary or minor nondisabling injuries (0 to 5).[15] The severity of injury was scored at the time the claim was closed by onsite reviewers for US cases and Dutch MediRisk cases, and by one author (EMEB) at the time of data extraction for the Centramed cases.

At the time of claim handling, appropriateness of anaesthesia care was assessed as appropriate, substandard or impossible to judge by the project anaesthesiologist reviewers based on prudent criteria for practice (US claims) and by medical and legal experts (Dutch claims), taking into account the year of event. The reliability of appropriateness of care of the US cases has been judged acceptable,[8] but the reliability of this variable is unknown for the Dutch cases.

Legal/medical experts or claim reviewers routinely raised discussion points concerning possible causes that may have contributed to the development of complications. These discussion points relate to the indication for the block, presence and content of informed consent, antihaemostatic medication errors, breaches of procedural sterility, documentation, monitoring, communication and delay in diagnosis/treatment of complications. For the US claims, these discussion points were judged by pairs of claim reviewers, and for the Dutch claims by legal and medical experts, at the time of claim analysis.

We identified the number of closed claims in which a decision for patient compensation was made. Payments were extracted from the databases; payments include indemnity payments, which the patient received. Dollars were converted to Euros at the time of payment using the exchange rate of

the year of (first) payment[20] and adjusted to European Union 2017 amounts using the Consumer Price Index.[21] Cases from the US include payments that were made on behalf of the anaesthesiologist or Anaesthesia Corporation. This may represent an underestimation of the true amount of payment, in case additional payments were made on behalf of other caretakers or if simultaneous claims were initiated at hospitals unaffiliated to the Closed Claims Project database. Contrarily, an overestimation of indemnity payment may be present as a proportion of the payment may be used for contingency fees to pay legal representatives. In the Netherlands, general claim costs are composed of patient compensations, compensation of the patient's deductible, extrajudicial costs, and remaining costs concerning external medical expertise, external claim representatives and legal fees of the insurance company. For the Dutch cases, the included and analysed indemnity payments generally constitute patient compensation only; however, in certain cases, a lump-sum payment was performed, also constituting extrajudicial costs, and thus overestimating the true indemnity payment.

Statistical analysis

Descriptive statistics were performed for patients with haematoma, abscess or meningitis. Mean ±SD or median [IQR] are reported based on normal or nonnormal distribution. We compared patient-related, neuraxial procedure-related, treatment-related and medicolegal characteristics between complications and we compared payment data between countries. Recovery after treatment in patients with spinal haematoma or abscess was compared between this closed claims analysis and our previous literature review.[14] We used a Kruskal–Wallis test to compare medians for skewed endpoints in three groups (haematoma, abscess and meningitis), a Mann–Whitney *U*-test to compare medians for skewed endpoints in two groups (haematoma, abscess), and we used a χ^2-test to compare proportions, with two-tailed tests and *P* less than 0.05 as the criterion for statistical significance. Sample size and analyses were based on available data; missing data were excluded from analyses on an item-by-item basis. Statistical analysis was performed using SPSS 25 for Windows (IBM Corporation, Armonk, New York, USA).

Results

The analysis of closed claims identified 41 patients with spinal haematoma (including one patient with both spinal and cranial haematoma and one patient with spinal haematoma that developed into an abscess), 18 patients with spinal abscess (including four cases with an abscess in the paraspinal muscles, two of whom had concomitant spondylodiscitis, and one who had both spinal abscess and meningitis) and 14 patients with meningitis after neuraxial block (Fig. 1).

Events from USA occurred between 2007 and 2014 because of an average 3-to-7-year delay between event, claim filing and closure. Events from the Netherlands occurred between 2005 and 2015; the reported average delays are 1.8 to 2.5 years[22,23] for the claims to be settled after claim initiation. An extended timeframe of events was maintained for the Dutch claims to prevent loss of information. The prevalence of complications was similar between countries.

Patient-related, neuraxial procedure-related, treatment-related and medicolegal characteristics in patients with haematoma, abscess or meningitis after neuraxial anaesthesia are shown in Table 1.

Spinal haematoma

Patients with spinal haematoma were generally 60 years of age or older, often had an ASA physical status 3 or 4 (68%) and frequently used antihaemostatic medication (90%). Patients with spinal haematoma generally presented with severe spinal cord injury; 47% of patients presented with ASIA A or B (complete neurological injury or preserved sensation only, respectively).

Conservative treatment was provided in seven patients and decompression (neurosurgery or percutaneous drainage) in 33 patients. Data regarding the timing of decompression were present for 30 patients; 43%(13 of 30) of patients had decompression less than 12 h after clinical diagnosis.

Full recovery after treatment of haematoma was reported in 18% (7 of 39) of patients within this closed claims analysis, which is less often than was reported in our previous literature review [full recovery in 47% (149 of 318) of patients, P=0.001, n=357].

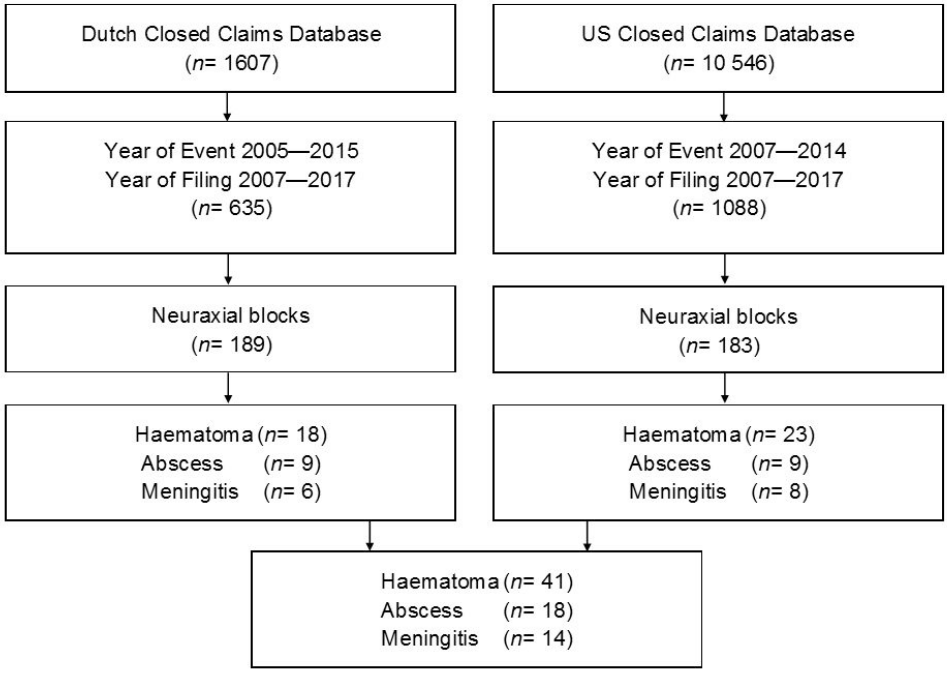

Figure 1 Flowchart of included closed claims concerning haematoma, abscess and meningitis after neuraxial anaesthesia

Table 1 Patient and neuraxial technique characteristics, clinical course and medicolegal characteristics in patients with haematoma, abscess or meningitis after neuraxial anaesthesia.

	Haematoma	Abscess	Meningitis	*P value*
Sample size	41	18	14	
Age (years)	66 [62 - 78], *n*=41	47 [41 - 54], *n*=17	50 [26 - 55], *n*=9	<.001
Male sex	16 (39%), *n*=41	10 (56%), *n*=18	7 (70%), *n*=10	0.16
BMI [IQR] in kg m^{-2}	26 [24 - 28], *n*=19	28 [26 - 36], *n*=9	25 [25 - 30], *n*=7	0.12
Obese; BMI >30	7 (30%), *n*=23	3 (30%), *n*=10	0 (0%), *n*=7	0.24
ASA physical status III-V	26 (68%), *n*=38	3 (19%), *n*=16	0 (0%), *n*=9	<.001
Emergency procedure	4 (10%), *n*=40	5 (31%), *n*=16	0 (0%), *n*=14	0.03
Antihaemostatic status				<.01
Normal	4 (11%)	5 (71%)	4 (100%)	
Antiplatelet	4 (11%)	-	-	
Anticoagulant	16 (42%)	2 (29%)	-	
Antiplatelet and Anticoagulant	3 (8%)	-	-	
Mistake in time or dose[a]	11 (29%)	-	-	
Missing	3	11	10	
Neuraxial Technique				0.13
Epidural analgesia	16 (39%)	7 (44%)	1 (7%)	
Spinal anaesthesia	4 (10%)	2(13%)	6 (43%)	
CSE	2 (5%)	-	-	
Epidural injection	15 (37%)	6 (38%)	7 (50%)	
Spinal catheter	2 (5%)	-	-	
Failed neuraxial block	2 (5%)	1 (6%)	-	
Missing	-	2	-	
Indication				0.44
Chronic pain	16 (39%)	7 (44%)	7 (50%)	
Acute pain (incl. trauma)	3 (7%)	4 (25%)	-	
Orthopaedic surgery	7 (17%)	1 (6%)	5 (36%)	
Digestive surgery	5 (12%)	2 (13%)	1 (7%)	
Aortic/Peripheral vascular	4 (10%)	-	-	
Gynaecologic oncology/surgery	2 (5%)	-	-	
Obstetric: Labour/Caesarean	1 (2%)	2 (13%)	1 (7%)	
Urologic/Thoracotomy/Debridement	3 (7%)	-	-	
Missing	-	2	-	
Complicated procedure	13 (45%), *n*=29	3 (27%), *n*=11	2 (33%), *n*=6	0.57
Injected agent[b]				0.41
Local anaesthetic (LA)	6 (18%)	1 (9%)	4 (33%)	
Opioid	1 (3%)	-	-	
Steroid	4 (12%)	2 (18%)	4 (33%)	
LA with opioid	7 (21%)	3 (27%)	-	
LA with steroid	9 (26%)	3 (27%)	2 (17%)	
LA with epinephrine	1 (3%)	2 (18%)	-	
LA with opioid with epinephrine	3 (9%)	-	1 (8%)	
Steroid with contrast with/without LA	3 (9%)	-	1 (8%)	
Missing	7	7	2	

	Haematoma	Abscess	Meningitis	*P value*
Clinical Course				
Time point of complication				0.05
Prior to procedure	-	1 (6%)	1 (7%)	
During puncture	2 (5%)	-	-	
During treatment with catheter	11 (28%)	2 (13%)	-	
After removal of catheter	6 (15%)	4 (25%)	-	
After spinal anaesthesia	4 (10%)	1 (6%)	6 (43%)	
After epidural injection	15 (38%)	7 (44%)	7 (50%)	
After failed spinal anaesthesia	2 (5%)	1 (6%)	-	
Missing	1	2	-	
Timeline, (h)[c]				
First symptoms	12 [2 – 30], *n*=40	84 [24 – 186], *n*=14	24 [15 – 30], *n*=10	<.01
First neurological symptoms (NS)	19 [2 – 37], *n*=40	168 [105 – 689], *n*=8	48 [30 – 48], *n*=4	<0.001
Duration NS to imaging diagnosis	15 [3 – 40], *n*=33	2 [2 – 24], *n*=7	NA	0.16
Duration NS to evacuation	19 [8 – 47], *n*=30	9 [4 – 180], *n*=6	NA	0.50
Duration diagnosis to evacuation	6 [2 – 10], *n*=25	18 [2-342], *n*=8	NA	0.20
Treatment				0.18
Conservative therapy	7 (18%)	4 (27%)	NA	
Neurosurgical decompression	32 (80%)	9 (60%)	NA	
Percutaneous drainage	1 (3%)	2 (13%)	NA	
Missing	1	3		
Recovery after treatment				0.19
Full recovery	4 (10%)	4 (24%)	1 (10%)	
Delayed but full recovery	3 (8%)	4 (24%)	3 (30%)	
Partial recovery	17 (44%)	4 (24%)	4 (40%)	
No recovery	12 (31%)	4 (24%)	-	
Death	3 (8%)	1 (6%)	2 (20%)	
Missing	2	1	4	
Medicolegal Characteristics				
Event-to-closing of claim (years)	3 [2 – 5]	4 [2 – 6]	2 [1 – 2]	0.01
Severity of injury				<.01
Temporary or Minor	7 (17%)	12 (67%)	7 (50%)	
Permanent disabling	31 (76%)	5 (28%)	5 (36%)	
Death	3 (7%)	1 (6%)	2 (14%)	
Judgement of care				0.08
Appropriate	25 (61%)	14 (78%)	10 (71%)	
Substandard	16 (39%)	2 (11%)	3 (21%)	
Impossible to judge	-	2 (11%)	1 (7%)	
Discussion points[d]				<0.001
No indication for block	2 (4%)	-	-	
No informed consent	2 (4%)	-	-	
Medication error - timing	10 (19%)	-	-	
Unsterile procedure	-	2 (11%)	8 (57%)	
Insufficient documentation	2 (4%)	2 (11%)	1 (7%)	

	Haematoma	Abscess	Meningitis	*P value*
Insufficient monitoring	4 (8%)	-	1 (7%)	
Insufficient communication	5 (10%)	-	-	
Delay (Diagnosis/Treatment)	13 (25%)	4 (21%)	1 (7%)	
Impossible to judge	-	2 (11%)	1 (7%)	
According to good practice	14 (27%)	9 (47%)	2 (14%)	
Claim conclusion				0.12
Complication	17 (43%)	14 (82%)	7 (50%)	
Culpable complication	11 (28%)	-	2 (14%)	
Amicable settlement	10 (25%)	3 (18%)	4 (29%)	
Dropped/Dismissed	2 (5%)	-	1 (7%)	
Missing	1	-	-	
Medicolegal Payment Characteristics				
Country		US	Netherlands	
Sample size		40	33	
Payment		15 (38%)	17 (52%)	0.23
Median indemnity payment in 2017€		€285 488	€31 031	<.01
Interquartile range		[€113 561 – €702 990]	[€15 026 – €162 293]	

Abbreviations: n, cases with available data on specific parameter; BMI, body mass index; ASA, American Society of Anaesthesiologists; CSE, combined spinal epidural; LA, local anaesthetic; NS, neurological symptoms; NA, not applicable; US, United States

[a]Mistake in time/dose of anti-haemostatic medication occurred in antiplatelet drugs (*n*=3), anticoagulant drugs (*n*=4), antiplatelet and anticoagulant drugs combined (*n*=3) and unspecified type of drug (*n*=1). [b]Drugs may or may not be approved by the Food and Drug Administration (FDA) for specific neuraxial administration/indication. [c]Median time in hours from onset of neuraxial block (time point 0). [d]Multiple points of discussion per claim may be present.

Spinal abscess

Patients with spinal abscess were involved in emergency surgical interventions in 31% of cases. Twenty-five percent of patients with spinal abscess presented with complete or severe spinal cord injury. When outcomes of recovery were compared with outcomes in our previous literature review,[14] 47% (8 of 17) of patients reported full recovery within this analysis vs. 68% (129 of 190) of patients in our previous literature review (*P*=0.08, *n*=207).

Meningitis

All patients with meningitis were treated with antibiotics and 4 of 14 patients were admitted to an ICU; 2 of these patients died. In 4 of 14 meningitis cases, headache was mistakenly confused with postspinal-puncture headache, and these patients were treated with an epidural blood patch after developing symptoms of headache. Patients with meningitis showed full recovery in 40% of events. Persistent symptoms constituted persistent headache, concentration/memory deficits, dizziness and/or deafness.

Potential preventable causes

Claim reviewers, legal and medical experts raised the following discussion points concerning possible causes that may have contributed to the development of complications: errors in timing of antihaemostatic medication related to neuraxial procedure or catheter removal (14% of claims, *n*=10), unsterile procedures (14% of claims, *n*=10) and delay in diagnosis/treatment of the complication (25% of claims, *n*=18). Delayed diagnosis was present in 12 of 18 claims, delayed treatment in one claim, delay in both diagnosis and treatment in four claims, and in one claim the delay of diagnosis or treatment was not further specified. Delayed diagnosis and treatment were reported both in the USA (*n*=10) and the Netherlands (*n*=8). Care was judged substandard in 10 of 18 claims with delayed diagnosis or treatment. No differences were present between timing of diagnosis and treatment between claims that were ultimately judged as appropriate or substandard within this series (neurological symptoms to diagnosis *P*=0.36, *n*=12, and diagnosis to treatment *P*=0.36, *n*=11).

Procedural sterility was questioned in 10 claims (USA *n*=5, Netherlands *n*=5), constituting failure to wear a surgical mask during spinal anaesthesia, performance of an epidural blood patch while signs of systemic infection were present or details of unsterile events were not clarified. Inadequate measures to guarantee sterility, and thus substandard care, was inferred in 3 out of 10 claims. Four of 10 claims were associated with a multistate healthcare-associated outbreak of fungal meningitis after epidural injections with contaminated methylprednisolone in 2012 in the USA.[24] In these specific cases, the infectious complications were unrelated to protocol violations or substandard anaesthetic care.

In addition, one case of abscess and one case of meningitis occurred prior to neuraxial block as judged by medical experts reviewing the claim. Consequently, as an active systemic infection or infection at the site of puncture is a (relative) contraindication to neuraxial block, these two complications were judged to have been associated with substandard care and may have been preventable.

Medicolegal payments

Within this closed claims analysis, we observed similarity between countries in the decision for payment. In contrast, median indemnity payment was considerably higher in the USA than in the Netherlands ($P<0.01$, *n*=31); median indemnity payment was €285.488 [€113.561 to €702.990] (*n*=14) in the USA vs. €31.031 [€15.026 to €162.293] (*n*=17) in the Netherlands.

Discussion

This closed claims analysis demonstrated that delayed diagnosis or treatment of complications, errors in timing of antihaemostatic medication related to the timing of the neuraxial procedure and unsterile procedures are prominent discussion points and potentially preventable causes of unfavourable outcomes both in the USA and the Netherlands. A delayed diagnosis of the complication was the most often reported discussion point by claim reviewers, legal and/or medical experts (22% of claims, *n*=16). Delayed diagnosis is detrimental, as well considered risk–benefit analyses between a conservative approach in patients with mild symptoms or spontaneous recovery (constituting thorough monitoring, consultation with neurologists/neurosurgeons and documentation) and urgent intervention is impossible as long as the underlying pathophysiological complication is unknown. Our previous research showed that delayed decompression of spinal haematoma for greater than 12 h after clinical diagnosis resulted in a worse neurological outcome compared with earlier decompression.[14] Within the present analysis, decompression of spinal haematoma occurred in 57% of patients after more than 12 h. It seems that the diagnostic process needs to be streamlined and is the main area for improvement of patient safety. Alarm symptoms, such as increasing back pain, new sensory or motor deficit, urinary retention or bladder/bowel incontinence must trigger treating physicians to initiate further diagnostics.

Protocols for patients with suspected spinal haematoma or abscess, such as epidural alert systems, help to designate which medical speciality has the lead in diagnosis and interdisciplinary consultations, advise active measures, such as trial stops of epidural medication, and lay out times by which imaging must be achieved and decisions on surgery be made. Unfortunately, many hospitals in the Netherlands (55%) do not have pre-agreed protocols for diagnostic workup and management of severe neurological complications of epidural analgesia.[5]

Furthermore, this analysis confirms that the severity of spinal cord injury after spinal haematoma is significant; a substantial proportion of patients had complete motor injury after treatment, with a major impact on quality of life. Our previous literature review[14] reported full recovery in 47% of patients after treatment of spinal haematoma; within the present analysis of closed claims, full recovery was seen in fewer patients (18% of patients). These differences in outcome may be explained by a longer duration of follow-up alongside the higher likelihood of claim initiation in patients who have developed severe symptoms and unfavourable outcomes.

An interesting finding in patients with spinal abscess is that these patients had more often undergone emergency surgery, which may be explained by a higher risk of infections within this patient category or by the emergency character of the intervention having caused breaches of sterility because of lack of time, and, consequently, to a higher rate of infection.

We also found that in all three categories (haematoma, abscess and meningitis), the majority of neuraxial procedures were performed to treat patients with chronic pain: in 39, 44 and 50%, respectively. Epidural injections were performed in a large proportion of these patients. Epidural (steroid) injections appear to provide short-term benefit in well selected patients, but long-term efficacy is difficult to determine because of the multiple and heterogeneous factors associated with this neuraxial technique. Differences in injection route, region, control group, injectate characteristics and underlying disease contribute to variation in outcomes, resulting in challenges in the interpretation of existing studies.[25] Consequently, evidence for beneficial characteristics as predictors of long-term relief is conflicting. Epidural injections to treat chronic pain can be a part of a multimodal treatment strategy, but should be used based on evidence, rather than done as a rote treatment in any patient with spinal pain.[25] Furthermore, neuraxial administration of some drugs included in this analysis are not approved by the Food and Drug Administration (FDA) for specific indications.[26] In addition, neuraxial procedures for the treatment of chronic pain are regularly performed in outpatients. This may influence the diagnostic process as physicians

are dependent on self-reporting by patients and travelling times for first assessment in case complications occur after hospital discharge. Patient information must include alarm symptoms and guidance on indications for urgent consultation with the treating physician to prevent unnecessary delays in diagnosis and treatment.

Both in this closed claims analysis and our previous literature review,[14] many patients developed symptoms of complications after removal of a spinal/epidural catheter, spinal anaesthesia, epidural injection or failed regional techniques. With respect to routine follow-up after neuraxial block, it is of note that symptoms typically occur when patients are no longer followed-up by the anaesthetist or physicians with neurological expertise, resulting in delayed recognition of symptoms, imaging and treatment.

Regarding payment outcomes, similarity was seen between countries in decisions made for payment, but the median indemnity payment was much higher in the USA compared with the Netherlands. Discrepancy is present between and within countries in the financial administration of expenses. Subsequently, the lack of transparency in financial administration may lead to inadequate comparison of indemnity payments. Nonetheless, when comparing publicly available data relating to claims from all medical specialties, average indemnity payment per paid claim was approximately €5.000 to €50.000 for claims closed between 2011 and 2015 in the Netherlands,[22,23] while the average indemnity payment was approximately €307.000 for claims closed between 2011 and 2015 in the USA.[27] In addition, a trend in increased indemnity payments has been reported between 2007 and 2016 in the Netherlands.[22]

Closed claims analyses, while valuable for gaining more insight into rare complications and adverse events, also suffer from several well described limitations, such as selection bias, nonrandom retrospective data collection and outcome bias.[28] By definition, as mentioned above, a delay is present between the event, and initiation and closing of the claim. Another limitation concerns the raised discussion points; for the US claims, these were judged by pairs of claim reviewers, for the Dutch claims by legal and medical experts.

The reliability of this variable is unknown; however, the discussion points described in this study were raised by multiple anaesthesiologists during the claim handling process both in the USA and the Netherlands. Also, data from the ASA Anaesthesia Closed Claims database are limited to information gathered by insurance companies for claims resolution. For the Dutch cases, an extensive analysis of all medical and judicial files has been executed, which is an advantage of this study.

Conclusion

Spinal haematoma was related to antihaemostatic medication use, medication errors and delay in diagnosis and/or treatment. Specifically, for patients with suspected spinal haematoma, the diagnostic process needs to be streamlined and seems to be the main area for improvement of patient safety. A delay in diagnosis is detrimental, and considered decisions on treatment cannot be made as long as the underlying pathophysiological complication is unknown. Spinal abscess was related to emergency interventions, whereas both infectious complications, i.e. abscess and meningitis, were associated with lack of sterility when performing the neuraxial procedure. Concerning legal outcomes, there is similarity between closed claims from the USA and the Netherlands in decisions for payment, but the median amount of indemnity payments is considerably higher in the USA than in the Netherlands.

Acknowledgements relating to this article

Assistance with the study: the authors thank Sandra Mulder, former healthcare inspector/anaesthesiologist, for her contribution in the initiation of this study, and Alice Hamersma, Centramed, Bart Jongbloed and Onno Dijt, MediRisk, for their cooperation and providing the required research data.

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Conflicts of interest: none.

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Supplemental Data File. Extracted data

Table A1. *Extracted data of closed claims of haematoma, abscess or meningitis after neuraxial block. ASA, American Society of Anaesthesiologists physical status; NB, neuraxial block; ASIA, American Spinal Injury Association Impairment Scale.*

Extracted data	
Type of complication	Haematoma / Abscess / Meningitis
Country	United States / the Netherlands
Type of hospital	Pain Clinic / General Hospital / Non-university Teaching Hospital / University Medical Centre
Event year	Year of event
Closing year	Year of closing of claim
Patient characteristics	
Age	In Years
Sex	Male / Female
Body Mass Index	Weight in kilograms, height in meters, in kg m^{-2}, 1 decimal
Obese	Yes: BMI>30 / No: BMI≤30
ASA physical status[1]	As reported in documentation or based on comorbidities reported in documentation, I - V
Medication use	Free text
Coagulation status	No regular anticoagulant or antiplatelet drugs / Antiplatelet, single therapy / Antiplatelet, double therapy / Prophylactic Low Molecular Weight Heparin (LMWH) / Therapeutic LMWH / Vitamin K antagonist / Factor Xa inhibition / Heparin infusion / Urokinase infusion / Multi-therapy (≥2 different anticoagulant drugs) / Coagulation disorder / Mistake in drug administration / Unspecified anticoagulant therapy
Blood test results	Haemoglobin in mmol l^{-1}, platelet count x10^9 l^{-1}, International Normalized Ratio, Activated Partial Thromboplastin Time in seconds, Prothrombin Time in seconds, leucocyte count x10^9 l^{-1}, eGFR in ml min^{-1}, Creatinine in µmol l^{-1}, Glucose in mmol l^{-1}, C-reactive protein in mg l^{-1}
Fever	Yes / No, defined as temperature >38 degree Celsius
Neuraxial technique characteristics	
Type of neuraxial technique	Continuous epidural analgesia / Spinal anaesthesia / Combined spinal epidural technique / Spinal catheter / Epidural injection / Failed neuraxial block

Report of complicated puncture	Uncomplicated puncture / Multiple punctures / Bloody tap / Inadvertent dural puncture / Paraesthesia
Local anaesthetic used	Lidocaine / Bupivacaine / Levobupivacaine / Articaine / Prilocaine / Ropivacaine
Additive	Opioid / Steroid / Epinephrine / Contrast
Number of attempts for neuraxial technique	Integer
Number of levels spinal cord attempted	Integer
Experience of anaesthesiologist performing neuraxial block (NB)	Resident (≤5 years of experience) / Anaesthesiologist (>5 years of experience)
Level of regional technique	Cervical / Thoracic / Lumbar / Sacral
Puncture height	Between two vertebras; upper vertebra noted
Needle size	In Gauge
Indication for neuraxial analgesic / anaesthetic procedure	Chronic pain management / Orthopaedic surgery / Digestive surgery / Aortic / Peripheral vascular / Endovascular aneurysm repair / Obstetric: Labour analgesia / Obstetric: Caesarean section / Urologic / Thoracotomy / Thoracoscopy / Gynaecologic oncology or surgery / Cardiac surgery / Trauma / Amputation or Extremities surgery / Neurosurgical / or: 'other', describe
Emergency intervention	Yes / No
Time line	
Hours to removal of catheter from time point 0	Time point 0 is first attempt NB, rounded to full hours
Hours to symptoms from time point 0	Time point 0 is first attempt NB, rounded to full hours
Hours to neurological symptoms from time point 0	Time point 0 is first attempt NB, rounded to full hours
Hours to diagnostics from time point 0	Time point 0 is first attempt NB, rounded to full hours
Hours to evacuation of complication from time point 0	Time point 0 is first attempt NB, rounded to full hours
Hours progression of symptoms	From onset of first symptoms to worst symptoms evaluated, rounded to full hours

Hours to symptom onset after predisposing causative event	Causative event is defined as: i.e. NB onset, removal of catheter or dose of anticoagulant, rounded to full hours
Hours to evacuation of complication from symptoms onset	Duration of first symptoms to evacuation of haematoma/abscess, rounded to full hours
Time point of complication	Prior to procedure / During puncture / During drug administration / After removal of catheter / After spinal anaesthesia / After epidural injection / After failed neuraxial block
Diagnostics	MRI-scan / CT-scan / Diagnostic Lumbar Puncture / Electromyography / Spinal X-ray / Urodynamic monitoring
Therapy	Surgical evacuation / Conservative therapy / Percutaneous drainage / Antibiotics / Intensive Care Admission
Reason conservative therapy, if chosen	Poor patient condition / Patient refused surgery / Spontaneous recovery while awaiting surgical evacuation / Decision for conservative therapy
Symptoms	
Pain / Sensory deficit / Motor deficit	Pain: Scored as Partial or Mild / Full or Severe / Present; degree not further specified Sensory deficit: Scored as Partial or Mild / Full or Severe / Present; degree not further specified Motor deficit: Scored as Partial or Mild / Full or Severe / Present; degree not further specified
Bilateral nerve injury	Yes / No
Reflexes	Absent / Partially present / Normal / Vivid
ASIA Impairment Scale (before and after treatment) – only for hematoma and abscess cases	Grade A, complete neurological injury Grade B, no motor function present, but preserved sensation may be present Grade C, preserved non-functional motor function Grade D, preserved functional motor function Grade E, normal motor and sensory function, but abnormal reflexes may persist
Neurological recovery	Full recovery / Delayed but full recovery (recovery after more than 1 month from symptom onset) / Persistent weakness or partial recovery / Persistent paralysis or no recovery
Complication characteristics	
Type of haematoma/abscess	Spinal, spinal and intracranial
Space	Epidural / Subdural / Subarachnoidal / Intraspinal (medullary) / Paraspinal muscles
Level of complication	Cervical / Thoracic / Lumbar / Sacral
Number of vertebrae involved	Integer

Medicolegal characteristics	
Claim conclusion	Complication / Culpable complication / Amicable settlement / Dropped or dismissed
Event-to-closing of claim	Date rounded to full year, in years
Severity of Injury Scale	1 Emotional only / 2 No delay in recovery: lacerations, contusions, minor scar, rash / 3 – 4 Recovery delayed: infections, missed fracture, fall in hospital, burns, surgical material left, drug side effect, brain damage / 5 Nondisabling injuries: loss of fingers, loss or damage to organs / 6 Deafness, loss of limb, eye, kidney, lung / 7 Paraplegia, loss of two limbs, blindness, brain damage / 8 Quadriplegia, severe brain damage, lifelong care / 9 Death
Severity of Injury Scale collapsed	Temporary or permanent minor non-disabling injuries: 0 – 5 / Permanent disabling: 6 - 8 / Death: 9
Judgement of Care	Appropriate / Substandard / Impossible to judge
Discussion points	No indication for block / No informed consent / Medication error – timing / Medication error – dose / Unsterile procedure / Insufficient documentation / Insufficient monitoring / Insufficient communication / Delay – Diagnosis / Delay – Treatment / Impossible to judge / According to good practice
Decision for Payment	Yes / No
Claim costs	Dollars converted to euros at time of payment using the exchange rate of the year of (first) payment.[2] Subsequently, euros were adjusted to European Union 2017 amounts using the Consumer Price Index.[3]
Payment patient	Dollars converted to euros at time of payment using the exchange rate of the year of (first) payment.[2] Subsequently, euros were adjusted to European Union 2017 amounts using the Consumer Price Index.[3]

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Chapter 7

Epidural Needle Damage after Difficult or Complicated Neuraxial Procedures

A Technical Analysis

Elke M.E. Bos, Cor J. Kalkman, Coen D. Dijkman,
Tim Daams, Markus, W. Hollmann

Journal of Clinical Anesthesia

To the Editor,

Sporadically, deformation or breakage of needles occurs during epidural or spinal puncture. Very seldom fragment(s) of the broken needle remain inside the patient after the neuraxial procedure. Most problems seem to occur with thin spinal needles (22–27 gauge),[1-3] but a few cases were described in the literature concerning broken epidural needles.[4-6]

We performed a technical analysis - simulating extreme forces - to investigate the vulnerability of epidural needles by analyzing the force needed to deform or break a needle. Biomedical engineers of the Amsterdam University Medical Center, built a model to simulate an epidural procedure puncture site. The model is made of two materials; Smooth-On Ecoflex 5, a silicone rubber of 20 millimeter, simulating the skin and subcutaneous tissue, and a 3D printed model of a cast with coating (Projet660pro 3D-printer with VisiJet® PXL material coated with StrengthMax infiltrant) simulating bone texture

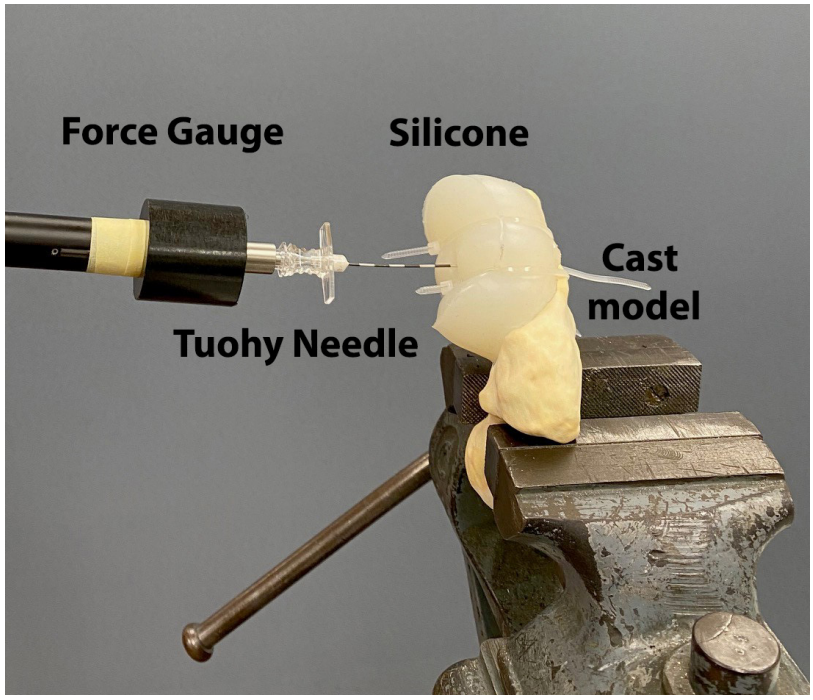

Figure 1. Simulation model of the epidural puncture site

of the vertebra. The silicone material was attached to the bone-model with tie-wraps. A Compact Force Gauge 100 newton (N) was used to measure the applied force. The stylet was removed from the epidural needle, the needles were then applied to the Force Gauge with a Luer Lock fitting and attached with 5mm metric thread to ensures a good fit. The simulation model of the epidural puncture site is shown in Figure 1.

The experiment was performed six times; with three 20 Gauge (G) and three 18G Tuohy epidural needles. Every needle was exposed to incremental forces aiming for 10N, 20N, 30N and 40N, until bending occurred. After application of each targeted force, the needles were examined macroscopically and microscopically. The outer diameter of the needle, the kinking force (force when the needle first began to kink) and the force after which needle tip deformation occurred, were reported. As a reference, to push the needle through the soft tissue until contact with the bone-model, takes approximately 6N.

The results of our experiment (i.e. the outer diameter and forces of kinking and tip deformation) are reported in Table 1. See the supplementary file for Figures of the bone-model and the macroscopic and microscopic evaluation of the 20G and 18G needles after the experiments. Specifically, tip deformation was seen, without further damage (e.g. metal shards), with integrity of the needle tip confirmed by microscopic evaluation. None of the needles broke.

Table 1. Outer diameter and forces of kinking and tip deformation of 20G and 18G Tuohy epidural needles. mm; millimeter, N; newton, SD; standard deviation, G: gauge.

Needle	Outer diameter, (in mm)	Kinking Force, (in N)	Tip deformation, (in N)	Mean (SD), Kinking Force (in N), n: 3	Mean (SD), Tip Deformation (in N), n: 3
20G	0,9	26,0	20,0	26,7 (1,2)	25,0 (5,0)
20G	0,9	26,0	25,0		
20G	0,9	28,0	30,0		
18G	1,3	30,0	40,0	39,7 (8,5)	43,0 (3,0)
18G	1,3	43,0	43,0		
18G	1,3	46,0	46,0		

During real-life epidural catheter placement, epidural needles are subjected to a range of forces. The magnitude of the forces depends on the course of the procedure (multiple punctures with the same needle), firmness of the ligaments, presence of bone contact and potential movement of the patient, as well as the maximum force the operator is willing to apply. In our experiment, 20G needles start to kink when exposed to forces of 25-30N and 18G needles when exposed to forces of 30-45N. These findings are in congruence with a previous study by Dunn and others, reported in 1992, evaluating the stiffness and malleability of 18G and 17G epidural needles.[6] They conclude that the bending force (representing stiffness) was proportional to the outer diameter of the needle, whereas displacement (representing malleability) of the needle correlated poorly with diameter. The average bending force for 18G epidural needles was 33,3N in their research compared to 39,7N in our experiment. The average outer diameter of the 18G needles was similar to the outer diameter of the needles used for our experiment. It is conceivable that 18G epidural needles manufactured today are less likely to bend compared to 18G needles that were manufactured three decades ago. Either the manufacturing process or materials could have been altered over the years, aiming for a higher resistance to bending.

In our experiment, tip deformation was seen without further damage (e.g. metal shards) and integrity of the needle tip was confirmed by microscopic evaluation. Furthermore, breakage of epidural needles was not observed in our experiment. On theoretical grounds, breaking may occur if a needle is bent back towards its original shape[6] after bending has occurred inside the patient or if the needle is damaged in the process prior to the epidural procedure. Case reports that have described epidural needle breakage concerned a filled fragment with a diameter of less than 1 mm and length of 0,7 cm that was considered to be a broken stylet of an epidural needle tip,[4] a 3,0-inch (7,6 cm) fragment of a 4,5-inch (11,4 cm) 17G Tuohy needle[5] and a 4,5 cm fragment of an 18G Tuohy needle (American Medical Instruments, New Bedford, Mass.).[6] Bending of epidural needles seems to occur more often in the midshaft, both in earlier reports (excluding the case of the stylet) and in

the present experiment. This is also seen in cases describing the breakage of spinal needles.[7,8] Suggesting that if breakage occurs, it may be more likely to result in a relatively large broken fragment. However, this situation is extremely difficult to realize in an actual clinical scenario.

Limitations of our experiment include the difficulties that were experienced to simulate a real-life epidural puncture site. For example, the bending force of the needle will be related to the angle of the surface onto which the needle tip impacts and possible lateral forces applied to the needle during insertion (by the operator or by the patient). We mainly applied long-axis forces straight onto the bone model during the experiment, this may be different from the forces applied during a clinical situation.

In conclusion, breaking of epidural needles is extremely rare and difficult to simulate. Bending occurs without breakage when significant forces are applied. The breakage of needles may be more likely once bending has occurred. Overall, bending of needles used for neuraxial procedures should be prevented as this may result in patient injury. In general, it is important to withdraw needles to superficial subcutaneous tissue prior to redirection of the needle[5] and to inspect the needle for damage or bending when significant forces are applied while attempting a neuraxial procedure.

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Supplementary file

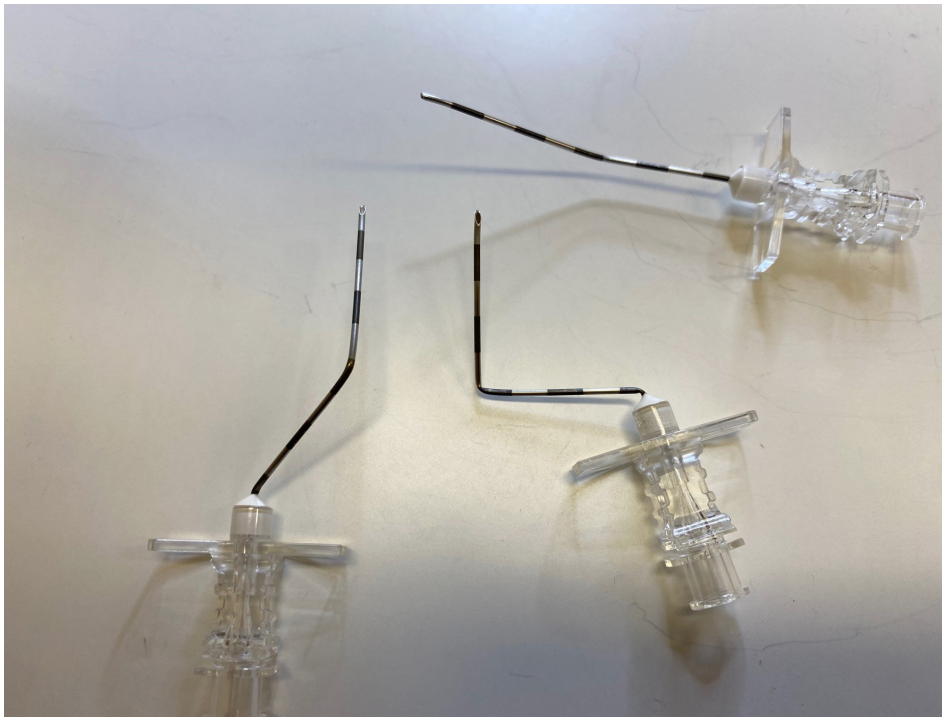


Figure 1. Kinking of 20G Tuohy epidural needles at 26N, 26N and 28N

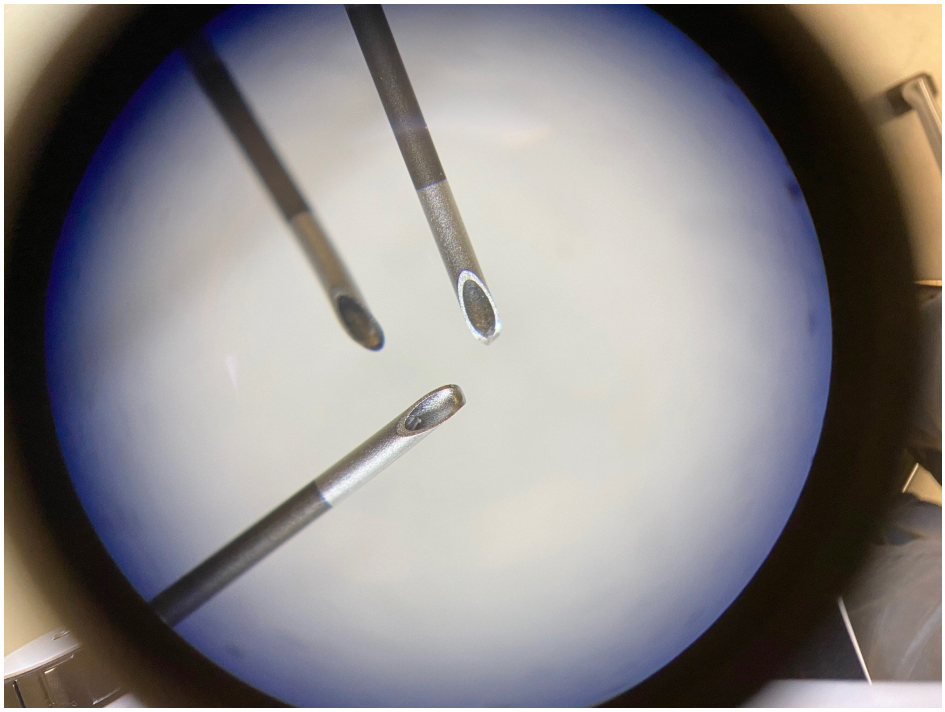


Figure 2. Tip deformation of 20G Tuohy epidural needles at 20N, 25N and 30N

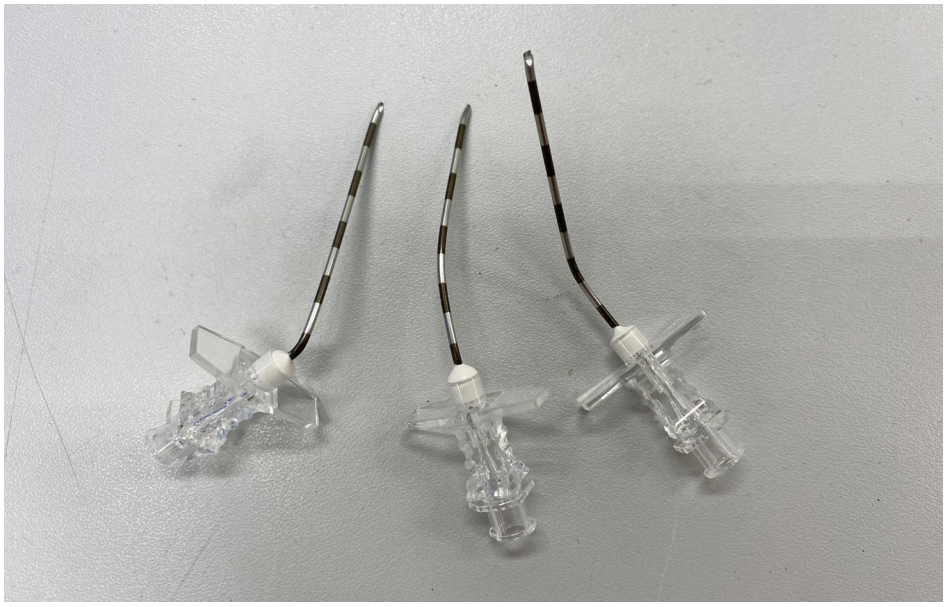


Figure 3. Kinking of 18G Tuohy epidural needles at 30N, 43N and 46N

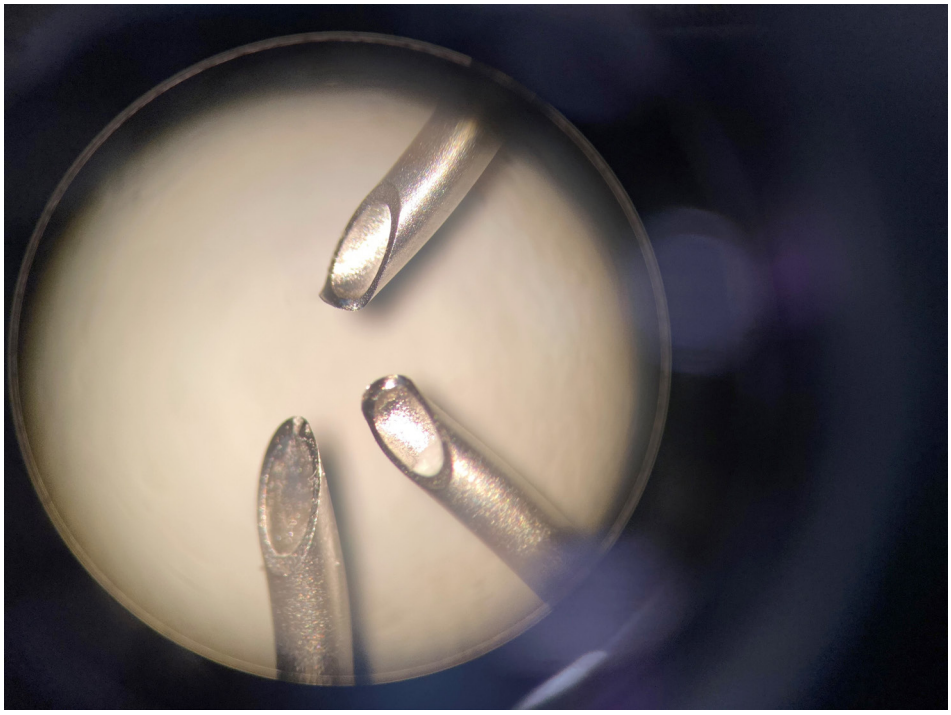


Figure 4. Tip deformation of 18G Tuohy epidural needles at 40N, 43N and 46N

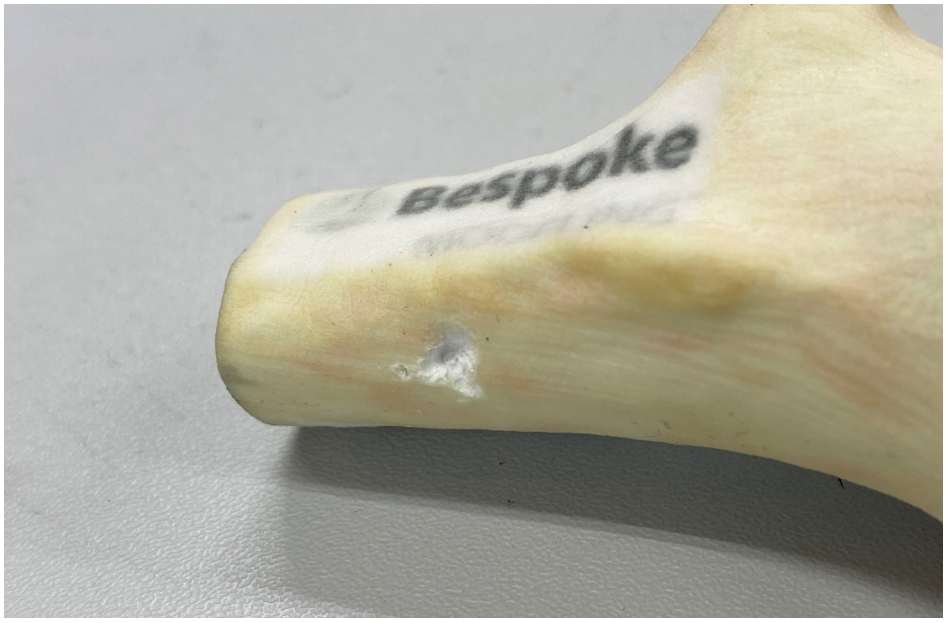
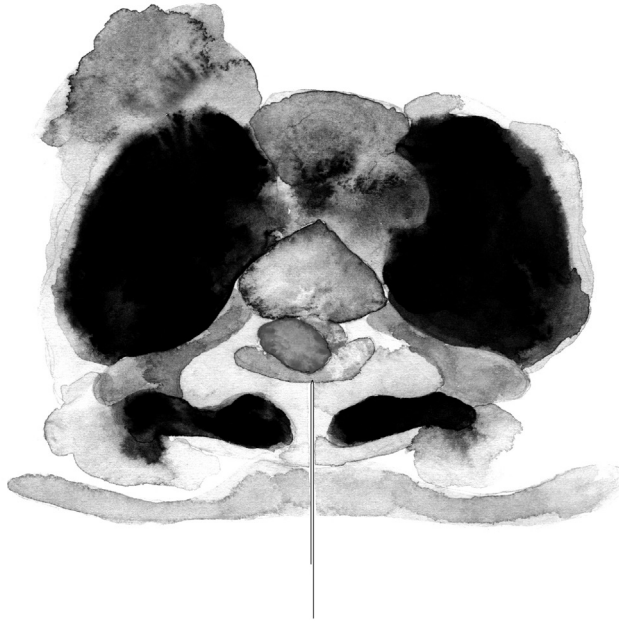


Figure 5. Destruction of bone model after the experiment

PART 3

Trends in neuraxial anesthesia practice



Chapter 8

Trends in practice and safety measures of epidural analgesia:

Report of a national survey

Elke M. E. Bos , Maartje E. Schut , Marcel de Quelerij,
Cor J. Kalkman, Markus W. Hollmann, Philipp Lirk

Acta Anaesthesiologica Scandinavica

Abstract

Background – The clinical use of epidural analgesia has changed over past decades. Minimally invasive surgery and emergence of alternative analgesic techniques have led to an overall decline in its use. In addition, there is increasing awareness of the patient-specific risks for complications such as spinal haematoma and abscess. Local guidelines for management of severe neurological complications during or after epidural analgesia, i.e., "epidural alert systems", have been introduced in hospitals to coordinate and potentially streamline early diagnosis and treatment. How widely such protocols have been implemented in daily practice is unknown.

Methods – We conducted a survey to analyse trends in practice, key indications, safety measures, safety reporting, and management of complications of epidural analgesia in the Netherlands. Data were gathered using a web-based questionnaire and analysed using descriptive statistics.

Results – Questionnaires from 85 of all 94 Dutch hospitals performing epidural analgesia were collected and analysed, a 90% response rate. Fifty-five percent reported a trend towards decreased use of perioperative epidural analgesia, while 68% reported increasing use of epidural analgesia for labour. Reported key indications for epidural analgesia were thoracotomy, upper abdominal laparotomy, and abdominal cancer debulking. An epidural alert system for neurological complications of epidural analgesia was available in 45% of hospitals.

Conclusions – This national audit concerning use and safety of epidural analgesia demonstrates that a minority of Dutch hospitals have procedures to manage suspected neurological complications of epidural analgesia, whereas in the remaining hospitals responsibilities and timelines for management of epidural emergencies are determined on an ad hoc basis.

KEYWORDS

epidural analgesia: complications, epidural analgesia: obstetrics, epidural analgesia: perioperative

Introduction

Although epidural analgesia is regularly used to provide pain relief for trauma, labour and several surgical procedures, the overall trend is to move away from neuraxial blocks in favour of truncal blocks, peripheral nerve blocks, and local anaesthetic wound infiltration where possible.[1] Less invasive surgical methods, sophisticated multimodal analgesia regimens, and increasing awareness for the rare but serious complications of epidural analgesia have contributed to this development.[2-5] Trends in the perioperative use of epidural analgesia have been reported in different countries, mostly in single-centre observations and for specific surgical procedures, but have not been investigated on a national level in the Netherlands.[6-9]

Meanwhile, as concerns of serious neurological complications of epidural analgesia are increasing, dedicated "alert systems" have been introduced. These epidural alert systems are local guidelines intended to direct caregivers in the process of recognition and effective treatment of patients with suspicion for spinal haematoma or abscess after neuraxial anaesthesia.[10-14] Proactive management is of importance, especially for patients with spinal haematoma, as an association between adversity of outcome and delay in surgical decompression is present.[15] However, there are no data to indicate to what extent epidural alert protocols are implemented in clinical practice.

Regarding the incidence of major complications of epidural analgesia, few studies have been performed in the Netherlands. A retrospective single-centre study, identified spinal abscess in 11 of 91 patients that received 137 epidural catheters for management of chronic pain for a total of 4.326 catheter days from 1993 to 1996.[16] Another single-centre study, identified zero spinal haematomas and abscesses in 3.035 postoperative patients treated with epidural analgesia for a mean duration of 2.1 catheter days from 2008 to 2013.[17] Historically, the incidence of serious complications after epidural analgesia has been considered to be extremely low, but nowadays it is accepted that the incidence may range from 1:6.000 to 1:1.000 epidural procedures depending on patient-related risk factors, such as antihaemostatic medication use and

anatomy of the spinal column.[4,18] The aim of this survey was to quantify trends in practice of epidural analgesia and to assess the extent to which epidural alert systems for neurological complications of epidural analgesia have been introduced in clinical practice.

Methods

This survey was developed by a study group consisting of the authors, who operate from separate anaesthesiology departments throughout the Netherlands (E.B., M.Q., C.K., M.H., P.L.). The questionnaire was revised four times to assure questions were clearly formulated and to minimize the likelihood of ambiguous interpretation.

A list of all hospitals in the Netherlands was obtained from the National Institute for Public Health and the Environment.[19] Children's hospitals, private practices, and outpatient clinics were excluded. In January 2016, the questionnaire was sent to one anaesthesiologist per hospital (typically the head of service or clinical lead for regional anaesthesia services), who was asked to complete the questionnaire or to identify the most appropriate person to answer the questionnaire, based on the extent of his/her clinical involvement in neuraxial anaesthesia. Nonrespondents were contacted by e-mail, telephone, or post. The last questionnaires were received in August 2016, and we implied consent by participants when the survey was completed. Questionnaires were only included for analysis when complete. Separate locations of university hospitals were individually included in the analysis.

The survey consisted of questions regarding characteristics of hospitals and anaesthesiology departments, types of surgical procedures, numbers of epidural procedures, trends and key indications for epidural analgesia, side effects/complications discussed with patients in the context of informed consent, presence of an epidural alert system, and handling of complications such as proven spinal haematoma or abscess. Concerning the number of epidural procedures, the questionnaire focused on procedures performed in 2014, since complete data concerning procedures in 2015 were not available

for all hospitals in January 2016. Other questions were answered based on current practice and local protocols.

An epidural alert system was defined as a written protocol streamlining the monitoring, recognition and ultimately the treatment of patients with new neurological symptoms or (sudden) increase in pain with suspicion for spinal haematoma or abscess during or after neuraxial analgesia. An example epidural alert system is described by Bampoe and colleagues.[13] The content of the questionnaire in English and Dutch is displayed in the Data S1.

After data collection, all responses were deidentified to make them nonattributable to a specific centre. Two authors (E.B. and M.S.) independently imported and controlled data from the online questionnaires.

Statistical analysis

IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) was used for analysis. Continuous variables are presented as median and interquartile range. Categorical variables are presented as absolute number and percentage, and were compared using Pearson Chi-square test. *P*-values <0.05 were considered statistical significant.

Results

Eighty-five of 94 eligible hospital locations returned a complete questionnaire, a 90% response rate. Figure 1 displays the flow diagram of included hospitals for analysis. Basic characteristics and data of respondent hospitals are reported in Table 1.

Practice and registration

Overall, approximately 37.400 perioperative epidural procedures and 29 500 labour epidural procedures were performed in 2014. Regarding the registration of epidural procedures, 18% of hospitals (15 hospitals) reported exact numbers of perioperative epidural procedures and 33% (26 hospitals) reported exact numbers of labour epidural procedures, the remaining hospitals reported estimates.

Table 1 Basic characteristics and data of respondent hospitals.

Characteristic		All hospitals n = 85
Inpatient surgeries per year		
< 10.000		37%
10.000 – 20.000		47%
> 20.000		17%
Outpatient surgeries per year		
< 5.000		40%
5.000 – 10.000		49%
> 10.000		11%
Medical specialties		
Trauma		87%
Orthopaedics		98%
Plastic surgery		94%
Gynaecology		99%
Obstetrics		93%
Urology		100%
Gastrointestinal surgery		99%
Vascular surgery		84%
Thoracic pulmonary surgery		57%
Cardiothoracic surgery		18%
Epidural procedures per hospital per year (median [IQR])*		
Perioperative		303 [178 – 528]
Labour		341 [200 – 500]
Perioperative epidural procedures per hospital per year (median [IQR])*		
< 10.000 inpatient surgeries per year		200 [107 – 300]
10.000 – 20.000 inpatient surgeries per year		400 [204 – 545]
> 20.000 inpatient surgeries per year		713 [500 – 1250]
Registration of epidural procedures[a]	Perioperative	Labour
Exact	18%	33%
Accurate estimate	34%	39%
Rough estimate	48%	28%
Informed consent prior to epidural procedure		
Failed epidural analgesia		80%
Post-dural puncture headache		65%
Multiple attempts needed		60%
Hypotension		42%
Neurological injury		55%
Spinal haematoma		46%
Spinal abscess		34%

Persistent neurological injury/spinal cord injury	13%
No potential complications discussed	5%
Patient information	
Written and verbal information	65%
Verbal information only	28%
Written information only	7%
Reporting of epidural incidents – Hospital Incident System (internal)	
Every spinal haematoma/abscess	97%
Spinal haematoma/abscess with persistent damage	3%
Reporting of epidural incidents – Healthcare Inspectorate (national)	
Every spinal haematoma/abscess	20%
Cases treated with surgery – no persistent damage	11%
Cases treated with surgery – with persistent damage	25%
Spinal haematoma/abscess with persistent damage	45%

n, number of hospitals; IQR, interquartile range; accurate estimate, number deviates <10% from actual number.

[a] Eighty-three hospitals were able to provide data concerning the number of perioperative epidural procedures per year; one hospital responded that numbers were unavailable and one hospital only performed perioperative epidural procedures in children and was excluded from analysis. Seventy-eight hospitals were able to provide data concerning the number of labour epidural procedures performed per year; one hospital responded that numbers were unavailable and six hospitals did not perform obstetric care.

When taking all hospitals into account, also those that reported estimates, the median annual number of perioperative epidural procedures per hospital was 303 [178-528] and 341 [200-500] for labour epidural procedures. The number of perioperative epidural procedures was higher in hospitals performing more inpatient surgeries per year (Table 1).

Fifty-five percent of hospitals reported a trend towards decreased overall use of perioperative epidural analgesia. At the same time, 68% of hospitals reported a trend towards increased use of labour epidural analgesia. Figure 2 shows the trends in utilization of perioperative and labour epidural procedures reported by all respondent hospitals. In hospitals reporting exact numbers, trends in perioperative epidural use were similar to hospitals

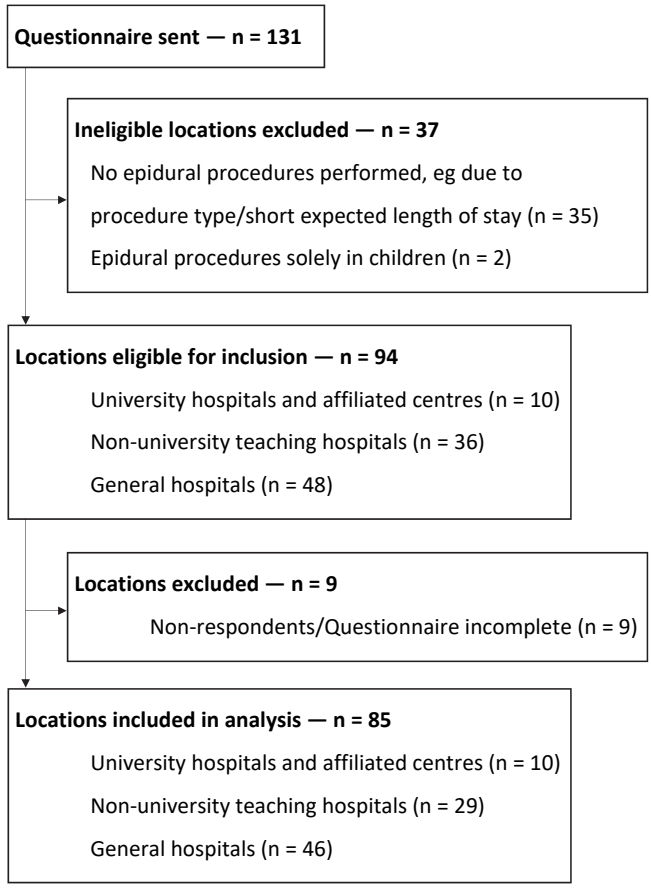


Figure 1 Flow diagram of eligible and included hospitals

reporting estimates (P = 0.445). Trends in use of labour epidural procedures were different between hospitals reporting estimates and exact numbers (P = 0.003); in hospitals reporting exact numbers, epidural use had seen a major/moderate decrease in 12%, constant numbers in 42%, and a moderate/major increase in 46% vs 2%, 12%, and 87% in hospitals reporting estimates, respectively.

Indications

Epidural analgesia combined with general anaesthesia is the preferred anaesthetic technique in most cases of thoracotomy, laparotomy of the upper abdomen and cancer-related abdominal debulking procedures. For laparotomy of the lower abdomen, 32% of hospitals preferentially used epidural analgesia.

Epidural analgesia was selected in a minority of cases of mastectomy and was infrequently selected for laparoscopic procedures. In the obstetric setting, 48% of hospitals preferred epidural analgesia. Three percent of hospitals with an obstetric department would never use epidurals during labour (n = 2). Specific indications for epidural analgesia are shown in Table 2.

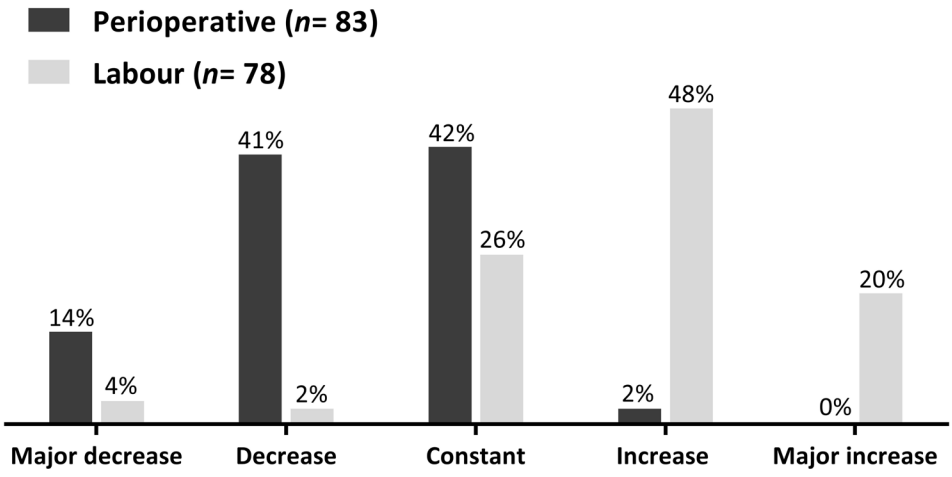


Figure 2 Trends in the utilization of perioperative and labour epidural procedures

Table 2 *Indications for epidural analgesia*

	Epidural analgesia			Alternative analgesic techniques					
Procedure	First choice	Individual patient	(Almost) Never	Incision size	Preferably PVB	Preferably SA	Preferably PNB	Preferably Remi IV-PCA	Other
Thoracotomy	82%	10%	4%	-	1%	-	-	-	4%
Thoracoscopy	33%	45%	19%	-	2%	-	-	-	1%
Mastectomy	2%	8%	77%	-	9%	-	-	-	4%
Laparotomy up. abdomen	80%	12%	0%	2%	-	-	-	-	6%
Laparotomy low. abdomen	32%	24%	7%	25%	-	-	-	-	13%
Laparoscopy up. abdomen	12%	31%	55%	-	-	-	-	-	2%
Laparoscopy low. abdomen	4%	24%	73%	-	-	-	-	-	0%
Abdominal debulking	77%	18%	2%	-	-	-	-	-	4%
Total hip prosthesis	0%	0%	29%	-	-	39%	1%	-	31%
Knee prosthesis	2%	1%	22%	-	-	37%	5%	-	33%
Obstetrics	48%	41%	3%	-	-	-	-	1%	8%

PVB, paravertebral block; SA, spinal anaesthesia; PNB, peripheral nerve block; Remi IV-PCA, remifentanil intravenous patient controlled analgesia; up, upper; low, lower; -, no response-option in this question; other, multiple response-options given

Epidural analgesia for surgical interventions is generally more likely to be selected for patients with chronic pain or with a history of chronic opiate/drug use in 65% of sites and for patients with Crohn's Disease or Ulcerative Colitis in 59% of sites.

Management of spinal haematoma

In case of spinal haematoma after epidural analgesia, the respondent hospitals reported diverse management strategies. Management was typically dependent on the clinical presentation of the patient. Conservative treatment was considered in one hospital for patients with pain as isolated symptom, but none of the hospitals considered conservative management for patients with neurological deficit. Figure 3 displays the diverse management strategies in patients presenting with pain and neurological deficit caused by a spinal haematoma after epidural analgesia. In patients with this clinical presentation, 46% of hospitals reported that management was determined on an individual basis and no clear preagreed management strategy was present. Furthermore, in case neurosurgical decompression was deemed necessary,

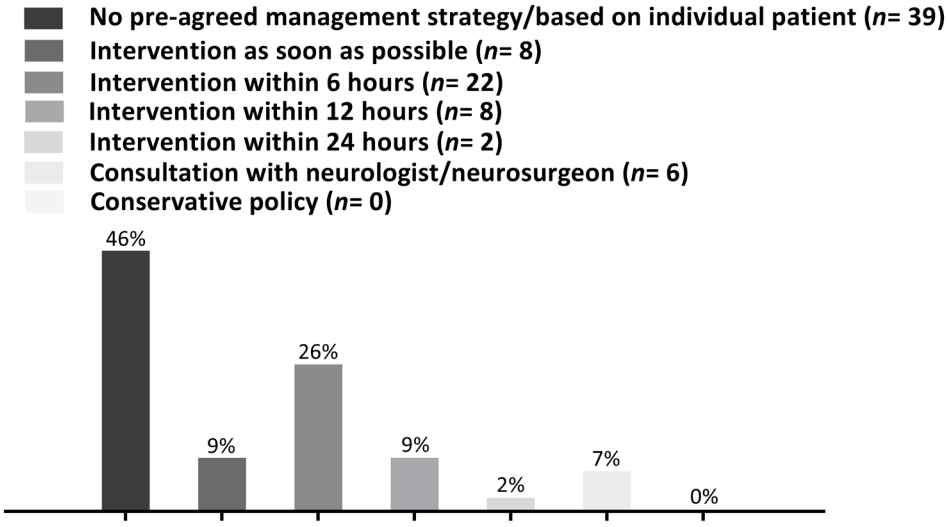


Figure 3 Management strategy in patients with confirmed spinal haematoma after epidural analgesia presenting with pain and neurological deficit

there was no clear consensus concerning the urgency of decompression; as soon as possible, within 6 hours, within 12 hours or within 24 hours after confirmation of spinal haematoma was each reported as suitable intervals by different hospitals.

Epidural alert system

A local protocol for the diagnostic workup and management of spinal complications of epidural analgesia, i.e., an "epidural alert system", was implemented in 45% of hospitals (n = 38) as a potential safety measure. In two hospitals (5%) with an epidural alert protocol, it was unclear which clinician is responsible for the coordination of the protocol. The diagnostic workup would be coordinated by the treating specialist (eg, orthopaedics, surgery, etc.) in three hospitals (8%), by the consulted neurologist or neurosurgeon in one hospital (3%), by the anaesthesiologist on call in 28 hospitals (74%) and by an Acute Pain Service in four hospitals (11%).

Discussion

This survey was designed to assess the current state of epidural analgesia practice in the Netherlands, a country that can be considered representative for most Western European healthcare systems in terms of perioperative policy. We found that for specific surgical indications, epidural analgesia remains frequently used, although 55% of respondents reported a decreasing trend in overall use of perioperative epidural analgesia. This finding is in accordance with previous studies that reported decreasing trends in perioperative epidural use.[3,4,9,20] In contrast, epidural procedures for labour analgesia are gaining in popularity in the Netherlands.

Moreover, this survey shows that the registration of epidural procedures is inconsistent. Only 18% of anaesthesiology departments were able to provide exact numbers for *perioperative* epidural procedures and 33% of anaesthesiology departments for *labour* epidural procedures.

Once patients who have received neuraxial anaesthesia leave the perioperative care units, they are frequently cared for by nonanaesthesiologist healthcare providers. This, combined with the low incidence of serious complications, makes it all the more important to standardize the response to suspected spinal haematoma or abscess. However, systematic safety measures are in place in only 45% of Dutch hospitals. Anaesthesiologists on call or (nurse-driven) Acute Pain Services mainly coordinate these alert systems.

Labour analgesia

The increasing use of epidural analgesia for labour indications is probably explained by the historically slow adaptation to epidural analgesia in comparison with other countries, caused by the prevalent continuation of home delivery, a unique situation in the Netherlands compared to other Western European countries. Approximately, 13%-25% of women deliver at home in the Netherlands.[21,22] For parturients delivering in hospitals, the Dutch Society of Obstetrics and Gynaecology and the Dutch Society of Anaesthesiology recommend epidural analgesia as the international

standard for labour analgesia. Consistent with this recommendation, a trend of increased epidural analgesia use can be observed. This trend is supported by estimates of a well-organized registry monitored by the Dutch Society of Obstetrics and Gynaecology. This register system has been used for decades to keep track of the characteristics of obstetric care that takes place under responsibility of midwives, general practitioners, or gynaecologists.[22] Of 166.733 women who gave birth in 2015, 33.276 (22%) received epidural analgesia. This is slightly more than the 20% of women that received epidural analgesia in 2014. Nonetheless, the rates of epidural use for labour indications in the Netherlands are considerably lower compared to other countries. For example, epidural rates vary from 30% to 69% between provinces in Canada. Likewise, 60% of American women in larger hospitals, and 67% of Finnish primigravid women receive epidural analgesia.[23-25]

Epidural alert system

Less than half of Dutch hospitals have implemented a specific epidural alert system for the management of patients with new neurological deficit or (sudden) increase in pain with suspicion for neurological complications during or after epidural analgesia. Due to the low a priori incidence of serious complications, there is no evidence-based way to test efficacy of epidural alert systems in clinical practice, but we surmise that spinal haematoma is a rare complication which very often occurs after the patient has been transferred to the general ward, such that several specialties need to be coordinated. Neurological outcome seems worse when decompressive surgery of spinal haematoma is delayed, and therefore prompt diagnosis, subsequent neurological, or neurosurgical consultation and an expedited decision regarding potential surgical intervention is of high importance.[15] Epidural alert systems help to organize the care for the patient when spinal haematoma is suspected. They typically delineate the responsibilities of the team members, designate which medical specialty has the lead in diagnosis and interdisciplinary consultations, advise active measures such as trial stops of epidural medication and imaging, and lay out times by which imaging

must be achieved and decisions on surgery be made. Given the urgency of the pathologic process, and the rarity of the complication, we feel it is prudent to introduce epidural alert protocols in hospitals that perform neuraxial anaesthesia.

Limitations

Although care was taken to minimize ambiguous questions in this survey, we cannot rule out that some questions were interpreted differently between respondents. For example, the focus in this survey was on epidural procedures, also including combined spinal-epidural analgesia. It is conceivable that respondents only reported epidural analgesia and that the use of combined techniques was underreported. Also, regarding the annual number of epidural procedures, no distinction was made between epidural use for perioperative care and chronic pain treatment. Furthermore, a discrepancy in the interpretation of timing of intervention may be present, as the time of clinical suspicion may be confused with the time of confirmed imaging diagnosis. Another limitation may be that one anaesthesiologist per hospital provided details on epidural analgesia practices for the entire department and was considered to be representative for that hospital by nature of his/her position as Department or Division chair. In reality, it is plausible that differences of opinion exist within a department, and consequently results may be somewhat distorted. Conversely, the high response rate of 90% is a strength of our survey. We consider it unlikely that response bias has influenced our results, and therefore this survey adequately reflects the current use and safety of epidural analgesia practice in the Netherlands.

Conclusion

Anaesthesiology departments in the Netherlands appear to follow the worldwide trend of decreased use of perioperative epidural analgesia. At the same time, epidural analgesia for labour is increasingly used. Most hospitals in the Netherlands do not have a preagreed protocol for the diagnostic workup and management of severe neurological complications of epidural analgesia. Since rare complications such as spinal haematoma or abscess can cause persistent neurological deficit, with great impact on quality of life, we consider the implementation of local epidural alert systems of importance, mainly to streamline diagnostic procedures and thereby accelerating potential interventional therapy when indicated.

Acknowledgement

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Conflicts of interest

The authors declare no conflicts of interest.

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Supplemental Data File

1.1 Questionnaire in English

Hospital and Department

1 Is your hospital a...
□ university hospital
□ non-university teaching hospital
□ general hospital

2 What is the number of *in*patient surgeries in your hospital on a yearly basis?
□ < 10.000
□ 10.000 - 20.000
□ > 20.000

3 What is the number of *out*patient surgeries in your hospital on a yearly basis?
□ < 5.000
□ 5.000 - 10.000
□ > 10.000

4 What is the number of staff anaesthetists in Fulltime Equivalent (FTE)?
□ <5
□ 5 - 10
□ 10 - 20
□ 20 - 40
□ > 40

5 What is the number of anaesthesiology residents in FTE?
□ None
□ <5
□ 5 - 10
□ 10 - 20
□ 20 - 40
□ > 40

6 Which types of surgery are represented in your hospital (Ear, Nose & Throat surgery and Ophthalmology excluded)?
□ Gastrointestinal surgery
□ Trauma surgery
□ Vascular surgery
□ Pulmonary surgery
□ Orthopaedic surgery
□ Cardiothoracic surgery
□ Plastic surgery
□ Gynaecology
□ Obstetrics
□ Urology

Epidural Analgesia in your Hospital

7 What is the number of epidural procedures performed in your hospital in the year 2014 (epidural procedures during labour excluded)?
[…]

8 The number stated above (question 7) is...
□ the exact number
□ an accurate estimate (the number will deviate <10% compared with the exact number)
□ a rough estimate

9 What is the number of epidural procedures during labour performed in your hospital in the year 2014?
[…]

10 The number stated above (question 9) is...
□ the exact number
□ an accurate estimate (the number will deviate <10% compared with the exact number)
□ a rough estimate

11 Is the number of epidural procedures (epidural procedures during labour excluded) in general decreasing, constant or increasing?
□ Major decrease
□ Decrease
□ Constant
□ Increase
□ Major increase

12 Is the number of epidural procedures during labour in general decreasing, constant or increasing?
□ Major decrease
□ Decrease
□ Constant
□ Increase
□ Major increase

13 A thoracotomy is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Preferably a paravertebral block is performed

14 A thoracoscopy is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Preferably a paravertebral block is performed

15 A mastectomy is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Preferably a paravertebral block is performed

16 A laparotomy of the upper abdomen is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Depending on the size of the incision (median laparotomy)

17 A laparoscopy of the upper abdomen is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never

18 A laparotomy of the lower abdomen is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Depending on the size of the incision (median laparotomy)
□ Preferably an abdominal wall block is performed

19 A laparoscopy of the lower abdomen is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never

20 Surgical abdominal cancer debulking is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never

21 A total hip replacement / hip fracture is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Preferably a peripheral nerve block is performed
□ Preferably a spinal procedure is performed

22 A knee prosthesis is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Preferably a peripheral nerve block is performed
□ Preferably a spinal procedure is performed

23 Obstetric analgesia is in my hospital a typical indication for epidural analgesia (more than one option possible).
□ First choice
□ Based on individual patient indication
□ (Almost) never
□ Preferably remifentanil intravenous patient controlled analgesia is used

24 Is the choice for epidural analgesia more likely in the following specific patient categories?
• Patients with chronic pain complaints:
□ Yes, the choice for epidural analgesia would be more likely.
□ No, this doesn't change the policy regarding epidural analgesia.
• Patients with chronic opiate and drugs use:
□ Yes, the choice for epidural analgesia would be more likely.
□ No, this doesn't change the policy regarding epidural analgesia.
• Patients with Crohn's disease or ulcerative colitis:
□ Yes, the choice for epidural analgesia would be more likely.
□ No, this doesn't change the policy regarding epidural analgesia.

25 In our hospital the following problems or potential complications would be specifically discussed with the patient beforehand (more than one option possible):
□ Post-dural puncture headache
□ Spinal (epidural) haematoma
□ Spinal (epidural) abscess
□ Neurological deficit
□ Neurological deficit with mentioning of spinal cord lesion
□ Failed attempts of epidural procedure
□ Several attempts necessary for epidural procedure
□ Blood pressure drop
□ No problems or potential complications are to be discussed with the patient

26 In our hospital information about problems or potential complications will be communicated to the patients in the following way:
□ Problems or potential complications will generally only be communicated **verbally**.
□ Problems or potential complications will generally be communicated **both verbally and in writing**.
□ Problems or potential complications will generally only be communicated **in writing** (for example an information leaflet / card).
□ No problems or potential complications will be discussed with the patient.

Epidural Safety measures

27 Is an epidural alert protocol existent in your hospital?
□ Yes
□ No

28 Is someone marked out for coordinating the epidural alert protocol?
□ No, in my hospital an epidural alert protocol does exist but an explicit coordinator is not described
□ No, in my hospital an epidural alert protocol is not existent
□ Yes, the physician at the ward
□ Yes, the neurologist
□ Yes, the anaesthetist in attendance
□ Yes, namely […]

29 Which time scale to intervention is recommended for surgery in the case of spinal (epidural) haematoma, without neurological deficit or pain complaints?
□ This patient would be observed with the intention of conservative policy
□ No specific agreement on management exists / management is determined on individual basis
□ Within […] hours

30 Which time scale to intervention is recommended for surgery in the case of spinal (epidural) haematoma, with pain complaints but without neurological deficit?
□ This patient would be observed with the intention of conservative policy
□ No specific agreement on management exists / management is determined on individual basis
□ Within […] hours

31 Which time scale to intervention is recommended for surgery in the case of spinal (epidural) haematoma, with neurological deficit but without pain complaints?
□ This patient would be observed with the intention of conservative policy
□ No specific agreement on management exists / management is determined on individual basis
□ Within […] hours

32 Which time scale to intervention is recommended for surgery in the case of spinal haematoma, with both neurological deficit and pain complaints?
□ This patient would be observed with the intention of conservative policy
□ No specific agreement on management exists / management is determined on individual basis
□ Within […] hours

Epidural Safety reporting

33 Which types of epidural incidents would your department report through the hospital incident reporting system?
□ Every spinal (epidural) haematoma / abscess
□ Spinal (epidural) haematomas / abscesses **without** the need of surgery or intervention without persistent neurological damage
□ Spinal (epidural) haematomas / abscesses **with** the need of surgery or intervention without persistent neurological damage
□ Spinal (epidural) haematomas / abscesses with persistent neurological damage

34 Which types of epidural incidents would your department report to the Health Care Inspectorate?
□ Every spinal (epidural) haematoma / abscess
□ Spinal (epidural) haematomas / abscesses **without** the need of surgery or intervention without persistent neurological damage
□ Spinal (epidural) haematomas / abscesses **with** the need of surgery or intervention without persistent neurological damage
□ Spinal (epidural) haematomas / abscesses with persistent neurological damage

1.2 Questionnaire in Dutch

Ziekenhuis en Afdeling

1 Is uw ziekenhuis een ...
□ universitair medisch centrum
□ topklinisch ziekenhuis
□ perifeer ziekenhuis

2 Hoeveel klinische operaties worden op jaarbasis in uw ziekenhuis uitgevoerd?
□ < 10.000
□ 10.000 - 20.000
□ > 20.000

3 Hoeveel ingrepen in dagbehandeling worden op jaarbasis uitgevoerd?
□ < 5.000
□ 5.000 - 10.000
□ > 10.000

4 Hoeveel stafleden zijn er binnen uw afdeling in Fulltime Equivalent (FTE)?
□ < 5
□ 5 - 10
□ 10 - 20
□ 20 - 40
□ > 40

5 Hoeveel AIOS zijn er binnen uw afdeling, in FTE?
□ Geen
□ < 5
□ 5 - 10
□ 10 - 20
□ 20 - 40
□ > 40

6 Welke van de volgende chirurgische specialismen zijn in uw ziekenhuis vertegenwoordigd (KNO en Oogheelkunde buiten beschouwing gelaten)?
□ Maag-Darm chirurgie
□ Traumachirurgie
□ Vaatchirurgie
□ Longchirurgie
□ Orthopedie
□ Cardio-thoracale chirurgie
□ Plastische chirurgie
□ Gynaecologie
□ Obstetrie
□ Urologie

Epidurale Anesthesie in uw Ziekenhuis

7 Hoeveel epidurale procedures werden in het jaar 2014 in uw ziekenhuis uitgevoerd (epidurale procedures durante partu buiten beschouwing gelaten)?

[…]

8 Bovenstaand aantal (vraag 7) is...
□ het precieze aantal
□ een nauwkeurige schatting (werkelijkheid zal hier minder dan 10% vanaf afwijken)
□ een grove schatting

9 Hoeveel epidurale procedures durante partu werden in het jaar 2014 in uw ziekenhuis uitgevoerd?

[…]

10 Bovenstaand aantal (vraag 9) is...
□ het precieze aantal
□ een nauwkeurige schatting (werkelijkheid zal hier minder dan 10% vanaf afwijken)
□ een grove schatting

11 Is het aantal epidurale procedures (epidurale procedures durante partu buiten beschouwing gelaten), over het algemeen, (fors) in afname, gelijk blijvend of (fors) in toename?
□ Fors in afname
□ In afname
□ Gelijk blijvend
□ In toename
□ Fors in toename

12 Is het aantal epidurale procedures durante partu, over het algemeen, (fors) in afname, gelijk blijvend of (fors) in toename?
□ Fors in afname
□ In afname
□ Gelijk blijvend
□ In toename
□ Fors in toename

13 Een thoracotomie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Wij zouden hier bij voorkeur een paravertebraal blok doen

14 Een thoracoscopie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Wij zouden hier bij voorkeur een paravertebraal blok doen

15 Een mastectomie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Wij zouden hier bij voorkeur een paravertebraal blok doen

16 Een bovenbuiks-laparotomie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Afhankelijk van grootte van incisie (mediane laparotomie)

17 Een bovenbuiks-laparoscopie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit

18 Een onderbuiks-laparotomie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Afhankelijk van grootte van incisie (mediane laparotomie)
□ Wij zouden hier bij voorkeur een buikwandblok doen

19 Een onderbuiks-laparoscopie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit

20 Een abdominale debulking is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit

21 Een totale heup prothese / heupfractuur is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Wij zouden hier bij voorkeur een perifeer zenuwblok doen
□ Wij zouden hier bij voorkeur een spinaal plaatsen

22 Een knieprothese is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Wij zouden hier bij voorkeur een perifeer zenuwblok doen
□ Wij zouden hier bij voorkeur een spinaal plaatsen

23 Obstetrie is in mijn ziekenhuis een typische indicatie voor epidurale anesthesie (meer dan een optie mogelijk).
□ Eerste keuze
□ Op individuele indicatie
□ (Vrijwel) nooit
□ Wij zouden hier bij voorkeur een remifentanil PCA instellen

24 Zouden de volgende condities de indicatie voor een epidurale anesthesie typisch beïnvloeden?

- Chronische pijn-patiënten
  □ Ja, dit zou de keuze voor epidurale anesthesie waarschijnlijker maken.
  □ Nee, dit verandert niet het beleid rondom epidurale anesthesie.
- Patiënten met opiaatdrugsgebruik
  □ Ja, dit zou de keuze voor epidurale anesthesie waarschijnlijker maken.
  □ Nee, dit verandert niet het beleid rondom epidurale anesthesie.
- Patiënten met Crohn / Colitis
  □ Ja, dit zou de keuze voor epidurale anesthesie waarschijnlijker maken.
  □ Nee, dit verandert niet het beleid rondom epidurale anesthesie.

25 Een informatiegesprek in ons ziekenhuis met een patiënt zou typisch de volgende problemen of potentiële complicaties specifiek benoemen:
□ Post-durale punctie hoofdpijn (PDPH)
□ Spinaal (epiduraal) hematoom
□ Spinaal (epiduraal) abces
□ Neurologische schade
□ Neurologische schade tot dwarslaesie
□ Falen epiduraal
□ Meerdere pogingen soms noodzakelijk
□ Bloeddrukdaling
□ Er worden geen complicaties besproken met patiënt

26 Een informatiegesprek met een patiënt betreffende problemen of potentiële complicaties van epidurale anesthesie, zou in ons ziekenhuis typisch op de volgende wijze worden uitgevoerd:
□ Problemen of potentiële complicaties (vraag 25) worden over het algemeen alleen **mondeling** besproken met patiënt
□ Problemen of potentiële complicaties (vraag 25) worden over het algemeen **mondeling én schriftelijk** besproken met patiënt
□ Problemen of potentiële complicaties (vraag 25) worden over het algemeen alleen **schriftelijk** gegeven aan patiënt (bijvoorbeeld informatie folder / kaart)
□ Er worden geen problemen of potentiële complicaties besproken met patiënt

Epidurale Veiligheidsmaatregelen

27 Bestaat in uw ziekenhuis een Epiduraal Alert protocol?
□ Ja
□ Nee

28 Is iemand in het protocol aangewezen die het Alert gaat coördineren?
□ Nee, in mijn ziekenhuis bestaat wel een Epiduraal Alert protocol, maar een duidelijk coördinator staat niet beschreven
□ Nee, in mijn ziekenhuis bestaat geen Epiduraal Alert protocol
□ Ja, de hoofdbehandelaar / zaalarts van de patiënt
□ Ja, de neuroloog
□ Ja, de dienstdoende anesthesioloog
□ Ja, namelijk […]

29 Welk tijdstip voor operatie is aanbevolen voor chirurgie in het geval van een spinaal hematoom, zonder neurologische uitval of pijnklachten?
□ Deze patiënt zou worden geobserveerd met in opzet conservatief beleid
□ Hier zijn geen duidelijke afspraken voor gemaakt / wordt per individuele casus bepaald
□ Binnen […] uur

30 Welk tijdstip voor operatie is aanbevolen voor chirurgie in het geval van een spinaal hematoom, met pijnklachten maar zonder neurologische uitval?
□ Deze patiënt zou worden geobserveerd met in opzet conservatief beleid
□ Hier zijn geen duidelijke afspraken voor gemaakt / wordt per individuele casus bepaald
□ Binnen […] uur

31 Welk tijdstip voor operatie is aanbevolen voor chirurgie in het geval van een spinaal hematoom, met neurologische uitval maar zonder pijnklachten?
□ Deze patiënt zou worden geobserveerd met in opzet conservatief beleid
□ Hier zijn geen duidelijke afspraken voor gemaakt / wordt per individuele casus bepaald
□ Binnen […] uur

32 Welk tijdstip voor operatie is aanbevolen voor chirurgie in het geval van een spinaal hematoom, met neurologische uitval en pijnklachten?
□ Deze patiënt zou worden geobserveerd met in opzet conservatief beleid
□ Hier zijn geen duidelijke afspraken voor gemaakt / wordt per individuele casus bepaald
□ Binnen […] uur

Epidurale Veiligheidsrapportage

33 Van welke soort epidurale incidenten zou uw afdeling een interne incident melding maken (MIP / VIM / DIM)?
□ Elk spinaal (epiduraal) hematoom / abces
□ Spinale (epidurale) hematomen / abcessen waarbij **geen** operatie / interventie nodig is met goede neurologische uitkomst zonder blijvende schade
□ Spinale (epidurale) hematomen / abcessen waarbij **een** operatie / interventie nodig is met goede neurologische uitkomst zonder blijvende schade
□ Spinale (epidurale) hematomen / abcessen met blijvende neurologische schade

34 Van welke soort epidurale incidenten zou uw afdeling in het algemeen aan de Inspectie Gezondheidszorg (IGZ) melden?
□ Elk spinaal (epiduraal hematoom / abces
□ Spinale (epidurale) hematomen / abcessen waarbij **geen** operatie of interventie nodig is met goede neurologische uitkomst zonder blijvende schade
□ Spinale (epidurale) hematomen / abcessen waarbij **een** operatie of interventie nodig is met goede neurologische uitkomst zonder blijvende schade
□ Spinale (epidurale) hematomen / abcessen met blijvende neurologische schade

Chapter 9

Discussion and future perspectives

Discussion and future perspectives

The "Safety of Neuraxial Anesthesia". Safety is defined as "being safe or bring to safety"[1] and describes a condition that is protected from danger, risk or injury.[2] This thesis proves that neuraxial anesthesia can be performed safely in young and healthy patients, however, it carries greater risks in other patient categories. Most importantly, in all patients exposed to neuraxial anesthesia, we can make additional efforts to create an even safer condition.

Future goals comprise improved education of patients and (non)anesthesia personnel to recognize and report potential symptoms that may indicate the development of severe complications. Alarm symptoms, such as increasing back pain or headache, new sensory or motor deficit, urinary retention or bladder/bowel incontinence must trigger treating physicians to initiate further diagnostics. Increased or prolonged monitoring after neuraxial techniques by an anesthesiologist or acute pain service can be considered in patients with a higher risk of unfavorable sequelae (for instance after failed neuraxial techniques or a bloody puncture in patients with a compromised coagulation system).

Moreover, this thesis illustrates that in many hospitals responsibilities and timelines for management of suspected neurological complications of neuraxial anesthesia are determined on an ad hoc basis, often including multiple consultations between the involved clinicians (i.e. first responsible clinician, anesthesiologist, neurologist and neurosurgeon), with possible delays in diagnostics and treatment as a result. Since adversity of outcome was related to the severity of the initial presentation and the delay in surgical decompression of patients with neurological injury due to spinal complications, a streamlined diagnostic process is important. Future goals comprise the implementation of a pre-agreed protocol for the diagnostic workup and management of severe neurological complications of neuraxial anesthesia to streamline diagnostic procedures and thereby accelerating potential interventional therapy when indicated.

Furthermore, we would like to promote more intensive sharing of data when encountering these rare and severe complications (without harming patients' privacy) to improve the understanding and to select patients for neuraxial anesthesia even more accurately. As we have promoted in the previous chapters, we believe that the implementation of uniform registries for rare complications will allow for collection of more accurate estimates of incidence rates in specific patients, prognostic factors, response to therapy and may assist in quality improvement efforts.[3] A registry for anesthetic complications (complications of the complete scope of the anesthesiology practice, also including neuraxial anesthesia) is available through the Dutch Society of Anesthesiology. We hope this registry will be used on a broader scale in the future.

Of interest is the implementation of ultrasound for neuraxial techniques, with the aim to improve the understanding of the anatomy, to lower failure rates, and to possibly lower complication rates. "Ultrasound-guided techniques are now considered standard care for central venous access and regional anesthesia",[4] however, ultrasound for neuraxial anesthetic techniques does not seem to be implemented in routine clinical care. Perhaps, we should be more critical towards the role of a 'blind' technique based on landmarks for identification of the epidural or subdural space when performing neuraxial anesthesia, specifically in high-risk patients.

In conclusion, the focus of future research must be on optimizing the presently used neuraxial regimens, the reduction of failure rates (for example by introducing imaging techniques), the prevention of complications and the streamlining of diagnosis and treatment of complications of neuraxial anesthesia. Keeping in mind that new and already existing alternatives for neuraxial analgesia such as peripheral nerve blocks, plane blocks and continuous wound infiltration are being optimized together with the evolvement of minimally invasive surgery. However, given the frequent use of neuraxial anesthesia in current practice, we hope this thesis has inspired you to bring neuraxial anesthesia into an even safer zone in your hospital.

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Chapter 10

Summary

Summary

Severe complications of neuraxial anesthesia are rare but more common than estimated in past decades. Complications appear in a heterogeneous patient population and together with the rare occurrence, decision making and treatment of complications is based on expert-opinion. The work presented in this thesis is a step towards more evidence-based care of patients with severe complications of neuraxial anesthesia. In **PART 1**, the safety of epidural analgesia is discussed by analyzing the risk-benefit ratio for epidural analgesia and the safety of the most widely used epidural drugs. **PART 2** of this thesis provides evidence-based insight on situations that lead to severe complications of neuraxial anesthesia and outcomes of treatment by evaluating patient characteristics, neuraxial block characteristics and treatment strategies. Trends in neuraxial anesthesia practice, key indications, safety measures, safety reporting, and management of complications of epidural analgesia are investigated in the final part, **PART 3**, of this thesis.

PART 1 – SAFETY OF EPIDURAL ANALGESIA

The safety of epidural analgesia and the safety of drugs used for epidural analgesia are addressed in **Chapter 2** and **Chapter 3**. **Chapter 2** critically acclaims the risk-benefit ratio for epidural analgesia by discussing the literature that focuses on the use of epidural analgesia for different indications in different patient populations. Main indications for epidural anesthesia and analgesia are major open abdominal surgery, thoracotomy and labor analgesia. In the perioperative setting, the number of solid indications for epidural analgesia has declined. In past and current literature, it has been shown that epidural analgesia leads to statistically significant, but possibly clinically less meaningful, reductions in pain scores compared to intravenous analgesia. Non-inferiority of alternative regional analgesic approaches, i.e. continuous wound infiltration or peripheral nerve blocks, is promising for the future for certain major surgical procedures with a historical preference for epidural analgesia, that is open hepato-pancreato-biliary surgery,[1] open-

liver resection[2] and thoracotomy.[3-6] Serious adverse events after epidural analgesia occur more often than was previously thought, specifically in certain perioperative patient populations. Therefore, adverse outcomes must be weighed against the efficacy and benefits of epidural analgesia in order to guide doctors in clinical decision-making. Careful selection of appropriate patients cannot be over-emphasized. Epidural analgesia for obstetric analgesic purposes is considered to be well tolerated in young and healthy women. Efficacy has been proven and complications leading to permanent neurological damage seldom occur, therefore, epidural analgesia can be considered as a safe technique in obstetric patients with uncomplicated pregnancies.

Chapter 3 is an expert opinion article discussing the safety of the most widely used epidural drugs. The article focuses on potential neurotoxicity, side effects, and complications in the adult, non-pregnant population. In previous years the search for the ideal epidural medication has resulted in a surplus of drug combinations with extensive heterogeneity amongst studies. Overall, clinicians should pursue safe epidural drug administration to patients and refrain from drugs with minimal proven benefit. Regarding specific drug-classes, we conclude that all local anesthetics (LA) have time- and dose-dependent neurotoxic properties[7,8] which correlate with their clinical potency.[9] Epidural neurotoxicity predominantly occurs after supraclinical LA doses and therefore has little clinical impact in daily practice. The same is valid for systemic toxicity of LA, at equipotent dosing, all LA have similar toxic properties. However, systemic LA toxicity after epidural injection is rare.[10] As regards to epidural opioids, none of the opioids that were reviewed, show ideal epidural analgesic properties without any side effects. All opioids share, to some extent, the adverse effects as known from their systemic administration. These include, among others; hypotension, sedation, nausea, vomiting, urinary retention, pruritus and respiratory depression, whereby pruritus occurs more often after epidural opioid administration compared to systemic administration.[11] Risk factors for delayed respiratory depression are usage of hydrophilic opioids, advanced age, morbid obesity or obstructive

sleep apnea.[12] Individual patient risk stratification is advised when using the hydrophilic opioid morphine (and extended release morphine) considering late respiratory depression. Because of its long duration of action of epidural morphine, continuous monitoring for 24–48 h is recommended to observe respiratory depression.[13] The use of epidural fentanyl and sufentanil appears safe when standard precautions for the use of opioids are taken. Overall, there is a place for opioids in epidural anesthesia, as the benefits of the synergistic LA with opioid mixture result in less side effects. We suggest avoiding all widely used opioids that are proven neurotoxic and have no proven benefit when administered epidurally, being hydromorphone,[14] buprenorphine[15] and tramadol.[16,17] Other epidural adjuvants, such as epidural alpha-adrenergic receptor agonists (i.e. epinephrine, clonidine and dexmedetomidine), ketamine, midazolam, dexamethasone and neostigmine are possibly neurotoxic and the added analgesic efficacy of epidural administration has not been well established. In general, we conclude that if no added benefit of administering drugs epidurally is seen as compared to the systemic or oral route, epidural application should be avoided.

PART 2: COMPLICATIONS OF NEURAXIAL ANESTHESIA

The second part of this thesis addresses complications of neuraxial anesthesia. **Chapter 4** is a systematic review that summarizes patient characteristics, symptoms, treatment and outcome of patients with spinal hematomas and abscesses associated with neuraxial blocks. In this review we analyzed 409 reports, including 647 patients (387 patients with spinal hematoma and 260 patients with spinal abscess). Spinal hematoma and abscess occurred predominantly after epidural anesthesia (58% and 83%, respectively). Individual presentation of patients with spinal hematoma or abscess after neuraxial block is highly variable, the classic triad of pain, sensory and motor deficit was present in under half of reported patients. First symptoms most often occur after removal of a catheter (either spinal or epidural), and typically when patients are no longer followed-up by the anesthesiologist. An association was found between the adversity of outcome and the delay

in surgical decompression; when decompression of spinal hematoma was delayed for >12 h after clinical diagnosis, neurological outcome was worse compared with earlier decompression (within 6 h). After spinal hematoma, 47% of published patients had full recovery, 28% had partial recovery, and in 25% no recovery was observed. After spinal abscess, 68% of reported patients recovered fully, 21% showed partial recovery, and no recovery was reported in 11%. Regarding outcomes, the severity to which the neurological deficit has progressed by the time of diagnosis is a strong predictor of outcome, indicating that early diagnosis is crucial. A less obvious 'new' insight is that in selected cases – those without or with mild neurological symptoms or those who show spontaneous recovery during the diagnostic process – one might consider a strategy of conservative management combined with frequent monitoring of neurological function.

In **Chapter 5** we describe a systematic review of intracranial complications. We used a similar approach as used for the analysis of spinal complications (**Chapter 4**) and collected all cases reported in the literature concerning intracranial hematomas or abscesses following neuraxial block. We analyzed 232 reports, including 291 patients with hematoma and six patients with abscess or empyema. Of the patients with hematoma, 48% concerned obstetric patients, the remainder received neuraxial block for various perioperative indications or pain management. Prior dural puncture was reported in 81%, either intended (e.g. spinal anesthesia) or unintended (e.g. complicated epidural catheter placement). After treatment, 11% had partial or no recovery and 8% died, indicating the severity of this complication. Headache was described in 217 patients; in 101 patients, symptoms resembled post-dural puncture headache (PDPH). The diagnosis intracranial hematoma was often missed initially, as the headache was presumed to be caused by the much more common cerebrospinal hypotension syndrome after dural cerebrospinal fluid leakage (PDPH). We conclude, that when the headache is prolonged for more than 5 days, does not improve, or worsens, with clinical treatment or after an epidural blood patch, changes from postural to non-postural, or if neurological symptoms develop besides the headache, alternative diagnoses

should be considered warranting neurological consultation and imaging studies. Intracranial abscess after neuraxial block seems to be very seldom and is hardly ever reported in literature; six reports were found. It is impossible to yield any conclusion based on the limited data.

Chapter 6 describes a closed claims analysis that focused on claims of hematoma, abscess or meningitis after neuraxial anesthesia. Closed anesthesia malpractice claims from the United States of America (USA) and the Netherlands that were initiated and closed between 2007 and 2017 were examined. We identified 41 claims of patients with hematoma, 18 claims of patients with abscess and 14 claims of patients with meningitis associated with neuraxial anesthesia for labor, acute and chronic pain. Patients experiencing spinal hematoma were predominantly above 60 years of age and using anti-hemostatic medication, whereas patients with abscess or meningitis were middle-aged, relatively healthy and more often involved in emergency interventions. Potential preventable causes of unfavorable sequelae constituted errors in timing/prescription of anti-hemostatic medication (10 claims, 14%), unsterile procedures (n=10, 14%) and delay in diagnosis/treatment of the complication (n=18, 25%). The number of claims resulting in payment was similar between countries (USA n=15, 38% vs. the Netherlands n=17, 52%; P=0.25). The median indemnity payment, which the patient received varied widely between the USA (€285 488, n=14) and the Netherlands (€31 031, n=17) (P=0.004). However, the considerable differences in legal systems and administration of expenses between countries may make meaningful comparison of indemnity payments inappropriate.

Chapter 7 is a short commentary discussing the results of a technical analysis investigating the vulnerability of epidural needles by analyzing the force needed to deform or break an epidural needle. During real-life epidural catheter placement, epidural needles are subjected to a range of forces. The magnitude of the forces depends on the course of the neuraxial procedure (multiple punctures with the same needle), firmness of the ligaments, presence of bone contact and potential movement of the patient, as well as the maximum force the operator is willing to apply. In the experiment we

simulated extreme forces with the use of a model to simulate an epidural procedure puncture site; 20 Gauge (G) epidural needles started to kink when exposed to forces of 25-30 Newton (N) and 18G needles when exposed to forces of 30-45N. As a reference, it takes approximately 6N to push a needle through soft tissue (simulating skin and subcutaneous tissue) until contact with the bone-model occurs. Tip deformation was seen without further damage (e.g. metal shards) and integrity of the needle tip was confirmed by microscopic evaluation. Furthermore, breakage of epidural needles was not observed in our experiment. We conclude that breaking of epidural needles is extremely rare and difficult to simulate. Bending occurs without breakage when significant forces are applied. The breakage of needles may be more likely once bending has occurred. In general, it is important to withdraw needles to superficial subcutaneous tissue prior to redirection of the needle[18] and to inspect the needle for damage or bending when significant forces are applied while attempting a neuraxial procedure.

PART 3 – TRENDS IN NEURAXIAL ANESTHESIA PRACTICE

The final part of this thesis focuses on trends in neuraxial anesthesia practice, **Chapter 8**. We conducted a web-based questionnaire to analyze trends in practice, key indications, safety measures, safety reporting, and management of complications of epidural analgesia in the Netherlands. Questionnaires from 85 of all 94 Dutch hospitals performing epidural analgesia were collected, a 90% response rate. Fifty-five percent reported a trend towards decreased use of perioperative epidural analgesia, while 68% reported increased use of epidural analgesia for labor. An explanation for the decreased used of perioperative epidural analgesia may be the wider implementation of minimally invasive surgery and emergence of alternative analgesic techniques. Reported key indications for epidural analgesia were thoracotomy, upper abdominal laparotomy, and abdominal cancer debulking. Local guidelines for management of severe neurological complications during or after epidural analgesia, i.e. "epidural alert systems", have been introduced in 45% of Dutch hospitals to coordinate and potentially streamline early diagnosis and

treatment of complications. In the remaining hospitals, responsibilities and timelines for management of epidural emergencies are determined on an ad hoc basis.

What the (non-)anesthesiologist can learn from this thesis:

- Neuraxial anesthesia can be used safely in young and healthy patients; complications are rarely seen in the obstetric population and the consequences of possible complications are often less severe.
- A relatively higher occurrence and worse outcome of complications is reported in perioperative patients with comorbidities.
- The individual presentation of patients with hematoma or abscess after neuraxial block is highly variable.
- First symptoms most often occur when patients are cared for by non-anesthesiologist, non-neurological, or non-neurosurgical healthcare providers. This, combined with the low incidence of serious complications and variable presentation, makes it difficult to recognize these complications as a result of the previous neuraxial anesthetic procedure.
- Increased or prolonged monitoring after neuraxial techniques by an anesthesiologist or acute pain service can be considered in patients with a higher risk of unfavorable sequelae (for instance after failed neuraxial techniques or a bloody puncture in patients with a compromised coagulation system).
- An association between the adversity of outcome and the severity of the initial presentation, and the delay in surgical decompression was seen.
- Besides neuraxial analgesia for obstetric patients, there is a role for neuraxial analgesia in the perioperative patient. However, new and already existing alternatives such as peripheral regional techniques are being optimized together with the evolvement of minimally invasive surgery, resulting in a continuously changing balance between risks and benefits of neuraxial anesthesia in the individual patient.

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Chapter 11

Samenvatting

Samenvatting

Ernstige complicaties van neuraxiale anesthesie zijn zeldzaam, maar komen vaker voor dan in de afgelopen decennia werd gedacht. De complicaties ontstaan in een heterogene patiëntenpopulatie, en samen met het zeldzame karakter, leidt dit ertoe dat besluitvorming en behandeling van complicaties in de meeste gevallen ad hoc bepaald moet worden op basis van consultatie met deskundigen. Met de bevindingen van dit proefschrift hopen wij bij te dragen aan evidence-based zorg voor patiënten met ernstige complicaties van neuraxiale anesthesie. In **DEEL 1** wordt de veiligheid van epidurale analgesie besproken door het analyseren van de risico-batenverhouding voor epidurale analgesie in het algemeen en de meest gebruikte epidurale medicatie. **DEEL 2** van dit proefschrift biedt inzicht in situaties die leiden tot ernstige complicaties van neuraxiale anesthesie, en bespreekt de resultaten van de behandeling van complicaties door patiëntkenmerken, technische kenmerken van de neuraxiale techniek en behandelstrategieën te evalueren. Trends in de dagelijkse praktijk van neuraxiale anesthesie, belangrijke indicaties, veiligheidsmaatregelen, incident rapportage en behandeling van complicaties van epidurale analgesie worden onderzocht in het laatste deel, **DEEL 3**, van dit proefschrift.

DEEL 1 – VEILIGHEID VAN EPIDURAL ANALGESIE

De veiligheid van epidurale analgesie en de veiligheid van geneesmiddelen die worden gebruikt voor epidurale analgesie worden behandeld in **Hoofdstuk 2** en **Hoofdstuk 3**. **Hoofdstuk 2** beschrijft een kritische analyse van de risico-batenverhouding voor epidurale analgesie door de literatuur te bespreken die zich richt op het gebruik van epidurale analgesie voor verschillende indicaties in verschillende patiëntenpopulaties. De belangrijkste indicaties voor epidurale anesthesie en analgesie zijn grote open abdominale chirurgie, thoracotomie en perinatale pijnstilling. In de perioperatieve setting is het aantal indicaties voor epidurale analgesie afgenomen in de laatste decennia. In vroegere en huidige literatuur is aangetoond dat epidurale analgesie leidt

tot statistisch significante, maar mogelijk klinisch minder relevante, reducties van pijnscores in vergelijking met intraveneuze analgesie. Non-inferioriteit van alternatieve regionale technieken (bijvoorbeeld continue wondinfiltratie of perifere zenuwblokkades) is veelbelovend voor de toekomst voor bepaalde grote chirurgische ingrepen met een historische voorkeur voor epidurale analgesie, zoals open hepato-pancreato-biliaire chirurgie,[1] open leverresectie[2] en thoracotomie.[3-6] Ernstige complicaties na epidurale analgesie komen vaker voor dan eerder werd gedacht, met name bij bepaalde perioperatieve patiëntenpopulaties. Daarom moeten nadelige uitkomsten worden afgewogen tegen de effectiviteit en voordelen van epidurale pijnbestrijding om artsen te begeleiden bij klinische besluitvorming. Zorgvuldige selectie van geschikte patiënten kan niet genoeg worden benadrukt. Epidurale analgesie voor obstetrische doeleinden wordt over het algemeen goed verdragen door jonge, gezonde vrouwen, waarbij de werkzaamheid is bewezen en complicaties met blijvende neurologische schade zeer zeldzaam optreden. Epidurale analgesie wordt daarom beschouwd als een veilige techniek bij obstetrische patiënten met ongecompliceerde zwangerschappen.

Hoofdstuk 3 is een opinieartikel waarin de veiligheid van de meest gebruikte epidurale geneesmiddelen wordt besproken. Het artikel richt zich op mogelijke neurotoxiciteit, bijwerkingen en complicaties in de volwassen, niet-obstetrische populatie. In voorgaande jaren heeft de zoektocht naar de ideale epidurale medicatie geresulteerd in een overschot aan combinaties van medicijnen met heterogeniteit tussen de studies. Wij adviseren te streven naar veilige epidurale toediening van geneesmiddelen en af te zien van geneesmiddelen met minimaal bewezen voordeel. Met betrekking tot specifieke geneesmiddelklassen concluderen we dat alle lokale anesthetica (LA), tijd- en dosisafhankelijke neurotoxische eigenschappen hebben[7,8] die correleren met hun klinische potentie.[9] Epidurale neurotoxiciteit treedt voornamelijk op bij supraklinische LA-dosering en heeft daarom weinig klinische impact in het dagelijks gebruik. Hetzelfde geldt voor systemische toxiciteit van LA; bij equipotente dosering hebben alle LA vergelijkbare toxische eigenschappen. Systemische LA-toxiciteit na epidurale injectie is

echter zeldzaam.[10] Met betrekking tot epidurale opioïden, vertoont geen van de geanalyseerde opioïden een combinatie van ideale analgetische eigenschappen zonder bijwerkingen. De toediening van opioïden in de epidurale ruimte resulteert tot op zekere hoogte in vergelijkbare bijwerkingen zoals bekend van hun systemische toediening. Deze omvatten onder andere; hypotensie, sedatie, misselijkheid, braken, urineretentie, pruritus en ademhalingsdepressie, waarbij pruritus vaker optreedt na epidurale toediening van opioïden in vergelijking met de systemische toediening.[11] Risicofactoren voor vertraagde ademhalingsdepressie zijn het gebruik van hydrofiele opioïden, hoge leeftijd, morbide obesitas of het obstructieve slaapapneu syndroom.[12] Vanwege de lange werkingsduur van epiduraal toegediende morfine, wordt continue monitoring gedurende 24 – 48 uur aanbevolen om mogelijke ademhalingsdepressie te monitoren.[13] Het gebruik van fentanyl en sufentanil voor epidurale toediening lijkt veilig wanneer standaardvoorzorgsmaatregelen voor het gebruik van opioïden worden genomen. Over het algemeen is er een plaats voor opioïden in epidurale anesthesie, omdat de voordelen van de synergetische combinatie met LA resulteert in een reductie van bijwerkingen. Wij benadrukken de neurotoxische opioïden te vermijden waarvan bewezen is dat ze geen voordeel hebben bij epidurale toediening, namelijk hydromorfon,[14] buprenorfine[15] en tramadol.[16,17] Andere epidurale medicatie, zoals epidurale alfa-adrenerge receptoragonisten (epinefrine, clonidine en dexmedetomidine), ketamine, midazolam, dexamethason en neostigmine, zijn mogelijk neurotoxisch en de toegevoegde analgetische werkzaamheid van epidurale toediening is niet goed vastgesteld. In het algemeen concluderen we dat epidurale toediening moet worden vermeden als er geen bijkomend voordeel wordt gezien in vergelijking met de systemische of orale toediening.

DEEL 2: COMPLICATIES VAN NEURAXIALE ANESTHESIE

Het tweede deel van dit proefschrift behandelt complicaties van neuraxiale anesthesie. **Hoofdstuk 4** is een systematische review die patiëntkenmerken, symptomen, behandelingen en uitkomsten bespreekt van patiënten met

spinale hematomen en abcessen na neuraxiale anesthesie technieken. In deze review analyseerden we 409 artikelen, waaronder 647 patiënten (387 patiënten met een spinaal hematoom en 260 patiënten met een spinaal abces). Spinaal hematomen en abcessen traden voornamelijk op na epidurale anesthesie (respectievelijk 58% en 83%). De individuele presentatie van patiënten die een spinaal hematoom of abces ontwikkelden na een neuraxiaal blok is zeer variabel, de klassieke trias van pijn, sensorische en motorische stoornissen was aanwezig bij minder dan de helft van de gerapporteerde patiënten. De eerste symptomen treden meestal op na het verwijderen van een katheter (spinaal of epiduraal), en meestal wanneer patiënten niet langer worden gevolgd door een anesthesioloog. Er werd een verband gezien tussen vertraging in neurochirurgische decompressie en een ongunstige uitkomst; wanneer decompressie van een spinaal hematoom >12 uur na klinische diagnose werd verricht, was de neurologische uitkomst slechter in vergelijking met eerdere decompressie. Na een spinaal hematoom, had 47% van de gepubliceerde patiënten volledig herstel, 28% liet gedeeltelijk herstel zien en bij 25% werd geen herstel waargenomen. Na een spinaal abces herstelde 68% van de gerapporteerde patiënten volledig, 21% vertoonde gedeeltelijk herstel en bij 11% werd geen herstel gemeld. Wat de uitkomsten betreft, is de ernst van de neurologische afwijkingen op het moment van diagnose een sterke voorspeller voor de uitkomst, wat aangeeft dat een vroege diagnose van cruciaal belang is. Een minder voor de hand liggend 'nieuw' inzicht is dat in een selecte groep patiënten – zonder of met milde neurologische symptomen of symptomen die spontaan herstellen tijdens het diagnostisch proces – een conservatief management in combinatie met frequente monitoring van de neurologische functie kan worden overwogen.

In **Hoofdstuk 5** beschrijven we een systematische review van intracraniële complicaties. We gebruikten een vergelijkbare methode als gebruikt voor de analyse van spinale complicaties (**Hoofdstuk 4**) en verzamelden alle gevallen van intracraniële hematomen of abcessen na een neuraxiaal blok die in de literatuur werden gerapporteerd. We analyseerden 232 artikelen, waaronder 291 patiënten met een hematoom en zes patiënten met een abces

of empyeem. Van de patiënten met een intracranieel hematoom, betrof 48% de obstetrische populatie, de overige patienten ondergingen een neuraxiale procedure voor verschillende perioperatieve indicaties of pijnbestrijding. Een durale punctie werd gemeld bij 81%, dit betroffen geplande (bijvoorbeeld voor spinale anesthesie) en ongeplande durale puncties (bijvoorbeeld tijdens een gecompliceerde plaatsing van een epidurale katheter). Na de behandeling was 11% gedeeltelijk of niet hersteld en 8% overleed aan de gevolgen van de complicatie. Hoofdpijn werd beschreven bij 217 patiënten; bij 101 patiënten leken de symptomen op postdurale punctie hoofdpijn (PDPH). In veel gevallen werd de diagnose intracranieel hematoom aanvankelijk gemist, vanwege de verdenking op het frequenter voorkomende cerebrospinale hypotensiesyndroom na durale lekkage van cerebrospinaal vocht (PDPH). We concluderen dat wanneer de hoofdpijn langer dan 5 dagen aanhoudt, niet verbetert of verergert ondanks medicatie of na een epidurale bloedpatch, verandert van posturale naar niet-posturale symptomen, of als zich naast de hoofdpijn tevens neurologische symptomen ontwikkelen, alternatieve diagnoses moeten worden overwogen die neurologische consultatie en beeldvormend onderzoek rechtvaardigen. Een intracraniaal abces na een neuraxiaal blok lijkt zeer zelden voor te komen en wordt in de literatuur nauwelijks vermeld; er werden zes casuïstieken gevonden. Het is onmogelijk om op basis van deze beperkte gegevens een conclusie te trekken.

Hoofdstuk 6 beschrijft een analyse van gesloten schadeclaims betreffende hematomen, abcessen of meningitis na neuraxiale anesthesie. Anesthesiologische schadeclaims uit de Verenigde Staten (VS) en Nederland die tussen 2007 en 2017 zijn gestart en gesloten, zijn onderzocht. We identificeerden 41 claims van patiënten met een hematoom, 18 claims van patiënten met een abces en 14 claims van patiënten met meningitis geassocieerd met neuraxiale anesthesie voor obstetrische indicaties, acute en chronische pijn. Patiënten met een spinaal hematoom waren overwegend ouder dan 60 jaar en gebruikten anti-hemostatische medicatie, terwijl patiënten met een abces of meningitis van middelbare leeftijd, relatief gezond en vaker betrokken waren bij spoedinterventies. Mogelijke vermijdbare

oorzaken van een ongunstig beloop waren onzorgvuldigheden in de timing van anti-hemostatische medicatie (10 claims, 14%), niet-steriele procedures (n=10, 14%) en vertraging in de diagnose/behandeling van de complicatie (n=18, 25%). Het aantal claims dat leidde tot een vergoeding voor de patiënt was vergelijkbaar tussen de landen (VS n=15, 38% vs. Nederland n=17, 52%; P=0,25). De mediane vergoeding die de patiënt ontving varieerde sterk tussen de VS (€ 285 488, n=14) en Nederland (€ 31 031, n=17) (P=0,004). Echter, de aanzienlijke verschillen in jurisprudentie en onkostenadministratie tussen de landen kunnen ertoe hebben geleid dat deze vergelijking van vergoedingen niet representatief is.

Hoofdstuk 7 is een kort artikel waarin de resultaten worden besproken van een technische analyse die de fragiliteit van epidurale naalden onderzoekt door het analyseren van de kracht die nodig is om een epidurale naald te vervormen of te breken. Tijdens het plaatsen van een epidurale katheter worden de naalden onderworpen aan verschillende krachten. De mate en richting van de krachten hangt af van het verloop van de neuraxiale procedure (meerdere puncties met dezelfde naald), de stevigheid van de ligamenten, het optreden van botcontact en mogelijke bewegingen van de patiënt, evenals de maximale kracht die de uitvoerder van de procedure bereid is om uit te oefenen. In het experiment hebben we extreme krachten gesimuleerd met behulp van een model om een punctieplaats van een epidurale procedure te simuleren; 20 Gauge (G) epidurale naalden begonnen te knikken bij blootstelling aan krachten van 25-30 Newton (N) en 18G naalden bij blootstelling aan krachten van 30-45N. Ter referentie: om een naald door zacht weefsel te duwen (de simulatie van huid en onderhuids weefsel totdat contact met het botmodel optreedt) betreft ongeveer 6N. Deformatie van de punt van de epidurale naald werd waargenomen zonder verdere schade. De integriteit van de naaldpunt werd bevestigd door microscopische beoordeling. Bovendien werd in ons experiment geen breuk van epidurale naalden waargenomen. We concluderen dat het breken van epidurale naalden uiterst zeldzaam en moeilijk te simuleren is. Buigen treedt op zonder breuk wanneer aanzienlijke krachten worden uitgeoefend. Het breken van naalden is mogelijk waarschijnlijker

als de naald reeds gebogen is. In het algemeen is het belangrijk om naalden terug te trekken naar oppervlakkig onderhuids weefsel voordat de naald van richting wordt veranderd[18] en om de naald te inspecteren op beschadigingen of buigingen wanneer er aanzienlijke krachten worden uitgeoefend tijdens een neuraxiale procedure.

DEEL 3 – TRENDS IN DE PRAKTIJK VAN NEURAXIALE ANESTHESIE

Het laatste deel van dit proefschrift richt zich op trends in de klinische praktijk van neuraxiale anesthesie, **Hoofdstuk 8**. We bespreken de uitkomsten van een online vragenlijst om trends in de praktijk, belangrijke indicaties, veiligheidsmaatregelen, veiligheidsrapportage en behandeling van complicaties van epidurale analgesie in Nederland te analyseren. Vragenlijsten van 85 van alle 94 Nederlandse ziekenhuizen die epidurale analgesie uitvoeren zijn verzameld, een respons-rate van 90%. Vijfenvijftig procent rapporteerde een trend naar een afgenomen gebruik van perioperatieve epidurale analgesie, terwijl 68% een toegenomen gebruik van epidurale analgesie voor de bevalling rapporteerde. Het afgenomen gebruik van perioperatieve epidurale analgesie kan worden verklaard door de implementatie van minimaal invasieve chirurgie en de opkomst van alternatieve analgetische technieken. De belangrijkste indicaties voor epidurale analgesie waren thoracotomie, laparotomie van de bovenbuik en debulking-procedures van abdominale maligniteiten. Lokale richtlijnen voor de behandeling van ernstige neurologische complicaties tijdens of na epidurale analgesie, "epidurale alert systemen", zijn geïntroduceerd in 45% van de Nederlandse ziekenhuizen om vroege diagnose en behandeling van complicaties te coördineren en te stroomlijnen. In de overige ziekenhuizen worden de verantwoordelijkheden in de diagnostiek en de behandeling van ernstige complicaties na epidurale analgesie op een ad-hoc basis bepaald.

Wat de (niet-)anesthesioloog kan leren van dit proefschrift:

- Neuraxiale anesthesie kan veilig worden toegepast bij jonge en gezonde patiënten; complicaties worden zelden gezien in de obstetrische populatie en de gevolgen van mogelijke complicaties zijn over het algemeen minder ernstig.
- In perioperatieve patiënten met comorbiditeiten, komen complicaties relatief vaker voor en is de uitkomst ongunstiger.
- De individuele presentatie van patiënten met een hematoom of abces na een neuraxiaal blok is zeer variabel.
- De eerste symptomen van een complicatie treden frequent op wanneer patiënten worden verzorgd door niet-anesthesiologische, niet-neurologische of niet-neurochirurgische zorgverleners. Dit, in combinatie met de lage incidentie van ernstige complicaties en de variabele presentatie, maakt het moeilijk om deze complicaties als gevolg van de eerdere neuraxiale techniek te herkennen.
- Intensievere of verlengde monitoring na neuraxiale technieken door een anesthesioloog of acute pijn service kan worden overwogen bij patiënten met een hoger risico op een ongunstig beloop (bijvoorbeeld na mislukte neuraxiale technieken of een bloederige punctie bij patiënten met een gecompromitteerd stollingssysteem).
- De ernst van de symptomen op het moment van diagnose en een vertraging in de neurochirurgische decompressie zijn geassocieerd met een ongunstige uitkomst.
- Naast neuraxiale analgesie voor obstetrische patiënten, is er een rol voor neuraxiale analgesie bij de perioperatieve patiënt. Echter, alternatieven zoals perifere regionale technieken, zijn onderhevig aan continue optimalisatie en samen met de ontwikkeling van minimaal invasieve chirurgie, resulteert dit in een steeds veranderende balans tussen de risico's en voordelen van neuraxiale anesthesie bij de individuele patiënt.

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PhD portfolio

Name PhD student	Elke Maria Elisabeth Bos
PhD period	January 2016 – December 2021
Name PhD supervisor	Prof. dr. M.W. Hollmann

	Year	Workload (ECTS)
General courses		
An Introduction to Good Clinical Practice	2014	0.25
BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2017	0.9
APROVE Introductory Meeting	2017	0.1
APROVE Science night	2017	0.125
Practical Biostatistics	2017	1.1
Clinical epidemiology; Systematic reviews	2017	1.1
Clinical epidemiology; Randomized Clinical Trials	2018	1.1
Clinical epidemiology; Observational Epidemiology	2018	1.1
Advanced Topics in Biostatistics	2020	2.1
Seminars, workshops and master classes		
Weekly department seminars, Anesthesiology and Intensive Care Department, Amsterdam UMC, *Amsterdam, Nederland*	2014-2022	4.0
Anesthesiology evening seminars (monthly)	2014–2020	4.0
Anesthesiology Journal Club (twice monthly)	2016–2017	2.0
Oral presentations		
Anesthesiologendagen, Dutch Society of Anaesthesiology (Nederlandse Vereniging voor Anesthesiologie), 11 – 12 May 2017, *Maastricht, Nederland*	2017	1.5
Euroanaesthesia 2017, European Society of Anaesthesiology, 3 – 5 June 2017, co-chairmanship, session 'Neuraxis', *Geneva, Switzerland*	2017	1.0
Dutch Association for Regional Anesthesia, European Society of Regional Anesthesia, Symposium, 2 – 3 february 2018, *Heeze, the Netherlands*	2018	1.0
Dutch Association for Regional Anesthesia, European Society of Regional Anesthesia, Symposium, 1 – 2 february 2019, *Heeze, the Netherlands*	2019	0.25

	Year	Workload (ECTS)
Poster presentations		
Euroanaesthesia 2017, European Society of Anaesthesiology, 3 – 5 June 2017, Geneva, Switzerland, poster presentation, *Systematic review of spinal and intracranial complications after central neuraxial blocks for perioperative and obstetric anaesthesia and analgesia. Part I: Hematoma*	2017	0.5
Euroanaesthesia 2017, European Society of Anaesthesiology, 3 – 5 June 2017, Geneva, Switzerland, poster presentation, *Systematic review of spinal and intracranial complications after central neuraxial blocks for perioperative and obstetric anaesthesia and analgesia. Part I: Abscess*	2017	0.5
Euroanaesthesia 2018, European Society of Anaesthesiology, 2 – 4 June 2017, Copenhagen, Denmark, poster presentation, *Trends in practice and safety measures of epidural analgesia: report of a national survey*	2018	0.5
Euroanaesthesia 2020, European Society of Anaesthesiology, 28 – 30 November 2020, Virtual Congress, poster presentation, *Analysis of Closed Claims concerning Hematoma, Abscess or Meningitis after Neuraxial Anesthesia in the United States and The Netherlands*	2020	0.5
(Inter)national conferences		
Nederlandse Vereniging voor Anesthesiologie, Anesthesiologendagen, *Maastricht, Nederland*	2014-2019	3.0
Christmas Stollingssymposium, AMC Amsterdam, *Amsterdam, Nederland*	2015	0.25
30th International Winter Symposium, February 2015, Obstetric Anesthesia Towards Better Care for Mother and Child, *Leuven, Belgium*	2015	0.5
Nederlandse Vereniging voor Anesthesiologie Wetenschapsdag, AMC Amsterdam, *Amsterdam, Nederland*	2017	0.25
Euroanaesthesia, European Society of Anaesthesiology	2016–2018, 2020	3.0
Dutch Association for Regional Anesthesia, European Society of Regional Anesthesia, Symposium, 2-3 february 2018, *Heeze, the Netherlands*	2018	0.75

	Year	Workload (ECTS)
Nederlandse Vereniging voor Anesthesiologie, november 2018, AIOS dag Obstetrische Anesthesie, Wilhelmina Kinderziekehuis, *Utrecht, Nederland*	2018	0.5
Christmas Stollingssymposium, Amsterdam UMC, *Amsterdam, Nederland*	2018	0.25
Teaching		
Jury Wetenschapsdag, AMC Amsterdam, *Amsterdam, Nederland*	2017	0.125
M.E. Schut, Epidurale Veiligheid, Trends in practice and safety measures of epidural analgesia: report of a national survey, Anesthesiology Department, Amsterdam UMC, *Amsterdam, Nederland*	2017–2018	2.0
Parameters of Esteem		
Award and Prizes		
Mathieu Gielen prijs – 2e plaats	2019	

Curriculum Vitae

Elke Bos werd geboren op 6 juli 1987 in Delft. Toen zij zeven jaar oud was, verhuisde zij met haar ouders en oudere zus van Nootdorp naar Haren (Gn), waar zij de rest van haar jeugd doorbracht. In 2005 behaalde zij haar diploma aan het Praedinius Gymnasium te Groningen, waarna zij een jaar in de Verenigde Staten doorbracht om te studeren en hockeyen aan Indiana University of Pennsylvania (Pennsylvania, USA).

In 2006 startte zij met de studie geneeskunde aan de Universiteit van Utrecht. Na aanvankelijke interesse in het vak urologie, verloor zij haar hart nog tijdens haar studie geneeskunde aan de anesthesiologie. Zij behaalde in 2013 haar artsendiploma, waarna zij kortdurend werkte als ANIOS Chirurgie in het Antoni van Leeuwenhoek ziekenhuis. In 2014 werd zij aangenomen voor de opleiding anesthesiologie in het AMC Amsterdam (Amsterdam UMC) onder leiding van prof. dr. W.S. Schlack. Stages werden afgerond in het OLVG te Amsterdam, het AMC Amsterdam en het Erasmus MC te Rotterdam, waarna zij in 2020 de opleiding met goed gevolg voltooide. In 2015 startte zij naast haar opleiding, een PhD traject 'Safety of Neuraxial Anesthesia' onder leiding van prof. dr. M.W. Hollmann, prof. dr. C.J. Kalkman en dr. P. Lirk, wat geresulteerd heeft in dit proefschrift. Gedeeltes van dit proefschrift werden voorgedragen tijdens nationale congressen, zoals de beroemde Anesthesiologendagen (Maastricht, 2017) en het DARA-Symposium (Heeze, 2018 en 2019), en tijdens internationale congressen in Geneve (Euroanaesthesia, 2017), Kopenhagen (Euroanaesthesia, 2018) en virtueel (Euroanaesthesia, 2020).

Na een aantal maanden te hebben gewerkt als anesthesioloog op Bonaire begon zij in 2021 een aanvullend fellowship Intensive Care geneeskunde, welke zij halverwege 2022 zal afronden.
Naast haar werk is Elke een fervent sportliefhebber, zij rende een marathon, roeide een ringvaart en hockeyde jarenlang fanatiek. Ze woont samen met Sjoerd de Groot en hun 2 dochters Bette en Lieve in Amsterdam.

Dankwoord

Dit proefschrift is mede tot stand gekomen dankzij waardevolle ondersteuning vanuit vele hoeken. Graag wil ik jullie allen bedanken, zowel de collega's van de werkvloer voor de wetenschappelijke bijdragen, als ook velen buiten de werkvloer, voor de ondersteuning en momenten van reflectie. Tezamen onmisbaar voor het eindresultaat zoals dat nu voor u ligt.

Allereerst, Prof. dr. Hollmann, beste Markus, dank voor het vertrouwen dat je me hebt gegeven. Ik heb aan jou te danken, dat ik mij zowel als arts-assistent met een kritische klinische blik, tevens heb kunnen ontwikkelen tot een wetenschapper met een kritische blik. Ik heb ontzag voor je ogenschijnlijk onbegrensde kennis, evenals je motivatie en drijfveer om ons vak continue te ontwikkelen. Dank dat ik hier onderdeel van kan zijn.

Associate Prof. dr. Lirk, beste Philipp, samen hebben wij de eerste stappen gezet voor de review betreffende spinale hematomen en abcessen. Jij bracht mij onder de aandacht van Markus, waardoor dit promotietraject tot stand kwam. Ondanks je vertrek naar Boston bleef je altijd betrokken. Zowel via de e-mail als telefonisch hebben wij wetenschappelijke beslissingen en invalshoeken doorgenomen. Dank dat je voor mij een klankbord bleef, ook al waren er vele kilometers en uren tijdsverschil te overbruggen.

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Medeauteurs, dank voor jullie input en kritische revisies van de manuscripten. Tevens wil ik in het bijzonder Maartje Schut, Alice Hamersma (Centramed), Bart Jongbloed (MediRisk), Onno Dijt (MediRisk), Prof. dr. Karen Domino, Prof. dr. Karen Posner, Sandra Mulder, Coen Dijkman en Tim Daams (afdeling Medisch Technische Innovatie en Ontwikkeling - Amsterdam UMC), en de dames van het secretariaat van de afdeling Anesthesiologie bedanken. Dankzij jullie bijdrage en ondersteuning is het schrijven van dit proefschrift mogelijk geworden. Thank you for the collaboration and guidance!

De groep onderzoekers van de afdeling Anesthesiologie, die ervoor heeft gezorgd dat er naast EndNote, Mendeley, Matlab, SPSS, Word, GraphPad en PowerPoint genoeg tijd werd besteed aan koffie, borrel, boottochten, congressen, posterpresentaties en lekker eten. Linda, Bram, Joachim, Marije, vele anderen die in de jaren daarna gevolgd zijn, en last but definitely not least, de AU collega's. Jullie zijn als de hop in het zelfgebrouwen bier van Werner.

Dank aan alle fijne collega's, supervisoren, hypervisoren, anesthesie-medewerkers, verpleegkundigen, en 'ketanest tijgers', nu verspreid over afdelingen Anesthesiologie en Intensive Care door het hele land, dat ik dagelijks zoveel van jullie mag leren en heb mogen leren.

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Mijn liefste vrienden, vanuit Haren en Groningen, van het bestuur, de Kromme Nieuwegracht, Rover en de studie uit Utrecht, van de opleiding Anesthesiologie en het fellowship Intensive Care in Amsterdam, en alle andere lieve vrienden en familie. Nuchterheid en relativeringsvermogen uit Groningen, creativiteit en emoties uit Utrecht, ik heb het allemaal meegenomen naar Amsterdam. Wat ben ik dankbaar voor zo'n fijne, intelligente, sportieve, geinige en aanstekelijk enthousiaste groep mensen om me heen. Liefste Wieteke, dankzij jou werd mijn laatste coschap, een keuzecoschap anesthesiologie. Je bent mijn gids door Amsterdam, en sinds wij op nog geen 20 meter afstand van elkaar wonen, nu ook een gids door de buurt. Belangrijker nog, met jouw stempel op mijn carrière, een gids door het leven. Dank dat ik mag meegenieten van jouw ongekende warmte en positiviteit.

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Lieve Marijn, wij staan aan elkaars zijde sinds ons zevende jaar. Samen hebben wij onderzoek 'ontdekt', een biologieopdracht naar de hoeveelheid vitamine C in spinazie en een profielwerkstuk naar gehoorbeschadiging door uitgaan. Het zat methodologisch feilloos in elkaar. Jaren later, en een rugzak vol met levenservaringen verder, kan ik alleen maar concluderen dat je nooit meer van me afkomt. Dank dat je bij deze belangrijke gebeurtenis opnieuw aan mijn zijde staat.

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