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Editorial comment

New knowledge reduces risk of damage to spinal cord from spinal haematoma after epidural- or spinal-analgesia and from spinal cord stimulator leads

Harald Breivik[a,b,c,*]

[a] University of Oslo, Faculty of Medicine, Oslo, Norway
[b] Oslo University Hospital, Department of Pain Management and Research, Oslo, Norway
[c] Oslo University Hospital, Department of Anaesthesiology, Oslo, Norway

In this issue of the *Scandinavian Journal of Pain* Michael Lagerkranser publishes two connected papers in which he analyses risk factors and management of 166 cases of bleeding into the spinal canal (spinal haematoma (SH)), rare complications that can damage the spinal cord, from epidural- or spinal-analgesia (central neuraxial blocks (CNB)) and from spinal cord stimulator (SCS) lead-electrodes [1,2]. These 166 case stories, published between 1994 and 2015, appeared in MEDLINE- or EMBASE-databases.

1. Why should we pay attention to case stories?

We know that there are many sources of publication bias in case-stories where patients suffered major complications or death: we seldom see publications of cases where the author(s) clearly made a unforgivable blunder, more often the authors publish their case-story when rare complications happened in spite of apparently perfect handling before and after the complication occurred. Still, such case reports, but only when reported honestly and in enough detail to make it possible to analyse risk factors and management, can be the only way to learn critical aspects of rare events or rare but serious complications [3].

2. Randomized and controlled study (RCT) of rare events is hardly possible

So, why can we not do large trials in which we can handle patients according to a protocol, comparing a procedure that may risk a serious complication (e.g. SH after epidural analgesia) with a procedure that cannot cause bleeding into the spinal canal (e.g. general anaesthesia and postoperative morphine analgesia)?

Rare events, rare complications of generally safe procedures, these belong in the statistical theories of rare events that are distributed according to a Poisson variable,

$$\lambda = \frac{\sum_{i=1}^{n} x_i}{n}$$

$$f(x;\lambda) = \frac{\lambda^x e}{x!}$$

where e is the base of the natural logarithm (=2.71828), x is the number of complications that occurred, the probability of x occurring is defined by the factorial of x (=$x!$). Lambda (λ) is the expected number of complications in a given number of patients (n).

This can be made practical for non-expert statisticians (=clinicians) by using Hanley's simple formula for estimating the upper limit of a 95% confidence limit ($CI_{95\%}$); $3/n$ where n is the number of observed patients without the rare complication occurring [4,5].

In Rikshospitalet, Oslo, we use epidural analgesia in about 100 liver transplant patients annually and after 10 years we have not observed one single spinal haematoma (Svein Osnes and John Hausken, personal communication). The "true" upper $CI_{95\%}$ limit for having a SH during the next 10 years would be about 3/10 000 = 0.03%, i.e. it is not zero in spite of this excellent record. This of course is true only if the same well qualified, highly conscientious and vigilant team continue to take well care of these patients, observing all the important risk factors and continuing with robust monitoring of these patients before, during and after this major operation where disturbed haemostasis is not unusual.

If someone would like to plan a RCT, comparing epidural analgesia with full general anaesthesia and postoperative morphine analgesia (note that NSAIDs (inhibit platelets) and paracetamol (liver-toxicity) would be contraindicated in these patients), the investigators would need a huge number of patients, which would require a multicentre and multinational study.

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* Corresponding author at: Oslo University Hospital, Department of Pain Management and Research, PO Box 4956 Nydalen, 0424 Oslo, Norway. Fax: +47 23073690.
E-mail address: harald.breivik@medisin.uio.no

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3. Multiple confounding factors in multi-centre randomized studies: learning from case-stories and observational studies continues to be the best option

Multi-centre studies would introduce a number of serious, and often unknown, confounding risk factors; local tradition and cultures are so different that protocol-compliance in major surgery would be difficult.

Even more difficult would be a multi-centre study trying to reduce further the already low risk of SH from epidural or spinal (or combinations of the two) analgesia for C-section and vaginal deliveries. Presently the risk for a SH may be around 1/1–200 000 obstetric spinal/epidural analgesias.

Therefore, it is practically impossible to imagine that we ever would be able to do such a study with a meaningful number of patients within a meaningful time [5].

An international agreement to *report systematically* all SH-events that do occur may be an option, as suggested by Owain Thomas [5].

At present we will have to look at published case stories, analyse them, and hope to learn about risk factors and how to increase haemostatic safety during epidural and spinal analgesia.

This is what Michael Lagerkranser has done, resulting in important new knowledge [1,2].

4. Increasing number of published spinal haematomas, does this mean a higher risk [1]?

During the last two decades, especially in the decade 2005–2015 there were increasing annual numbers of published case reports where the patient had this rare but potentially serious complication of a spinal haematoma. Since the introduction of low-molecular weight heparins (LMWH) for thromboprophylaxis about 25 years ago, this is now mandatory in patients having a reasonably long and complex operation, especially in older patients. These are the patients that often also will have benefits on postoperative morbidity and even mortality from a spinal or epidural analgesia [6,7].

This means that the numbers of patients at higher than average risk of bleeding are offered spinal or epidural analgesia because of the recognition of important benefits for the patients [6,7]. Therefore, it is possible there now is an increased risk. But we do not know the number of patients who have had epidural or spinal analgesia. It is also possible that to publish case-reports is increasingly considered important by editors of scientific journals. Therefore, we can only guess what these increasing numbers of published case stories mean. However, Michael Lagerkranser's studies demonstrate clearly that it is possible to learn important new knowledge from analysing case reports [1,2].

5. At least half of all published cases of SH occur after removal of the epidural catheter

This is an important finding. I believe most anaesthesiologists are now aware of the most common risk factors when inserting a spinal needle or epidural catheter and make sure these are in proportion to the benefits expected for each patient by having an optimal CNB [6,7]. Whereas we have emphasized the fact that removing the epidural catheter is not without risks of SH [6], we now have to pay even more attention to possible risk factors when planning to remove an epidural catheter [1,2,5,7,8]. This is new knowledge and highly important.

6. Laboratory evaluation of the haemostatic safety before removing epidural catheter

This is underscored by the research and publication of Owain Thomas' doctoral thesis in 2016 [5,8]. He documents that patients can have increased risk of bleeding during the first 2(3) days after major surgery, which means that manipulating or withdrawing an epidural catheter during the early postoperative phase may be more risky than pulling the epidural catheter after day 3. He also emphasized that using more advance *viscoelastic haemostatic tests* with ROTHAM® - or TEG® -equipment can be useful when they show clear abnormal haemostasis, but a normal TEG-or ROTHAM-reading does not mean there are no risks of bleeding.

Slightly prolonged activated thromboplastin time (aPTT), slightly increased INR (up to 1.5) and slightly lowered platelet counts (but above $80 \times 10^9\ L^{-1}$) can be accepted, but values clearly different from these limits mean that the risk of precipitating a bleeding into the spinal canal by removing an epidural catheter is not acceptable [5,7,8].

7. Be aware of platelet-inhibiting drugs

In the 166 case stories analysed by Michael Lagerkranser it is documented that platelet-inhibiting drugs, even low dose acetylsalicylic acid (ASA) and NSAIDs like diclofenac or ibuprofen, without any other known risk factor, can precipitate a SH when an epidural catheter is removed. The practice in some places to prescribe such drugs during an ongoing epidural analgesia therefore appears to be unsafe practice [1,2,7].

8. Be aware of age-related decrease in kidney function and renal excretion of potent antihaemostatic drugs

Many drugs that are used in surgical patients to regulate thrombogenesis and reduce risk of venous thromboembolic complications after surgery are excreted via the kidneys. Many more elderly patients are now offered major surgery, e.g. hip or knee replacement, major cancer surgery. They are at high risk of having thromboembolic complications and are always on antihaemostatic drugs to reduce that risk. This is true for LMWH, and for the NOACs now frequently used for atrial fibrillations. There are cases of SH in whom this contributed to the development SH [1,2].

Clinicians may be mislead if they rely solely on serum creatinine for evaluating kidney functions in elderly patients: creatinine comes from muscles and with decreasing muscle-mass in the elderly physically inactive patients, serum creatinine can be low, in spite of severely reduced kidney function [1,2,7]. There are formulas for estimating GFR from serum creatinine, formulas that take age into consideration, but most of them are not accurate enough. It is safer to measure serum cystatin C that is independent of muscle-mass [7].

9. Diagnosis and management of a spinal haematoma

Michael Lagerkranser's analysis of how the 166 spinal haematomas were diagnosed and treated is important. MRI is the best method for verifying the diagnosis when a spinal haematoma is suspected from new back-pain or weakening legs, sensory loss in the perineum, rectal and urinary incontinence. However, when MRI is not available, or is contraindicated, a CT-scan can also document fluid in the spinal canal.

Management of an epidural haematoma is most successful when a surgical laminectomy and removal of the blood is done *less than 12 h after* the first neurological symptoms indicating an ongoing spinal bleeding [2].

New knowledge also is that surgical removal of the haematoma *more than 24 h after* start of symptoms can also be successful – it is never too late if symptoms are severe, or increasing [2].

With only back-pain and no, or only slight leg weakness, *wait and see* is indicated if the symptoms and signs are stable or receding.

Another important finding from Michael Lagerkranser's case analysis is that *spinal subdural haematomas* from CNBs have poor prognosis even when laminectomy and removal of the blood is done before 12 h after symptom start.

10. Conclusions and implications

The Herculean effort by Michael Lagerkranser in collecting and analysing case-stories of the rare but serious complications of spinal or epidural (or combined) analgesia published during the last two decades has revealed important new knowledge. This knowledge could not have been obtained by randomized and controlled studies – RCTs. His findings have strengthened guidelines that are intended to reduce the risk of spinal cord injury when practicing these most effective pain-relieving methods [6,7]. There is no doubt that what he has documented about risk factors and how to best to manage these rare and potentially tragic complications is of great value for all of us who offer these most effective pain relieving methods during and after major thoracic and abdominal surgery [7]. Epidural, and subarachnoid, catheter infusion of a local anaesthetic, a potent lipophilic opioid, and adrenaline are valuable methods for effective relief of pain in palliative care when all other means of pain relief fail [9–11]. By following guidelines based also on Michael Lagerkranser's observations [7], we now should feel safe that we are doing our best to offer safe and optimal spinal and epidural analgesia also to patients with increased risk of bleeding [1,2,5,7].

Conflicts of interest

None declared.

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