Topical review

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Reducing risk of spinal haematoma from spinal and epidural pain procedures

<https://doi.org/10.1515/sjpain-2018-0041>

Received February 22, 2018; accepted March 6, 2018; previously published online April 21, 2018

Abstract

Background and aims: Central neuraxial blocks (CNB: epidural, spinal and their combinations) and other spinal pain procedures can cause serious harm to the spinal cord in patients on antihaemostatic drugs or who have other risk-factors for bleeding in the spinal canal. The purpose of this narrative review is to provide a practise advisory on how to reduce risk of spinal cord injury from spinal haematoma (SH) during CNBs and other spinal pain procedures. Scandinavian guidelines from 2010 are part of the background for this practise advisory.

Methods: We searched recent guidelines, PubMed (MEDLINE), SCOPUS and EMBASE for new and relevant randomised controlled trials (RCT), case-reports and original articles concerning benefits of neuraxial blocks, risks of SH due to anti-haemostatic drugs, patient-related risk

factors, especially renal impairment with delayed excretion of antihaemostatic drugs, and specific risk factors related to the neuraxial pain procedures.

Results and recommendations: Epidural and spinal analgesic techniques, as well as their combination provide superior analgesia and reduce the risk of postoperative and obstetric morbidity and mortality. Spinal pain procedure can be highly effective for cancer patients, less so for chronic non-cancer patients. We did not identify any RCT with SH as outcome. We evaluated risks and recommend precautions for SH when patients are treated with antiplatelet, anticoagulant, or fibrinolytic drugs, when patients' comorbidities may increase risks, and when procedure-specific risk factors are present. Inserting and withdrawing epidural catheters appear to have similar risks for initiating a SH. Invasive neuraxial pain procedures, e.g. spinal cord stimulation, have higher risks of bleeding than traditional neuraxial blocks. We recommend robust monitoring routines and treatment protocol to ensure early diagnosis and effective treatment of SH should this rare but potentially serious complication occur.

Conclusions: When neuraxial analgesia is considered for a patient on anti-haemostatic medication, with patient-related, or procedure-related risk factors, the balance of benefits against risks of bleeding is decisive; when CNB are offered exclusively to patients who will have a reduction of postoperative morbidity and mortality, then a higher risk of bleeding may be accepted. Robust routines should ensure appropriate discontinuation of anti-haemostatic drugs and early detection and treatment of SH.

Implications: There is an on-going development of drugs for prevention of thromboembolic events following surgery and childbirth. The present practise advisory provides up-to-date knowledge and experts' experiences so that patients who will greatly benefit from neuraxial pain procedures and have increased risk of bleeding can safely benefit from these procedures. There are always individual factors for the clinician to evaluate and consider. Increasingly it is necessary for the anaesthesia and analgesia provider to collaborate with specialists in haemostasis.

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Surgeons and obstetricians must be equally well prepared to collaborate for the best outcome for their patients suffering from acute or chronic pain. Optimal pain management is a prerequisite for enhanced recovery after surgery, but there is a multitude of additional concerns, such as early mobilisation, early oral feeding and ileus prevention that surgeons and anaesthesia providers need to optimise for the best outcome and least risk of complications.

Keywords: epidural analgesia; spinal analgesia; spinal haematoma; anticoagulants; platelet inhibitors; practise advisory; postoperative complications.

1 Introduction

Bleeding into the spinal canal caused by central neuraxial blocks (CNB), i.e. spinal or epidural analgesia procedures, are rare but potentially tragic complications that may result in permanent paraplegia and urinary and/or rectal incontinence. The occurrence varies enormously with the presence or absence of risk factors [1, 2]. Experienced clinicians from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) published in 2010 common Nordic guidelines on how to minimise the risk of spinal haematoma (SH) from CNBs for pain relief during and after major surgery or childbirth [1]. Randomised controlled trials (RCT) with a rare occurrence such as SH as primary outcome do not exist. Therefore, guidelines in this area are mainly based on knowledge of drugs that increase the risk of bleeding. There are, however, a number of other risk factors related to CNB procedures, how they are performed and monitored, and on patients' comorbidities [2].

The present review is a stand-alone practise advisory as defined by the American Society of Anesthesiologists in 2017: "Practise advisories summarise the state of the literature and report opinions obtained from expert consultants ... they are not supported by scientific literature to the same degree as standards or guidelines because of the lack of sufficient numbers of adequately controlled studies" [3].

Four experts of the 2010 publication and three new experts developed the present practise advisory. Therefore, this practise advisory, while in part based on the 2010 Nordic guidelines [1], differs as we updated evidence of benefits from CNBs that supports the practise of offering a CNB despite increased risk of bleeding. This practise advisory is also based on more experience with antihaemostatic drugs that were new or introduced after 2010 [4]. There is new knowledge about monitoring of

antihaemostatic drugs [5], and new insight in risk factors, treatment and outcome of this rare complication from a recent analysis of published case reports of SH [2, 6].

2 Methods

Literature search

We searched PubMed (MEDLINE), SCOPUS and EMBASE for RCT comparing the occurrence of SH as primary outcome in patients having CNB with or without antihaemostatic drugs. We found none. We searched recently updated guidelines from authoritative institutions, and selected three for close scrutiny of any new evidence [7–9].

Analysing published case reports of SH

As there is no RCT-based evidence, our senior author, Michael Lagerkranser, published separately a large review on risk factors for post-CNB SH based on 166 case reports published since 1994 by searching PubMed and EMBASE [2, 6]. The findings of his reports are included in the present practise advisory document.

Methods for estimating disturbed haemostasis

Christian Fenger-Eriksen summarised monitoring of new anticoagulants [4]. Owain Thomas ensured expertise in novel, advanced laboratory tests of haemostasis, as well as on standard tests, with his PhD-thesis monograph summarising several years of research and comprehensive literature search on haemostatic safety in epidural analgesia [5].

3 Results and recommendations

Therefore, based on the expert consensus document from 2010 [1], new knowledge and experts' experiences since then, we emphasise benefits of well performed and monitored CNBs, and we emphasise that the degree of benefits expected from a CNB will determine how high risk of SH may be accepted. We evaluated three categories of risk factors for SH, i.e. antihaemostatic drugs, patients' comorbidities and specific risk factors of different spinal and epidural pain management procedures. We discuss and indicate safe practise of various spinal pain management procedures, emphasising importance of solid regimens of monitoring for early signs of SH and routines for how to handle these rare and potentially serious complications.

3.1 Benefits on postoperative morbidity, postoperative mortality and on obstetric outcome from central neuraxial acute pain management procedures

The present practise advisory would be redundant if no benefit for patients' outcome would result from CNB. Any increased risk of bleeding would then exclude CNB as alternative to general anaesthesia (GA) or peripheral local anaesthetic techniques [1]. If, however, we expect reduced risk of serious postoperative complications by administering a CNB, we can accept some increased risk of SH. It is mandatory that resources are available for monitoring and that routines are in place for detection of early signs and treatment of SH (see Section 3.5.) [1, 6].

The strength of the indication for a CNB determines the degree of increased risk that may be accepted [1]:

Weak indication means that a CNB will provide better comfort and less pain after surgery; no or only low risk of SH may be accepted. **Strong indication** means that a CNB will cause less postoperative morbidities than GA; higher risks for SH may be accepted. **Vital indication** means that a CNB will reduce mortality compared with GA; relatively high risks of SH may be accepted, Table 1.

3.1.1 30-day Mortality after surgery is reduced with spinal and epidural analgesia

Studies based on “big data” [11, 12], systematic reviews [13–15], as well as prospective observational studies [16], document reduced 30-days mortality with a CNB alone or in combination with GA, compared with GA alone. Anaesthesia-related maternal mortality is reduced

with CNBs compared with GA for operative obstetric procedures, caesarean section in particular [15].

3.1.2 Perioperative morbidity is reduced with thoracic epidural analgesia

The 2014 systematic review by Pöpping and co-workers [14] confirms reviews in 2000 [13] and 2010 [1] that epidural alone, or combined with GA during surgery, and followed by postoperative epidural analgesia, reduces risks for supraventricular tachycardia, deep venous-thrombosis, atelectasis, pneumonia, respiratory failure, paralytic ileus and postoperative nausea and vomiting when compared with GA followed by pharmacological postoperative analgesia. According to an enhanced recovery after surgery (ERAS) programme for open gastrointestinal surgery, thoracic epidural analgesia provides better postoperative analgesia and accelerates recovery of gastrointestinal functions [17].

3.1.3 Benefits of neuraxial blocks for outcome of vaginal delivery and caesarean-section

Thoraco-lumbar epidural and combined spinal-epidural (CSE) most effectively relieve severe obstetric pain and appear to reduce the risk of persistent pain after C-section and postpartum depression [18]. Spinal or epidural anaesthesia are accepted as standard of care for caesarean section (In the USA: cesarean delivery), reducing maternal mortality as a rare but feared complication of GA for caesarean section [15].

Importantly; a low dose adrenaline (2 µg/mL) added to the epidural infusion does not impair uterine contractions, nor placental perfusion, because much larger

Table 1: Acceptable number of platelets or levels of INR at different levels of benefit from neuraxial blocks (experts' opinions) [1].

Type of CNB	Potential benefit of central neuraxial blocks (CNB) ^{a,b,c}					
	Single shot spinal anaesthesia			Epidural analgesia		
	Weak ^a indication	Strong ^b indication	Vital ^c indication	Weak ^a indication	Strong ^b indication	Vital ^c indication
Platelet count $\times 10^9 \text{ L}^{-1}$ (normal 150–350)	>100	>50	>30	>100	>80	>50
INR (normal = 0.9–1.2)	≤1.4	<1.8	<2.2	≤1.2	<1.6	<1.8

INR = international normalised ratio.

Stratification of indication for CNB in patients with increased risk of a spinal haematoma (see text Section 3.1.).

^aA CNB provides better comfort and less pain after surgery; only low risk of SH accepted.

^bA CNB causes less postoperative morbidities compared with GA; higher risks for SH accepted.

^cA CNB reduces mortality compared with general anaesthesia; relatively high risks of SH accepted [10].

epidural adrenaline doses (80–100 µg) had no effect on utero-placental or foetal circulation, nor on foetal cardiac function during caesarean section [19, 20].

Adrenaline in the epidural infusion reduces serum fentanyl concentration in the parturient [21], reducing fentanyl-exposure of the foetus. Fentanyl in the new-born baby may be unfavourable for mother-baby interactions and bonding – for background see Leffert et al. [15].

3.1.4 Requirements for maximal benefits from an optimal and safe thoracic epidural analgesia for thoracic and major abdominal surgery

For the benefits mentioned in Sections 3.1.1–3.1.3 to be true, a thoracic epidural or spinal analgesic procedure must be performed and monitored well.

This is a challenge, as technically and procedurally failed epidurals range from less than 5 to above 50% [14, 22]. A failed epidural is mostly due to catheter problems, e.g. it is placed segmentally too low, or too high, its tip is located in a dural nerve root sleeve on one side, it is removed too early or accidentally. The catheter can accidentally move through a weak area of the dura mater to the subdural space [23]. Wrong drug, or inappropriate composition of the drug(s) injected through the catheter, catheter-tract infection, dural puncture or dural tear causing positional postdural puncture headaches are significant complications.

The most serious complications are haematoma [2, 6], or abscess [3]: it is a double tragedy when the patient experiences a failed epidural with no pain-relief, at the same time as having a damaged spinal cord from a haematoma or an abscess in the spinal canal.

3.1.4.1 Correct segmental catheter placement, maintenance and monitoring

Attention is required to every detail of the procedure: strict hygienic practise [3], placing and maintaining the epidural catheter in an appropriate thoracic segmental level [22, 23], and continuous and vigilant monitoring of effects and of early signs of any complications, continued until after a well-planned procedure for weaning and removal of the epidural catheter [1, 6, 22, 23].

3.1.4.2 Epidural infusion containing three additive spinal cord pain-relieving drugs

The infused mixture should contain a **local anaesthetic** (e.g. bupivacaine) and a **lipophilic opioid** (e.g. fentanyl)

that easily penetrate to the cerebro-spinal-fluid (CSF) and act on spinal nerve roots and spinal cord synapses. They have different mechanisms of spinal cord analgesia (voltage-gated $\text{Na}_{1,7}$ -channel block, opioid-receptor-agonist) and therefore synergize so that the total dose of each drug can be reduced, thereby reducing systemic absorption from the epidural space and dose-related systemic side effects [21–27].

Morphine is much less lipophilic than fentanyl, penetrates more slowly from the epidural space to the CSF, and morphine is therefore more absorbed into the systemic circulation to give supra-spinal or systemic side effects, such as sedation, respiratory depression, nausea, vomiting, pruritus, constipation, urinary retention. The morphine that does reach the CSF will be distributed with the flow of CSF more widely to more spinal cord segments compared with fentanyl or sufentanil. Therefore, the spinal analgesic effect of morphine depends less on correct segmental epidural catheter positioning than lipophilic opioids that are rapidly absorbed from the CSF into the spinal cord. However, if infused with a local anaesthetic, correct segmental application is still mandatory for a morphine-containing solution.

An **α_2 -receptor agonist** (e.g. clonidine, dexmedetomidine, adrenaline) has another specific analgesic mechanism at the dorsal horn of the spinal cord. This will additionally synergize with the local anaesthetic and the opioid, further reducing the necessary doses of these drugs and their dose-related side effects. Clonidine and dexmedetomidine are potent analgesics but cause sedation and hypotension. Adrenaline at 2 µg/mL is equally effective as an analgesic at the spinal cord and does not cause sedation or blood-pressure changes [22–27].

3.1.4.3 Adrenaline in an epidural infusion may reduce risk of spinal bleeding

Adrenaline's **α_1 -receptor** agonist-effects may reduce risk of bleeding via two mechanisms:

1. It activates platelets via a G-protein coupled receptor that **increases platelet adhesion**, re-enforcing the first phase of haemostasis [28].
2. It causes **vasoconstriction in the epidural space**, but not in the subarachnoid space [22–24]. Vasoconstriction in the epidural space may reduce the risk of vascular injury [29], systemic absorption and systemic side effects of fentanyl [21–23]. The dose of local anaesthetic needed for analgesia is reduced and also the risk of motor nerve block and leg weakness [22, 23].

An epidural solution containing adrenaline 2 µg/mL, fentanyl 2 µg/mL and bupivacaine 1 mg/mL, stabilized with disodium edetate, is stable for several months at 2–8 °C, and at least for 7 days at room temperature without the addition of antioxidant sulphites that may be neurotoxic and allergenic [30].

Because of these beneficial pharmacological effects and interactions, an **adrenaline-containing** thoracic epidural solution should be considered from the first injection through the epidural needle [29] and the infusion **continued until withdrawal of the epidural catheter**.

Bolus injection or continuous infusion of epidural analgesic mixture?

In his doctoral thesis, Geir Niemi documented that the rate of epidural infusion determines the degree of segmental distribution, whereas a bolus injection will deepen the analgesia [23].

3.1.4.4 Why not lumbar epidural infusion?

Note that in low lumbar epidural infusion (below L2 and below the spinal cord) the specific spinal cord analgesic mechanisms of the local anaesthetic, the lipophilic opioid and adrenaline will be lost [1, 22]. A low lumbar infusion with a local anaesthetic will cause nerve-root motor nerve blockade, causing leg paresis or paralysis. Therefore, leg-weakness will not be an early sign of a developing SH during an on-going lumbar epidural [1, 22].

A thoracic epidural with local anaesthetic will cause coronary artery dilatation, increased myocardial oxygen supply/demand ratio, reduced risk of postoperative myocardial ischaemic events and improved postoperative lung functions [1]. None of these beneficial effects of a thoracic epidural will occur during a lumbar epidural infusion. Due to a vasodilatation in the lower parts of the body from a lumbar epidural, an unfavourable compensatory vasoconstriction may even result in coronary arteries [1].

3.2 Identifying and reducing risk factors for SH and spinal cord damage

Thorough knowledge of risk factors is necessary to be able to reduce the incidence of complications and increase haemostatic safety in epidural analgesia. The risk factors may be related to anti-haemostatic drugs (Section 3.2.1), to patients' co-morbidities (Section 3.2.2) and to the epidural and spinal pain procedures (Section 3.2.3).

3.2.1 Risk factors related to antihaemostatic drugs

There are three main categories of anti-haemostatic drugs: (1) **platelet inhibitors**, interfering with platelet-plug formation (first stage of haemostasis), (2) **anticoagulants**, interfering with formation of the coagulum (second stage of haemostasis) and (3) **fibrinolytics**, interfering with formation of the final clot (third and final stage of haemostasis).

Monitoring of haemostasis with standard tests

These include platelet count (PLT), activated partial thromboplastin time (aPTT), international normalised ratio (INR). In the 2010 Nordic guidelines [1], the permissible limits for INR and PLT varied depending on the strength of indication for CNB, and technique used. We agree with those limits as seen in Table 1.

Monitoring of haemostasis with advanced haemostatic tests

Viscoelastic tests, like thromboelastography (ROTEM®), or thromboelastometry (TEG®), have been extensively evaluated in liver disease [31] and for hepatic [31] and cardiac surgery [32]. Thomas [5] and Thomas et al. [33] studied safe epidural catheter removal with advanced haemostatic viscoelastic tests and found the tests not well validated in this context; there are frequent false negative (apparently normal) test results. However, a clearly abnormal TEG® or ROTEM® curve indicates deranged haemostasis, and must be taken seriously [5, 34].

Factor Xa activity can be measured, and where available, can be an important help in evaluating bleeding risk from factor Xa inhibitors (Table 2b).

Safe time intervals between preceding and subsequent dose of antihaemostatic drugs and CNB

Tables 3–6 indicate recommended time intervals between last dose and a CNB-procedure, including manipulation or removal of an epidural catheter, and next dose following a CNB-procedure. Given the individual pharmacokinetic variability and individual comorbidities, these recommendations may reduce but cannot eliminate the risk of spinal bleeding [2].

It is also important to weigh the risk of bleeding against the risk of recurrent thromboembolic events when a dose of an anti-thrombotic medication is delayed or discontinued. Therefore the recommended time intervals in Tables 3–6 should not be exceeded other than for specific reasons, especially conditions that prolong

Table 2: Properties of antihaemostatic drugs. Drugs added since 2010 in bold.

Class/drug	Antithaemostatic target factor	Antithaemostatic effect ^a	Time to peak effect	Plasma half-life	Renal elimination	Time to 50% recovery of platelet function	Monitoring	Reversal and treatment
a. Platelet inhibitors								
Dipyridamol	Phosphodiesterase inhibitor, reversible	(+)	2–3 h	2–3 h	(+)	1 day	Platelet count	Symptomatic
Acetyl salicylic acid (ASA, low dose)	COX-1 irreversible	+	~1 h	0.5 h ^b	+	3 days	(PLT) and Platelet function analysers	Desmopressin + tranexamic acid
NSAIDs (non-selective)	COX-1 reversible	+	Varies	See Table 3b	+	Varies		Desmopressin + tranexamic acid
Clopidogrel	ADPr, irreversible	++	4 h–4 days ^c	1–2 h ^b	++	3 days		Desmopressin ^d + tranexamic acid, Platelet transfusion ^f
Prasugrel	ADPr, irreversible	+++	1 h	2 h ^b	++	6 days		Platelet transfusion ^f
Ticagrelor	ADPr, reversible	++++	2.5 h	7–8.5 h^e	0	3 days		Platelet transfusion ^f
Abciximab	GPIIb/IIIa	++++	2 h	10–30 min	0	24–48 h		Platelet transfusion ^f
Eptifibatide	GPIIb/IIIa	++++	2 h	2.5 h	++	4 h		Platelet transfusion ^f
Tirofiban	GPIIb/IIIa	++++	2 h	2 h	++	4–8 h		Platelet transfusion ^f

NSAID = non-steroidal anti-inflammatory drug; COX = cyclo-oxygenase; ADPr = adenosine diphosphate receptor; GP = glycoprotein.

^aRating of antihaemostatic effect and renal elimination: (+) = insignificant; + = low; ++ = moderate; +++ = pronounced; ++++ = high.

^bDuration of antihaemostatic effects of irreversible inhibitors is more dependent on platelet regeneration than drug half-life.

^cFour hours with loading dose (300 mg), up to 4 days with regular dose (75 mg).

^dDesmopressin has some effect on clopidogrel, but no demonstrated effect on the other ADP-r inhibitors.

^eSeven hours for the parent compound and 8.5 h for the active metabolite (AR-C124910XX).

^fTransfused platelets are inhibited by residual drug in the plasma.

Class/drug	Target factor(s)	Antithaemostatic effect ^a		Time to peak effect	Plasma half-life	Renal elimination	Monitoring	Reversal and treatment
		Prophylactic dose	Therapeutic dose					
b. Anticoagulants								
Parenteral								
Heparin (i.v.)	II and Xa (1/1)	++	+++	<30 min	1–2 h	+	aPTT	Protamine
Dalteparin	II and Xa (1/3)	++	+++	3–4 h	4 h	+	Anti Xa activity	Protamine
Enoxaparin	II and Xa (1/3)	++	+++	3–4 h	4–7 h ^b	++	Anti Xa activity	Protamine
Tinzaparin	II and Xa (1/3)	++	+++	3–4 h	4 h	+	Anti Xa activity	Protamine
Fondaparinux	Xa and ATIII	++	+++	2–3 h	17–20 h ^b	+++	Anti Xa activity	–
Oral								
Dabigatran	IIa (Thrombin)	++	+++	0.5–2 h	14–28 h ^b	++++	Hemoclot ^c	Idarucizumab, PCC ^d
Rivaroxaban	Xa	++	+++	2–4 h	8–10 h ^b	++	Anti Xa activity ^c	PCC ^e
Apixaban	Xa	++	+++	3–4 h	15–19 h ^b	+	Anti Xa activity ^c	PCC ^e
Edoxaban	Xa	++	+++	1–2 h	10–17 h ^b	++	Anti Xa activity ^c	PCC ^e
Vitamin K antagonist (warfarin)	II, VII, IX and X	++ at INR ≤ 3 +++ at INR > 3–6 ++++ at INR > 6		5 days	Vary	0 ^f	INR	PCC or Vitamin K

aPTT = activated partial thrombin time; INR = international normalised ratio; PCC = prothrombin complex concentrate.

^aRating of antihaemostatic effect and renal elimination: + = low; ++ = moderate; +++ = pronounced; ++++ = high.

^bDepending on kidney function.

^cPlasma concentrations can be measured directly.

^d**Idarucizumab** (Praxbind[®]) is a specific antidote to dabigatran and first hand choice if reversal is required. If unavailable, PCC is second hand choice.

^eThe specific antidote to direct oral Xa-inhibitors, **andexanet alfa**, is more effective than PCC, but not yet available for clinical use (Feb 2018).

^fDespite warfarin's renal independency, patients with renal impairment may need dose reduction to achieve therapeutic level (INR 2–3).

Table 3: Recommendations for platelet inhibitors. New recommendations since 2010 in bold.

Antiplatelet drugs	Recommended minimum time interval	
	From last dose of drug to CNB or to catheter manipulation	From CNB or catheter manipulation to next dose of drug (see Table 4)
Phosphodiesterase inhibitor		
Dipyridamole (secondary prevention of stroke or TIA)	12 h for traditional CNB Stop for 2 days before high-risk procedures – see [8]	Resume as soon as possible after CNB or surgery
Cyclo-oxygenase inhibitors		
ASA and combinations for secondary prevention after stroke, TIA, or coronary disease	12 h ^{a,b}	Resume as soon as possible after CNB or surgery
ASA for other purposes	7 days	24 h
NSAID	Drug dependent, see Table 4	See Table 4 ^{c,d}
ADP-receptor inhibitors		
Clopidogrel 75 mg/day	5 days	After catheter removal (After 300 mg bolus 24 h later)
Prasugrel	7 days	24 h
Ticagrelor	5 days	24 h
GPIIb/IIIa inhibitors		
Abciximab	48 h	24 h
Eptifibatide	12 h	24 h
Tirofiban	12 h	24 h

TIA = transitory ischaemic attack.

^aIncreased risk of bleeding also after 12 h if there are other risk factors, e.g. other antihaemostatic drug(s), spinal stenosis, high-risk procedures (spinal cord stimulator, intrathecal catheter, epiduroscopy, “bloody tap”). However, in patients on secondary prevention this risk of bleeding is outweighed by the risk of recurrent cardiovascular events. Careful risk/benefit evaluation is necessary.

^bNo interval necessary in emergency cases.

^cIf paracetamol gives inadequate analgesia after epidural catheter removal, a supplementary NSAID can be administered after 24 h.

^dIn a patient with an indwelling epidural catheter and simultaneous LMWH or other antihaemostatic treatment, NSAIDs should be avoided.

Table 4: Half-lives and recommendations for discontinuation of some NSAIDs before surgery.

Drug	T _{1/2}	Recommended time interval	
		From last dose to CNB ^a	From CNB/cath removal to next dose
Diclofenac	1–2 h	12 h	24 h
Ibuprofen	2 h	12 h	24 h
Ketoprofen	2 h	12 h	24 h
Lornoxicam	4 h	24 h	24 h
Indomethacin	4.5 h	24 h	24 h
Ketorolac	4–6 h	24 h	24 h
Naproxen	10–17 h	48 h	24 h
Meloxicam	15–20 h	4 days	24 h
Piroxicam	10–70 h	2 weeks	24 h
Tenoxicam	72 h	2 weeks	24 h
COX-2 specific inhibitors	Varies	No clinical effect on platelets, but can reduce kidney function [35]	

^aNo interval in emergency cases.

drug elimination, such as impaired renal function (Tables 2 and 5, see Section 3.2.2. about risk factors related to patient-comorbidities).

Pharmacodynamics and pharmacokinetics of antihaemostatic drugs

Most guidelines are founded on knowledge of the pharmacology of antihaemostatic drugs, in particular onset-time and rate of elimination [1, 7–9]. Important aspects of their pharmacology are summarised in Table 2. The risk of bleeding increases when antihaemostatic drugs with different mechanisms of action are combined, e.g. LMWH or a NOAC and an NSAID. Reduced renal function delays excretion of several antihaemostatic drugs. This is often seen in elderly patients without overt renal disease (when evaluated by serum creatinine concentration), especially in the postoperative period (see Section 3.2.2.) [35].

3.2.1.1 Platelet inhibitors (Tables 2a, 3, 4)

These comprise COX-1 inhibitors, such as acetylsalicylic acid (ASA) and the non-selective NSAIDs (both COX-1 and COX-2 inhibitors), adenosine diphosphate (ADP)-receptor inhibitors and the more potent and short-acting antiplatelet GPIIb/IIIa inhibitors used during invasive cardiovascular procedures.

Table 5: Recommendations for anticoagulants. New recommendations since 2010 in bold in the Table.

Antithrombotic drugs	Recommended minimum time interval	
	From last dose of drug to CNB or catheter manipulation	From CNB or catheter manipulation to next dose of drug
UFH		
≤5,000 U (<70 U/kg)/day	4–6 ^a h, normal aPTT and platelet count ^b	1 h ^{c,d}
>5,000 U (>70–100 U/kg)/day	4–6 ^a h, normal aPTT and platelet count ^{b,c}	6 h
>100 U/kg/day	4–6 ^a h, normal aPTT and platelet count ^{b,c}	6 h ^d , EDA the evening before? ^{c,d}
LMWH, for thromboprophylaxis		
Dalteparin ≤5,000 U/day	10–12 h ^{a,e}	2–6 h ^f
Enoxaparin ≤40 mg/day		
Tinzaparin ≤5,000 U/day		
Higher doses	24 h ^a	2–6 h ^f
Fondaparinux		
≤2.5 mg/day	36 h	6 h ^f
NOACs		
Dabigatran	2–5 days ^{g,h,i}	24 h ^k
Rivaroxaban	2 days ^{g,i}	24 h ^k
Apixaban	2 days ^{g,i}	24 h ^k
Edoxaban	2 days ^{g,i}	24 h ^k
Vitamin K antagonists		
Warfarin	(1–4 days, dose-dependent) ^j INR ≤1.4–2.2 – see Table 1	Restart after catheter removal

UFH = unfractionated heparin; LMWH = low molecular weight heparin; NOAC = non-vitamin K-antagonist oral anticoagulant.

^a**Non-elective** cases with **high risk of VTE** (e.g. hip fractures) should have LMWH 2,500 U or 20 mg twice daily, and with a strong/vital indication, give SPA when ready for surgery. **Non-elective obstetric procedures** – see text-Section 3.3.2. and SOAP-statement [15].

^b**After 4–5 days of UFH:** Do platelet counts to rule out heparin induced thrombocytopenia (HIT-II).

^c**If vascular surgery requires intraoperative UFH >5,000 U,** consider inserting the epidural catheter the evening before surgery.

^d1–2 h after CNB, an iv dose of 50–100 U/kg is **common practise during extracranial vascular surgery**, but an increased risk of bleeding is possible.

^eIn patients with **renal impairment**, LMWH, enoxaparin in particular, the interval should be longer, up to 24 h when renal impairment is severe.

^fThe balance between risk of bleeding and thrombosis is optimal when the **first dose is given 6 h after end of elective surgery** in low-thrombogenic patients. **Highly-thrombogenic patients:** Major cancer surgery, prolonged surgery, very ill patients, age >75 years and **parturients**, may need preoperative start of thromboprophylaxis and **restart of LMWH already 2 h after surgery or CNB** [36]. See text-Section 3.3.2 with [93]. **The 2018 – SOAP-statement recommends waiting 4 h** [15].

^gIn **non-elective** cases with strong indication for CNB (see Table 1), 24 h may be enough in patients with normal renal function, but a **NOAC taken less than 24 h ago is contraindication for CNB**.

^h**Depending on kidney function:** 3 days at eGFR 50–80, 4 days at eGFR 30–50, dabigatran contraindicated if eGFR <30 mL/min/1.73 m².

Consider determination of drug serum concentration, and, in case of critical bleeding, give idarucizumab (Praxbind®), 5 g iv.

ⁱIn emergency cases, the interval can be reduced with 50% (24 h in most cases) provided the indication for CNB is at least strong.

^jStart LMWH prophylaxis when INR <2.0 in patients at high risk of thromboembolism, e.g. mechanical mitral valve, aortic valve, recent thromboembolic episode.

^kResumption of a NOAC is contraindicated during on-going thromboprophylaxis with LMWH or fondaparinux.

Table 6: Recommendations for fibrinolytics.

Fibrinolytic drug	Recommended minimum time interval	
	From last dose of drug to CNB or catheter manipulation	From CNB or catheter manipulation to next dose of drug
Alteplase	48 h ^a	At least 2 h (?) if strong indication for fibrinolytics, but clots are not completely stabilized until about 10 days, and the risk of bleeding is probably increased if a thrombolytic drug is given within 10 days Do individual assessment based on risk/benefit analysis
Reteplase	48 h ^a	
Tenecteplase	48 h ^a	

^aIf the indication for CNB is weak (see Table 1, text Section 3.1.), or epidural catheter removal is not urgent, wait for 48 h before a CNB or catheter manipulation. If the indication is strong or vital, decision is guided by risk/benefit considerations.

Acetylsalicylic acid – ASA

ASA is no longer recommended for primary prevention of cardiovascular diseases [37]. Problems with major bleeding outweigh possible benefits of prevention of myocardial infarction (MI) and stroke by ASA [38–40].

Therefore, we distinguish between low dose ASA for secondary prevention of cardiovascular events when discontinuation can cause life threatening cardiovascular events, and ASA for other indications where ASA can be discontinued without risk of recurrent life threatening cardiovascular events.

ADP-receptor (P2Y₁₂) inhibitors

Among the new antiplatelet drugs, our recommendation for discontinuation of the ADP-receptor inhibitor prasugrel is prolonged from 5 to 7 days based on a recovery trial from 2012, showing a slower platelet recovery with prasugrel than with clopidogrel [41]. Since 2010 a new ADP-receptor inhibitor, ticagrelor, has been introduced. This is a direct acting, reversible platelet inhibitor with a half-life at 7–9 h (Table 2a) [42]. It is more potent than the other oral platelet inhibitors. Most guidelines recommend 5 days cessation of ticagrelor [7–9]. Another difference from 2010 [1] is that the present recommendations respect time to peak effect (Table 2a). With clopidogrel, this varies with dose; a loading dose of 300 mg reaches peak effect already after 4 h [43], while this may take several days with the regular daily dose of 75 mg [44]. The time to peak effect is 1 h with prasugrel [43, 45], and 2–4 h with ticagrelor [42].

Non-selective NSAIDs

These are used in some countries as adjuncts to epidural analgesia in patients receiving thromboprophylaxis with LMWH [1]. However, several case-reports suggest that this combination has caused or contributed to SH after CNB [2]. Heller and Litz [44] concluded that the combination of heparin and NSAID was a possible explanation for the high incidence of SH in orthopaedic patients.

Low-dose ASA and non-selective NSAIDs have a relatively small direct impact on platelets and haemostasis. However, they may aggravate an already impaired kidney function (see Section 3.2.2.).

COX-2 selective inhibitors

These have no direct effect on platelets, but the combination of COX-2 inhibitors and a restrictive fluid intake, as in some ERAS protocols, may aggravate a kidney injury [46]. These effects of NSAIDs may increase the bleeding risk by accumulation of LMWH, fondaparinux, NOACs and other drugs excreted by the kidneys (Table 2, Section 3.2.2.). Therefore, we recommend paracetamol, rather than

NSAIDs and COX-2 inhibitors, as a first choice of adjunctive non-opioid analgesic during epidural analgesia (see Table 3) [1, 8].

More strict recommendations for discontinuation of NSAIDs and ASA before invasive spinal pain procedures

The 2010 Nordic guidelines were alone among guidelines published at that time in recommending non-selective NSAIDs to be discontinued before a CNB [1]. The 2015-guidelines of ASRA, ESRA and four associated societies now include this recommendation for interventional spinal pain procedures [8]. The German guidelines from 2016 recommend suspension of the evening dose before CNB [9].

We recommend the thorough discussion of ASA and NSAIDs in the 2015 review by the ASRA/ESRA-task-force [8]. We agree fully with their conclusions that these drugs can be risky in “high-risk spinal-procedures”, whereas in most patients with no other risk factors, their negative effects on haemostasis are probably minor [1, 8].

Increased risk of MI from non-selective NSAIDs and COX-2 inhibitors

The 2010 guidelines [1] stated: “All NSAIDs should be avoided if possible in patients with severe ischaemic heart disease, cerebrovascular and peripheral vascular diseases...” and “even short-term, post-operative treatment with COX-2 inhibitors has been implicated in cardiovascular events” [1]. These statements were strengthened by a recent Bayesian meta-analysis of individual patient data of almost 450,000 patients documenting an increased risk of acute MI with exposure to ibuprofen, diclofenac, naproxen and the COX-2 specific celecoxib. In patients with cardiovascular risk factors, the risk of MI associated with NSAID use may increase already during the first week of exposure [47].

Specific serotonin reuptake-inhibiting antidepressant drugs (SSRI)

These drugs have some effect on platelet-aggregation [1, 8]. However, a recent observational study found no increased risk of bleeding during and after cardiac surgery in patients on SSRI or serotonin and noradrenaline uptake inhibitors (SSNRI) [48]. An SSRI in combination with ASA or an NSAID may have additive effects on platelets, but the clinical significance is uncertain [1].

Herbal medicinal and omega-3 enriched products

Some herbal medicinal and omega-3 enriched products have minor antihaemostatic effects, but there are no solid

data indicating a clinically significant antithrombotic problem [1].

Potent and short-acting GPIIb/IIIa platelet-inhibitors used during invasive cardiovascular procedures

Should a CNB-procedure be needed after a cardiovascular procedure including one of these potent platelet inhibitors, the required time from end of infusion to regained sufficient platelet function for haemostasis is decisive. These are shown in Table 2a, and recommended time intervals in Table 3. Patients on GPIIb/IIIa treatment should be managed in cooperation with the cardiologist or neurologist and a haemostasis specialist.

Recommendations (Tables 3 and 4)

- For ASA we make two recommendations:
 - when ASA is used for secondary prevention: 12 h cessation prior to CNB or interventional spinal pain procedure, (same as the 2010 Nordic recommendations [1]),
 - when ASA is used for other indications: 7 days cessation.
- For clopidogrel, 75 mg/day: a cessation interval of 5 days (as 2010 [1]).
- For prasugrel the cessation interval is prolonged to 7 days.
- For ticagrelor the recommended cessation interval is 5 days.
- Clopidogrel 300 mg, prasugrel and ticagrelor may be resumed 24 h after catheter removal, provided normal haemostasis as evaluated by standard haemostatic tests (INR, aPTT, PLT).
- For NSAIDs, cessation intervals varies with half-life, see Table 4. Same as 2010 [1].
- In patients with on-going epidural analgesia and thromboprophylaxis, the administration of a non-selective NSAID is contra-indicated.
- If there are no major cardiovascular risks, NSAIDs can be administered 24 h after catheter removal (Table 4).

3.2.1.2 Anticoagulants

Anticoagulants affect one or more of the factors active in the coagulation processes.

Heparins

Heparins inhibit factor IIa (thrombin) and factor Xa, and are used for thromboprophylaxis, and in higher doses, for treatment of deep vein thrombosis and pulmonary embolism (Table 2b).

Unfractionated heparin (UFH)

UFH is mostly used for treatment of deep vein thrombosis or pulmonary embolism, and it is still used during vascular surgery. After stopping an iv infusion for at least 4 h and the aPTT is normalised, a CNB can usually be performed safely, provided there are no other risk factors. After a CNB-procedure it is safe to restart UFH 6 h later (for more details see Table 5 with footnotes) [1].

Low molecular weight heparins (LMWH)

For dalteparin, enoxaparin and tinzaparin in doses for thromboprophylaxis, a CNB procedure can start 10 h after last dose, for higher doses the interval should be 24 h (see Table 5 with footnotes for more details).

Vitamin K antagonist (VKA)

Warfarin has effects on several of the coagulation factors (II, VII, IX, X), and is monitored with the INR. In the Nordic countries, warfarin is used mainly for prevention of thrombosis and cerebral embolization in patients with atrial fibrillations, but it is rapidly being replaced by NOACs – see below. The risk of bleeding is dose dependent and can be estimated with the INR. Time interval from a last dose of warfarin until a CNB can be administered varies with dose and INR – see Tables 2b and 5.

Non-vitamin K-antagonist oral anti-coagulants (NOACs)

There are two pharmacological classes of NOACs: factor II – thrombin inhibitor (only dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). Because these NOACs act directly on factor II or factor Xa, they are often referred to as the direct acting oral anti-coagulants (DOACs). The 2015 guidelines from The European Heart Rhythm Association recommended that a NOAC should be used instead of a vitamin K antagonist for stroke prevention in patients with non-valvular atrial fibrillation [49]. Dabigatran, rivaroxaban and apixaban are also licenced for postoperative thromboprophylaxis after total hip or knee arthroplasties. The NOACs have gained increasing popularity in the Nordic countries, and accounted for about 50% of prescribed oral anticoagulants in 2016.

NOACs have an advantage over warfarin since the risk of major haemorrhagic complications seems to be less: in meta-analyses over controlled trials, where additional risk factors have been well balanced, intracranial as well as fatal haemorrhage were significantly decreased [50–53], whereas the risk of gastro-intestinal haemorrhage was somewhat increased (with the exception of apixaban [52]).

There are three published cases of post-CNB SH where NOACs were implicated; one with dabigatran [54] and two with rivaroxaban [55, 56].

The excretion of NOACs is dependent on renal function, although to a lesser degree with the factor Xa inhibitors (25–35%) than with dabigatran (80%) [4] (Table 2, see effect of renal impairment, Section 3.2.2.).

Most guidelines [7, 9] recommend that NOACs should be discontinued for 2 days before a CNB, whereas the ASRA/ESRA guidelines recommend longer interval for higher risk interventional spinal pain procedures [8]. A prolonged interval with dabigatran in patients with renal impairment is necessary (Tables 2 and 5).

Specific antidotes for stopping bleeding caused by oral anticoagulants

A specific antidote to dabigatran, idarucizumab, was marketed in 2015. This is extremely efficient; dabigatran binds to idarucizumab with affinity that is more than 350 times higher than that to thrombin [57]. A specific antidote to the factor Xa inhibitors, andexanet-alfa [58], awaits approval by FDA and European Medicine Agencies. Until its release, prothrombin complex concentrate is recommended for reversal of the factor Xa inhibitors (Table 2b).

Whether specific antidotes should be administered to stop bleeding caused by oral anticoagulants depends on whether the site of bleeding is critical, major bleeding occurs, and in particular what the risks are for causing new cardiovascular events after discontinuation and reversal of oral anticoagulants [59].

Recommendations (Table 5)

- For heparins (UFH and LMWH), fondaparinux and warfarin the recommendations for cessation before a CNB are shown in Table 5 (same as 2010 [1]).
- See special recommendation for enoxaparin in renal failure in Section 3.2.2.
- For NOACs the recommended secession time interval is 2 days in haemostatically healthy individuals (Table 5). For dabigatran in patients with renal impairment, the interval is prolonged up to 5 days (Table 5, see Section 3.2.2.).
- Thromboprophylaxis with LMWH or fondaparinux can be initiated 6–12 h after end of surgery, during on-going epidural analgesia.
- Resuming or initiating administration of a NOAC is contraindicated during on-going epidural analgesia, and during thromboprophylaxis with LMWH or fondaparinux. Such treatment can be (re-)started earliest 24 h after catheter removal and/or termination of thromboprophylaxis, whichever comes last.
- Recommendations for safe removal of epidural catheter – see Section 3.4.

3.2.1.3 Fibrinolytics

Fibrinolysis is the third and final stage of haemostasis when the platelet-plug and coagulum successfully have stopped a bleeding episode; fibrinolysis remodels and adopts the coagulum to appropriate size and function. A clot may require up to 10 days to be fully stabilized [60].

Fibrinolytic drugs

These drugs are used in critical situations to open cerebral arteries clogged by an embolus of coagulated blood, and during interventions in coronary arteries and other vessels where potent but short-lived thrombolytic effects are necessary for successful outcome.

Recommendations (Table 6)

- Initiation of a CNB-procedure within 48 h from administration of a fibrinolytic drug is contraindicated unless the indication for the CNB is strong or vital (see Section 3.1.).
- Rarely, a patient with an indwelling epidural catheter may urgently need thrombolytic intervention. It may be better to leave the catheter, continue with an adrenaline-containing infusion, and withdraw the catheter at a later time, preferably at least 48 h later (Table 6) [8].

Clots are not completely stabilized until several days after formation; therefore, there will be a significant risk of SH after removal of an epidural catheter and thrombolytic therapy after a short time. Firm recommendation is not possible; optimal timing depends on a careful risk/benefit consideration (risk of SH vs. need of urgent intervention) in each case. Vigilant observation for possible early signs and symptoms of a SH developing is obviously important.

3.2.2 Risk-factors related to patients' co-morbidities

Inborn haemostatic disorders

Haemophilia A or B and von Willebrand's disease are usually contraindications to CNB. A thorough risk/benefit analysis may occasionally justify a CNB in such patients. A specialist in haemostasis should be responsible for prophylactic treatment with specific factor-concentrates.

Spinal disorders

Spinal stenosis and ankylosing spondylitis are overrepresented in published case reports of SH after CNB, as documented by Lagerkranser [2] and Horlocker [61]. Also, osteoporosis is pointed out as a risk factor in women in a large epidemiological study from Sweden [62].

Renal impairment

Uraemia or end-stage-renal failure [glomerular filtration rate (GFR) ≤ 15 mL/min/1.73 m²] is associated with spontaneous haemorrhage, in part due to platelet dysfunction [63]. The aetiology is due to uraemic acid toxicity and overproduction of NO, both inhibiting platelet aggregation. Altered blood rheology also contributes (“shearing”) due to anaemia from reduced production of erythropoietin [63]. Dialysis improves platelet function and reduces the risk of haemorrhage somewhat [63].

Among published cases with post-CNB SH; 10 of 166 cases reported renal impairment [2], but only one of these had end-stage renal failure [64].

The risk of SH after CNBs is also increased in patients with moderate renal impairment because many commonly used antithaemostatic drugs are excreted by the kidneys (Table 2a and 2b). Apart from overt renal disease, decreased GFR is associated with complicated diabetes, and with hypertension [65]. There is further an age-related decrease in GFR that may be as much as 1.1 mL/min per year from 30 years of age [66]. Elderly (>65 years) also carry a higher risk of acquiring acute kidney injury in the postoperative period [35].

In the 1990s, an “epidemic” of epidural haematomas occurred foremost in elderly women after total knee or hip arthroplasty in the USA [67]. High-dose enoxaparin (30 mg twice daily) obviously contributed to those SHs. Enoxaparin is more than other LMWHs dependent on renal excretion (Table 2b) [68, 69]. In patients with renal impairment a normal dose for thrombo-prophylaxis will accumulate and increase risk of bleeding [69]. Concomitant administration of NSAIDs, including coxibs, may aggravate renal impairment [35, 46], and further increase accumulation and the risk of bleeding. Perioperative fluid-restriction as part of ERAS-programme [46] may also increase risk of renal impairment in elderly patients [35]. Elderly patients should therefore not have NSAIDs or coxibs for postoperative pain relief.

The kidneys excrete NOACs, especially dabigatran (Table 2b). The dose should be reduced in patients with moderately reduced kidney function, and in the elderly. The time interval of dabigatran before a CNB must be prolonged in patients with eGFR <80 mL/min/1.73 m² (Table 5). Dabigatran is contraindicated in patients with severe renal failure (GFR <30 mL/min/1.73 m²) [70].

Of the 10 cases with renal impairment mentioned above [2], all except the uraemic patient received antithaemostatic drugs, UFH or LMWH, and COX inhibitors. Notably, in none of these cases were guidelines clearly violated [2]. This indicates that guidelines need to be more strict in patients with renal impairment [2].

Estimate glomerular filtration rate (eGFR) in elderly patients on drugs excreted by the kidneys

An accurate indicator of renal function enables estimation of the duration of the effects of anti-haemostatic drugs excreted by the kidneys. The absolute value of serum creatinine is not a reliable measure of GFR unless muscle-mass is normal for sex and age. For children and frail elderly patients, the best estimate is obtained from the muscle-mass-independent cystatin C-based estimating equation. Further advice from the University of Lund, the origin of the cystatin C method (by Anders Grubb) (www.egfr.se):

“If the muscle mass of the patient deviates considerably from that of his/her age and sex category (e.g. because of paralysis, immobility, anorexia, or excessive bodybuilding) or if the patient recently ingested boiled meat or a medicine affecting the tubular excretion of creatinine, a GFR-estimate based solely upon cystatin C should be used. If the patient is treated with glucocorticoids, synthesis of cystatin C is significantly increased and in this case a GFR-estimate based solely upon creatinine (with age and sex-corrections) should be used. In hyperthyroidism the cystatin C level will increase and the creatinine level decrease without corresponding changes in GFR”.

Recommendations

- Patients with end-stage renal failure (uraemic patients) (GFR <15 mL/min/1.73 m²) should be managed in collaboration with a nephrologist.
- eGFR should be routinely calculated in patients with renal disease. Decreased renal function at the preoperative visit should be followed up postoperatively during on-going epidural analgesia. eGFR can be easily and automatically calculated on various Internet sites. We recommend www.egfr.se
- If eGFR <80 mL/min/1.73 m², dabigatran must be discontinued from 3 up to 5 days, depending on the degree of renal impairment (Table 5, footnote h). Dabigatran is contraindicated if eGFR is below 30 mL/min/1.73 m²
- In patients above 65 years on enoxaparin >40 mg/day eGFR based on cystatin C should be calculated before epidural catheter manipulations, even if serum creatinine is within normal limits.
- If eGFR is below 30 mL/min/1.73 m² in patients treated with enoxaparin a dose reduction, or a longer interval from an unadjusted dose, before catheter manipulations should be considered.

Hepatic failure

The haemostatic pattern in hepatic failure is complex [34, 71, 72]. All coagulation factors except FVIII are synthesized in the liver. Hepatic failure is therefore connected with

factor deficiencies, but also imbalance between production and destruction of platelets, resulting in thrombocytopenia [73]. Reductions in both pro- and anti-coagulant factors seem to be able to balance each other, and platelet dysfunction is compensated, at least in part, by a concomitant increase in the von Willebrand factor [34, 72]. In patients with liver cirrhosis, the risk of systemic thromboembolism can be greater than the risk of bleeding [34].

Among 166 cases of SH after CNB reported since 1994 [2], there were four with liver disease (2.4%) after CNB for non-hepatic procedures, two with liver cirrhosis, one with chronic hepatitis, and one with alcohol dependent pancreatitis “with raised liver enzymes” [2]. In all those cases, no other tentatively contributing factor was reported [2].

A possible bleeding risk is better predicted by clinical criteria than by standard laboratory tests (INR, PLT, aPPT), except possibly PLT $<50 \times 10^9/L$ [34, 72]. These standard laboratory tests, and especially PLT, are recommended before CNB procedures and during on-going epidural analgesia in patients with hepatic disease.

Liver resection is followed by a decline in PLT and a rise in INR during the first postoperative days, despite normal values preoperatively [73, 74]. Platelet transfusion should be considered at PLT $<50 \times 10^9/L$. Treatment should be governed by viscoelastic testing (VET), including TEG® or rotational thromboelastometry (ROTEM®) [34, 74, 75]. Fresh frozen plasma is not recommended.

Some liver-transplant units avoid CNB, while epidural analgesia is used successfully in others, assisted by bedside standard coagulation tests and TEG®-curves, (John Hausken, Oslo University Hospital, personal communication).

Recommendations

- A careful record of individual bleeding tendency and pre- and post-operative screening for PLT and INR are necessary measures. Table 1 indicates permissible levels of these tests in various situations.
- For surgical units without specialised experience and monitoring with VET, CNBs should usually be avoided in patients with significant liver failure [75].

3.2.3 Risk factors related to the CNB-procedures

3.2.3.1 Interventional spinal procedures for chronic pain

Strict guidelines for interventional spinal procedures for chronic pain were published 2015 by ASRA, ESRA and four other societies [8]. The procedures were classified with high, intermediate, or low risk for serious bleeding in the spinal canal:

High-risk procedures

These are associated with significantly increased risk for serious bleeding complications compared with traditional CNBs for anaesthesia or analgesia [8].

Spinal cord stimulation (SCS) with percutaneous implantation and removal of SCS-leads involves feeding a thick and stiff electrode into the epidural space through a large bore, long-bevelled needle. There are four published case-reports of SH after SCS, three of which occurred in connection with retraction or removal of the leads [76–78]. In a large cohort of patients undergoing stimulator implantation, either percutaneously or surgically via laminectomy, the incidence of spinal hematoma after SCS was 0.75% [79]. This is approximately 150 times higher than after traditional epidural analgesia [2].

Intrathecal (subarachnoid) catheter and pump implantation for chronic non-cancer pain and for otherwise intractable cancer pain. The techniques may cause increased risk of bleeding [8]. However, in his collection of published cases of SH related to CNB, Michael Lagerkranser did not find any cases of SH complicating intrathecal catheter procedures for chronic pain [2]. In the late 1990s, when intrathecal catheters were used for acute perioperative pain, four cases with SH were published [2].

Epiduroscopy and epidural decompression is a treatment of chronic pain from failed back surgery in patients who often have abnormal anatomy in the epidural space with fibrous tissue bands, scar tissue and obstructed and distended epidural veins [8].

Procedures with intermediate and low risk

Paravertebral block (PVB) is listed as a procedure with moderately increased risk of serious bleeding complications [8], but no published case-report of SH after PVB has been found in the literature review [2]. However, the paravertebral space communicates with the epidural space [80], and an arterial bleeding in the paravertebral space can reach the spinal canal. There are other serious complications from PVB, such as total spinal anaesthesia [81] and risk of systemic toxicity from the large doses used for continuous thoracic paravertebral blocks [82].

Transforaminal or interlaminar epidural steroid injection, facet joint denervation, intradiscal procedures and sympathetic blocks are listed by ASRA/ESRA as procedures with moderately increased risk of SH [8]. The risk of bleeding into the spinal canal must be low unless other risks of SH are also present, e.g. epidural injection of steroid in a patient with low back pain on dabigatran caused a SH [54].

3.2.3.2 Traditional CNBs for acute pain: spinal, epidural and combined spinal-epidural

The risk of spinal canal bleeding and a haematoma compressing the spinal cord is low from these procedures *per se*. However, the risk varies with the many additional risk factors described and evaluated in this practise advisory. In this section we emphasise some anatomical, technical and pharmacological aspects that should be considered in order to reduce the specific risks from the CNB procedures.

A **single shot spinal anaesthetic (SPA)** with a small calibre spinal needle carries a lower risk of SH than insertion of an epidural catheter. Accordingly, lower PLTs or higher INR levels may be accepted for SPA [1]. Table 1 indicates how the choice of CNB-procedure and how a strong indication for a CNB may influence the admissible limits for number of platelets or INR.

When blood appears in the spinal or epidural needle or in the catheter (a “**bloody tap**”), the risk of a subsequent SH increases [2]. **Multiple failed attempts** may increase the risk [83]. Multiple failed attempts in the mid-thoracic region with an epidural needle occur more often during a midline approach, since bony structures prevent the needle from entering the vertebral canal: a **paramedian approach avoids the bony obstructions** in this region [22].

Spinal anaesthesia and analgesia

In order to prevent spinal cord damage by the needle, a single shot spinal anaesthesia with a low calibre pencil-point spinal needle is inserted at a lumbar interspace between L3-L4 or lower, well below the end of the spinal cord at the upper boarder of the second lumbar vertebra.

However, in elderly, osteoporotic female patients, but also in elderly men with degenerative changes in their spinal column, often with spinal canal stenosis, a paramedian approach, using the spinal lamina as a bony landmark, is superior and safer technically. The **paramedian lumbosacral interspace (L5-S1) is usually wide open**, even in elderly patients who cannot flex their lower back, especially when in severe pain from a fractured hip (“Taylor’s lumbosacral subarachnoid tap”) [84].

Epidural analgesia (See Section 3.1.4.)

The principles of safe and effective epidural procedures are described in Section 3.1.4 [1, 22]. We re-emphasise these because poorly handled epidurals reduce the positive effects, create complications and a false negative impression of benefits that can be achieved with optimal and safe thoracic epidural analgesia for patients with strong or vital indications for CNB. This clearly was the case in a flawed multicentre RCT almost two decades ago [85]. About 1/3 of patients randomised to have epidural analgesia had

failed epidurals and many had their epidural discontinued already on the first day after major surgery.

Poor anatomical knowledge, lack of experience, low quality monitoring and follow-up routines cause technically failed epidurals: epidural catheters placed in too high or too low segmental position; epidural catheters are not fastened well and are accidentally removed early, catheters are curled up in one side or in a nerve-root pocket of the epidural space. Disconnections in tubing to the epidural catheter increase the risk of catheter-tract infections [3].

Insertion site and approach to the epidural space in the thoracic region

It is often not possible for an ill elderly patient to flex the stiff thoracic part of the spinal column; therefore a **paramedian approach is highly recommended**: With the patient in a comfortable lateral decubitus position, due to the broad shoulder part (or pelvic part in women), the spinal column will flex slightly laterally with the convex part in the low lateral side. This opens the interlaminar space and enables the needle approaching **paramedially from below** to successfully reach the epidural space [22].

Inserting the epidural catheter more than about 5 cm beyond the needle tip may cause the catheter tip to curl up and end in a lateral position, causing one-sided analgesia.

This leads to attempts at catheter repositioning by retracting it. **Catheter manipulations** can be as risky as removing the catheter; if a vascular damage occurred during insertion of the epidural catheter, a clot may have formed where the curled-up catheter is located. During repositioning or removal of the catheter this coagulum may be torn off the injured vessel, causing an epidural haematoma.

Opening the sterile bandage at the catheter insertion site when repositioning the catheter, may also increase the risk of catheter tract infection and abscess formation [3].

Adrenaline in an epidural infusion may reduce risk of SH (See Section 3.1.4.)

In addition to increasing analgesic effects through its α_2 -receptor agonist interactions in the dorsal horn of the spinal cord, positive effects from its α_1 -receptor agonist stimulation in the epidural space are important. (1) Adrenaline increases platelet adhesion, promoting a platelet plug at a bleeding site [28]. (2) Adrenaline causes vasoconstriction in the epidural space, but not in the subarachnoid space [23, 24]. Vasoconstriction reduces systemic absorption from the epidural space of fentanyl [21, 26] and bupivacaine [22, 24] allowing doses to

be reduced. The low dose of bupivacaine reduces risk of motor-blockade [22–27]. Should the patient note that the legs are becoming weaker, this may be an early symptom of compression of the spinal cord from an epidural haematoma – see Section 3.5.

3.2.3.3 Peripheral nerve blocks – alternative to CNB when risk of bleeding is high?

Deep plexus blocks near non-compressible vessels require similar strict precautions as CNBs in patients with haemostatic disturbances [8].

Ultra-sound guidance for accurate placement of needles or catheters near peripheral nerves or a nerve plexus has contributed to a renaissance for peripheral nerve blocks. They provide good immediate postoperative analgesia after hip or knee joint replacements and one-sided thoracic or abdominal surgery. The risk of spinal canal haematoma is low.

However, these techniques have their specific complications, e.g. needle injuries of nerves causing chronic neuropathic pain, serious local anaesthetic systemic toxicity from infusions of large doses of local anaesthetic drugs [86, 87]. Local infiltration analgesia (LIA) – for hip replacement, containing a local anaesthetic and an NSAID has caused renal failure [88].

Recommendations

- Difficulties and complications during a CNB-procedure, especially a bloody tap, but also several failed attempts, would make most experienced anaesthesiologists hesitant to proceed and instead administer GA for the operation. Close supervision for symptoms and signs of a SH for at least 24 h after a complicated and failed CNB-procedure is mandatory.
- Ultrasound-guided peripheral nerve blocks and LIA are possible alternatives to CNBs in patients with disturbed haemostasis. These techniques have their own specific complications.

3.3 Recommendations for special situations

3.3.1 Non-elective, non-obstetric cases

- In patients with low or moderate risk of thromboembolic complications after surgery, who have taken ASA or an NSAID within the last 12 h, a CNB may be administered if there is a strong indication with clear benefits on morbidity or mortality, but the administration of a thromboprophylactic drug should be delayed until 6 h after surgery.

- If remaining platelet inhibition is suspected, and platelet-function test is not available in time, desmopressin (0.3 µg/kg) may be given. Desmopressin has a weak fibrinolytic effect [89]. For this reason, and especially if local fibrinolysis is suspected (e.g. in a fracture-haematoma), the anti-fibrinolytic tranexamic acid (10 mg/kg) should be given as well.
- If any NOAC was taken less than 24 h ago, this is a contraindication to CNBs.
- In patients on dabigatran, whose kidney function is reduced (usually in patients >75–80 years), when surgery is urgent, CNBs should not be used in these cases. Plasma concentration of dabigatran can be rapidly measured in many hospitals [70]. If unavailable, aPTT may give an indication whether dabigatran levels are significantly increased [70].
- In non-elective patients at high risk of thromboembolic complications (e.g. elderly patient with hip fracture), thromboprophylaxis should be initiated as soon as possible after admission to the hospital, with half of the daily LMWH dose (e.g. dalteparin 2500 U or enoxaparin 20 mg) every 12 h. In these patients, epidural or spinal anaesthesia may be administered without delay if the patient requires immediate surgery and there is at least a strong indication for CNB (Section 3.1.) [1].

3.3.2 Elective and non-elective obstetric cases

Venous thromboembolism (VTE) with pulmonary embolism (PE) is a leading cause of obstetric morbidity and mortality [15]. VTE is responsible for 9.2% of maternal deaths in the USA [15]. The incidence of VTE in Denmark around the millennium was 175/100,000 puerperal-years [90]. The risk of postpartum VTE after elective caesarean section is at least twice and after emergency caesarean section four times that after a vaginal delivery [90–92].

Thromboprophylaxis is therefore important in obstetric practise. Parturients are in a hypercoagulable state and thromboprophylactic doses are higher than in non-pregnant women [15, 90–92]. Spinal, epidural, or CSE anaesthesia or analgesia are the optimal procedures for operative and non-operative obstetric delivery. SH is a rare complication (1:200,000–1:250,000) in parturients [15, 62, 91], but a mismanaged SH is especially tragic should it occur.

When considering the risk of regional techniques for parturients having thromboprophylaxis, clinicians must also consider the significant **risks of GA for caesarean section**, e.g. failed intubation and serious respiratory and

cardiac complications, severe hypertension and cerebrovascular injuries, increased bleeding, persistent pain, reduced skin-to-skin bonding and breast feeding, and intrauterine exposure to the foetus of anaesthetic drugs causing postpartum respiratory depression and risk of delayed neuro-behavioural development [15, 92].

Tests for haemostasis: aPTT (assessing heparin effects) and anti-factor Xa activity (from LMWH) are less reliable in parturients. PLTs are often reduced, but platelet aggregation is increased so that thrombocytopenia is better tolerated in parturients (see below). Safe ranges have not been well established for TEG and thromboelastometry (ROTEM) for parturients on VTE-prophylaxis [15].

The Society for Obstetric Anesthesia and Perinatology (SOAP) consensus statement on the anaesthetic management of pregnant and postpartum women receiving thromboprophylaxis [15], suggests that neuraxial (spinal) anaesthesia for elective cases may be considered 4–6 h after last **low dose** UFH of 5,000 U twice daily, 12 h after dalteparin $\leq 5,000$ U/24 h or $\leq 2,500$ U twice daily, enoxaparin ≤ 40 mg/24 h or ≤ 30 mg every 12 h [15]. With the hypercoagulable state of the parturients in mind, we consider that waiting for 10 h after the last prophylactic dose (as for not-pregnant women) is sufficient (Table 5). For urgent or emergency caesarean section an individual risk/benefit evaluation must be done by the responsible anaesthesiologist and obstetrician. Considering the risks of GA (see above), placement of neuraxial anaesthesia without delay may be appropriate even less than 10–12 h after last dose [15].

With higher doses of LMWH the Nordic guidelines from 2010 [1] and the present practise advisory document for non-obstetric practise (Table 5) advice waiting for 24 h after the last dose. However, according to the 2018 SOAP consensus statement [15], parturients on **intermediate dose** between low dose (see above) and high dose (see below) VTE-prophylaxis, if last dose of LMWH was given between 10 and 24 h ago, the risk of GA may be considered higher than the risks placing a neuraxial (spinal) block in those who need urgent or emergency caesarean section.

With **high doses** of UFH (daily dose $>20,000$ U) or of LMWH (dalteparin 120 U/kg twice daily; or 200 U/kg once daily; enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily) the SOAP statement indicates that there is likely low risk of SH from a CNB >24 h after last dose. For UFH if aPTT is within reference values and anti-factor Xa is undetectable, a neuraxial block has likely low risk [15].

In **urgent or emergency caesarean section**, if less than 24 h since last intermediate or high dose and aPTT and anti-factor Xa values indicate bleeding risk (from UFH) or such data are unavailable, there may be increased risk of SH from a CNB and GA should be considered [15].

This decision **will always be difficult**, personal experience and resources available will influence our decisions in individual cases [15, 92].

The SOAP consensus statement emphasises that the recommendations they make are **not** “a legal standard of care” [15], the recommendations are intended as decision aids based on experts’ experiences and on available knowledge of pharmacology of these drugs in parturients without renal disease or any other contraindications to CNB [15, 90–92]. The same is true for the recommendations in this practise advisory.

We recommend the “Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving unfractionated heparin” and “Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving low molecular weight heparin”, in the consensus document from the SOAP [15].

The SOAP-statement recommends waiting 4 h after removal of an epidural catheter before restarting LMWH-prophylaxis. The Swedish guidelines recommend restarting LMWH already 2 h after removal of an epidural catheter [93]. Considering the importance of effective thromboprophylaxis in parturients, we support this (Table 5).

It is important that the SOAP-statement emphasises that NSAIDs should not be allowed as long as the epidural catheter is in place [15]. This was recommended already in 2010 in the Nordic guidelines [1].

Thrombocytopenia is common in parturients, up to 10% have $<150 \times 10^9/L$ [94]. A PLT $<100 \times 10^9/L$ is generally a risk factor for SH, but when there are strong or vital indications for a spinal anaesthesia in a non-elective caesarean section, we agree with the 2010 Nordic guidelines, that low platelet numbers can be accepted (Table 1) [1]. Due to the hypercoagulable state of pregnant women and parturients, increased platelet aggregation in particular [15], they tolerate thrombocytopenia significantly better than non-pregnant women [10, 94, 95]. This recommendation agrees with recent publications documenting low risk of SH in thrombocytopenic parturients, based on data from 1,524 parturients with PLTs below $100 \times 10^9/L$ [10]. These were non-elective and elective cases. No SH was observed in patients with PLTs between 50 and $70 \times 10^9/L$, but due to relatively few cases, the upper bound of the 95% CI for the risk of a SH with $<100 \times 10^9/L$ was estimated to be 3% [10]. Bernstein et al. [95], based on 256 parturients with platelets $<100 \times 10^9/L$ having CNB, estimated the upper 95%CI to be 1.2%. Goodier et al. [94], based on 499 thrombocytopenic parturients (range $28\text{--}99 \times 10^9/L$) who had epidural, combined epidural-spinal, or spinal analgesia/anaesthesia, calculated the 95% confidence interval for the risk of spinal-epidural

haematoma from 0.0 to 0.6%. They also estimated the 95% confident interval for serious complications to GA, chosen because of thrombocytopaenia (mean $60 \times 10^9/L$), from 2.1 to 14.5% [94].

Reasons for the low risk of SH in parturients having CNB for anaesthesia or pain relief

Pregnancy related coagulation changes include increased platelet aggregation, increased coagulation factor levels (II, VII, VIII, IX, X, XII, XIII, von Willebrand Factor), decreased endogenous anticoagulation effects, and modified fibrinolytic capacity [15].

Important pregnancy-related physiological changes, e.g. increased renal blood flow and GFR, causing more rapid clearance of drugs excreted by the kidneys (e.g. enoxaparin), and changes in drug metabolism related to placental and foetal metabolic effects, may also influence coagulation [15].

Should a SH occur in association with obstetric pain relief, it would be especially tragic. Therefore, optimal care of obstetric patients must be provided in collaboration between a specialist in haemostasis, the obstetrician and an experienced anaesthesia provider, both in planning thromboprophylaxis to make neuraxial analgesia or anaesthesia possible when appropriate, and during and after obstetric interventions that require such joint expertise [15].

When can thromboprophylaxis be restarted?

After a CNB for obstetric procedures in a parturient on low-, intermediate-, or high-dose thromboprophylactic treatment (see above) it must be important to restart the thromboprophylaxis as soon as possible and as soon as it is safe: in Table 5 the interval from a CNB-procedure for surgery to restart of UFH or LMWH is 2–6 h. For parturients with their high risk of VTE this interval must be short. The Swedish guidelines [93] indicate 2 h as a safe interval. We agree that this can be accepted as a general rule for parturients, but whenever possible consult a specialist in haemostasis and VTE-prophylaxis in parturients: restarting too soon may cause uterine haemorrhage, too late will increase the risk of serious VTE.

Recommendations

Elective caesarean section and vaginal delivery:

- aPTT, INR and PLT within normal limits; if indication is strong or vital, INR and PLT according to Table 1.
- UFH should be discontinued at least **4–6 h** before a CNB.
- LMWH should be discontinued at least 10 h before a CNB at prophylactic doses (Table 5), 24 h at higher doses.

- In complicated cases, the procedure should be planned in cooperation between the anaesthesiologist, the obstetrician and a haematologist.
- Prophylactic LMWH may be restarted 2–4 h after the procedure.

Urgent or emergency caesarean section, in cases where the above limits are violated:

- Individual assessment in cooperation with the obstetrician, weighing risks vs. benefits with spinal and GA, taking the strength of indication for a CNB into account (Table 1).

3.4 When is it safe to remove an epidural catheter?

Among case-reports of SH in relation to CNBs, about 60% happened after epidural catheter removal [2]. Thomas [5] and Thomas et al. [33, 36] studied safe catheter removal extensively with standard and advanced haemostatic test-evaluations in the postoperative period.

They found that there is a risk of hypocoagulation during the first 1–2 postoperative days after major surgery. This can be due to loss of coagulation factors during surgical haemorrhage, haemodilution and hypothermia [5, 33, 36].

The normal inflammatory response to tissue trauma gradually causes a state of hypercoagulation due to hyperfibrinogenaemia and thrombocytosis about 2–3 days after major surgery, necessitating effective thromboprophylaxis, yet INR and aPTT may remain slightly elevated longer [5, 33, 36]. Therefore, should an epidural catheter need manipulation (e.g. re-positioning when in a lateral position) or removal during the first couple of days after major surgery, the risk of bleeding may be increased.

Recommendations (Table 5)

- Appropriate timing of safe epidural catheter removal should be guided by tabulated intervals from last dose of an antihaemostatic drug (Tables 5 and 6) and routine haemostatic tests (INR, aPTT and PLT) [5, 33, 36]. If these are significantly abnormal, catheter manipulations should be delayed.
- Especially during the first 1–2 days after major surgery, if INR, aPTT and/or PLT indicate that a patient may be at risk of bleeding, manipulation or removal of the epidural catheter should be delayed.
- An epidural catheter may be safely withdrawn from a patient doing well after major surgery even with a slightly elevated INR (but below 1.5) and a moderate prolongation of aPTT.

- In patients recovering well and with normal standard haemostatic tests the catheter may be manipulated or removed 10 h after a prophylactic dose of LMWH, and 24 h after higher doses of LMWH, or 36 h after the last dose of fondaparinux (Table 5).
- Epidural catheter-removal should be postponed in patients who are not recovering normally: for example, those with continued haemorrhage, sepsis, kidney- or liver-failure, or bone marrow failure.
- **Plan to remove the epidural catheter in the morning**, so that should a SH develop, it will be more likely that early signs and symptoms are detected during daytime, and timely diagnostics and therapeutic approaches obtained.

3.5 Early detection and treatment of a haematoma in the spinal canal reduce the risk of permanent spinal cord damage

Fortunately SH is a rare complication to CNB, and therefore it is highly recommended to have an agreed-upon protocol for early diagnosis and effective treatment should this potentially catastrophic complication occur (Table 7). The following statements are based on experienced experts' opinions and published case reports [1, 2, 6].

Measures that facilitate early detection and treatment of a haematoma (Table 7)

- **Place the end of the epidural catheter at the centre of the thoracic spinal cord segments covering the surgical area.** This means always thoracic segment for thoracic and major abdominal surgery and thoracolumbar for hip- or knee-arthroplasty, and obstetric procedures. Optimal thoracic epidural analgesia is spinal cord analgesia without motor blockade; it is not a spinal nerve or nerve-root local anaesthetic

Table 7: Postoperative surveillance and management during continuous epidural analgesia.

-
- Monitor leg mobility every 4–6 h
 - At any sign of a developing spinal haematoma: new or aggravated back pain, especially if radiating, leg weakness, bladder or bowel disturbances, sensory loss unrelated to the block, turn off the epidural infusion.
 - If symptoms/signs do not resolve, act immediately:
 - Consult a neuro- or orthopaedic surgeon
 - Arrange for an urgent MRI
 - Try to evacuate blood via the epidural catheter [96]
-

- blockade [1, 22]. This will facilitate mobilisation and monitoring: **if legs become weak, this means that a SH is developing** (until proven otherwise).
- **Use the lowest possible concentration of local anaesthetic** combined with a lipophilic opioid. Adrenaline reduces the required dose of each drug and thereby dose-related side effects, e.g. leg weakness [1, 22].
- **Adrenaline** increases platelet aggregation and adhesion, and adrenaline constricts epidural vessels, reducing the risk of epidural blood vessel damage and bleeding. Therefore, epidural catheter manipulation or removal may be safer with a still on-going epidural infusion, or bolus, containing adrenaline. Note that adrenaline does not constrict subarachnoid vessels.
- **Do not manipulate or remove the catheter when the patient has a haemostatic abnormality**, especially if there may still be effects of antithrombotic drugs.
- **Assess leg weakness and sensory levels every 4–6 h during on-going epidural analgesia and for at least 24 h after removal of an epidural catheter.** Upper and lower sensory levels assessed every 4–6 h using an ice-cube in a plastic glove will facilitate detection of abnormal progress of a continuous post-operative epidural analgesia [22].
- **New leg weakness may be a sign of a developing spinal canal haematoma.** Additional early symptoms and signs are new or more severe back pain, perineal sensory loss and urinary retention. Symptoms are typically aggravated over time, from back pain to paresis and finally paralysis [6].
- **Verify diagnosis by stopping epidural infusion and arrange for an urgent magnetic resonance imaging (MRI)** (or CT if MRI is not available, or when wire-reinforced catheter or Spinal Cord Stimulation-electrodes are not MRI-compatible).
- Without delaying these measures, try to evacuate blood via the epidural catheter. This may lead to a temporary relief of symptoms [6, 96].
- **The most effective treatment is surgical evacuation of haematoma within less than about 12 h** of appearance of neurologic symptoms, but longer delays do not justify refraining from surgery [6]. When signs and symptoms are slight (e.g. back pain only), or neurological signs are already regressing, the indication for surgical intervention is weakened even if MRI demonstrates a SH, but the surveillance for aggravated symptoms should be intensified [6].
- **Inform the patient** of the significance of leg weakness, loss of sensation in the legs and/or perineum, incontinence (urinary and/or anal) and new

back-pain. The patient should be informed about the importance of these symptoms after discharge from the hospital. If they appear, the patient must immediately report to the hospital. The patient should be transported to the nearest emergency department. A late haematoma or an epidural abscess may need urgent therapy [3, 6].

3.6 Conclusion and implications

Patients at high risk of cardio-vascular, respiratory, or gastrointestinal postoperative complications may benefit from CNB. This is especially true for optimal thoracic epidural analgesia for major open thoracic and abdominal operations, but also for obstetric analgesia and anaesthesia. The risks of SH and spinal cord injury are higher in elderly patients, in patients on antihaemostatic drugs, patients having spinal stenosis and patients with renal impairment. Patients receiving interventional spinal procedures for chronic pain are at higher risk than those who receive neuraxial procedures for acute pain. Weighing benefits from central neuraxial pain-relieving procedures against increased risk of bleeding requires knowledge of pharmacology of antihaemostatic drugs, risk factors due to patients' co-morbidities, and the ability to conduct optimal CNB-procedures. Possible complications of alternatives to CNB should always be considered, GA in particular for obstetric patients. Peripheral nerve or nerve plexus blocks may require subtoxic doses of local anaesthetics for prolonged blocks. Vigilance and a robust regimen for monitoring are required in order to detect early signs of SH, as well as an agreed-upon protocol for appropriate treatment of these rare but potentially tragic complications.

Optimal pain management is a prerequisite for enhanced recovery after surgery, but there are a multitude of additional concerns that surgeons and anaesthesia providers need to optimise for the best outcome and least risk of complications [97].

Authors' statements

Research funding: In-house departmental support has been available to some of the authors.

Conflict of interest: None declared by any of the authors.

Informed consent: Not applicable.

Ethical approval: This practise advisory document is based on literature review and consensus between experienced experts. No ethical board review was considered necessary.

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