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Review Article

Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

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Background: Central neuraxial blocks (CNBs) for surgery and analgesia are an important part of anaesthesia practice in the Nordic countries. More active thromboprophylaxis with potent antihaemostatic drugs has increased the risk of bleeding into the spinal canal. National guidelines for minimizing this risk in patients who benefit from such blocks vary in their recommendations for safe practice.
Methods: The Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) appointed a task force of experts to establish a Nordic consensus on recommendations for best clinical practice in providing effective and safe CNBs in patients with an increased risk of bleeding. We performed a literature search and expert evaluation of evidence for (1) the possible benefits of CNBs on the outcome of anaesthesia and surgery, for (2) risks of spinal bleeding from hereditary and acquired bleeding disorders and antihaemostatic drugs used in surgical patients for thromboprophylaxis, for (3) risk evaluation in published case reports, and for (4) recommendations in published national guidelines. Proposals from the taskforce were available for feedback on the SSAI web-page during the summer of 2008.
Results: Neuraxial blocks can improve comfort and reduce morbidity (strong evidence) and mortality (moderate evidence) after surgical procedures. Haemostatic disorders, antihaemostatic drugs, anatomical abnormalities of the spine and spinal blood vessels, elderly patients, and renal and hepatic impairment are risk factors for spinal bleeding (strong evidence). Published national guidelines are mainly based on experts' opinions (weak evidence). The task force reached a consensus on Nordic guidelines, mainly based on our experts' opinions, but we acknowledge different practices in heparinization during vascular surgery and peri-operative administration of non-steroidal anti-inflammatory drugs during neuraxial blocks.
Conclusions: Experts from the five Nordic countries offer consensus recommendations for safe clinical practice of neuraxial blocks and how to minimize the risks of serious complications from spinal bleeding. A brief version of the recommendations is available on http://www.ssai.info.

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Incidence of spinal bleeding caused by spinal or epidural anaesthesia/analgesia

In the Nordic countries, we have a strong tradition of using a central neuraxial block (CNB), including spinal/subarachnoid (SPA), epidural (EDA), and combined spinal–epidural (CSE) techniques, for anaesthesia and pain relief. This tradition is based on the conviction that CNB, in selected cases, is beneficial to the patients. Complications are relatively rare, the most serious ones being spinal haematoma (SH) and epidural abscess, which may both lead to permanent paraplegia if adequate treatment is not instituted promptly. In a large survey, covering all complications associated with CNB in Sweden during the 1990s,[1] 33 cases of SH, corresponding to an incidence of 1 : 52,000 CNBs, were reported. Notably, 24 cases (72%) occurred during the second half of the decade. Further, the incidence was nearly 10 times higher after EDA or CSE (1 : 18,000), than after SPA, (1 : 160,000). The highest incidence of SH was seen

among elderly female patients after a major orthopaedic surgery, often under CSE (1 : 3600). A high incidence was also found after vascular surgery.[1]

The need for common guidelines in the Nordic countries

The widespread use of low molecular weight heparins (LMWH) for prophylaxis of post-operative thromboembolic complications in later years,[2,3] and the commonly used drugs that inhibit platelet aggregation, have increased the risk of SH.[1,3] This has prompted several national anaesthetists' societies to compile guidelines, with varying recommendations, in order to reduce the risk of spinal bleeding when CNB is indicated in patients receiving antihaemostatic drugs, such as LMWH, vitamin-K antagonists (VKA), or platelet inhibitors.[2,3] Because of a high degree of interchange and collaboration among health care providers in the five Nordic countries, the Board of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) established a task force to develop Scandinavian guidelines for evidence-based clinical practice of CNB in peri-operative and obstetrical settings in the presence of an increased risk of spinal bleeding.

Aims

In order to help clinicians in the often difficult evaluation of risks and benefits in individual patients, the task force focused on the following issues:

- Benefits of CNB for various types of surgery and obstetric procedures.
- Risk factors for spinal bleeding during the practice of CNB.
- A Scandinavian consensus on recommendations to minimize the risks of intraspinal bleeding when CNB is indicated.
- Strength of evidence for the agreed recommendations.

Methods

A literature search was performed using PubMed and appropriate key words to access MEDLINE citations, references found in reviews, published guidelines, case reports, and other relevant articles.

Table 1

The grading scheme and hierarchy of evidence used in this guideline.

Evidence category	Source of evidence:
Ia – b	Meta-analysis of randomized controlled trials (Ia), or At least one randomized controlled trial (Ib)
IIa – b	At least one controlled study without randomization (IIa), or At least one other type of quasi-experimental study (IIb)
III	Non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Expert committee reports or opinions and/or clinical experience of respected authorities

Recommendation grade	Evidence directly based on:
A	Category I evidence
B	Category II evidence, or Extrapolated recommendation from category I evidence
C	Category III evidence, or Extrapolated recommendation from category I or II evidence
D	Category IV evidence, or Extrapolated recommendation from category I, II, or III evidence

Adapted from Eccles and Mason.[4]

The literature in English, German, and Scandinavian languages was considered. The category of available evidence and the recommendation grade were assessed according to Eccles and Mason (Table 1).[4] If we could not find any published evidence, the recommendation is based on the consensus opinion of the members of the task force, i.e. recommendation grade D. The list of references comprises recent reviews and key references from which the reader can find more comprehensive documentation. Preliminary proposals from the taskforce were available on the SSAI web-page during the summer of 2008 for feedback from members of the national societies of anaethesiologists.

Results

Benefits of CNB for surgical and obstetric procedures

Indications for spinal and epidural blocks were originally to provide surgical anaesthesia. With the introduction of epidural catheters, EDA has been increasingly used outside the operating room for

post-operative, obstetric, and chronic pain relief,[5] and it has become an indispensable tool in pain management.

Table 2 lists some surgical and obstetric procedures in which CNB may improve peri-operative comfort, morbidity, or mortality. The list is not complete and outcome varies with details of CNB techniques and with patient factors. The evidence indicated may be influenced by patient and practice factors, and a risk–benefit analysis has to be performed separately, in each individual case. Fear of a major complication should not deprive the patient of this form of treatment when the benefits outweigh the risks.

Benefits of epidural anaesthesia and analgesia (EDA)

EDA improves comfort and facilitates mobilization after surgery. During surgery, epidural analgesia is used in combination with general anaesthesia (GA) in order to reduce the anaesthetic drug requirements, and to facilitate a smooth awakening from anaesthesia to a pain-free post-operative state. Post-operative epidural analgesia can provide high-quality dynamic pain relief, thereby increasing patient comfort and markedly facilitating early mobilization and rapid rehabilitation after surgery.[6–8]

EDA reduces post-operative complications and morbidity, and possibly mortality. Epidural anaesthesia and analgesia have been shown to reduce cardiovascular and pulmonary morbidity and possibly also post-operative mortality.[6–12] In a systematic review of over 9500 patients who received neuraxial anaesthesia, Rodgers et al.[10] demonstrated a reduced 30-day mortality and morbidity (venous thrombosis, pulmonary embolus, myocardial infarction (MI), pneumonia, respiratory depression, renal failure) after thoracic epidural or

Table 2

Surgical and obstetric procedures in which a central neuraxial block (CNB) may improve peri-operative outcome – compared with general anaesthesia (GA).

Procedures	Type of CNB*	Potential advantages of CNB compared with GA or opioid analgesia	Benefit on pain (comfort), morbidity, or mortality	Evidence category†
Intraoperative pain (combined with GA, if necessary)	EDA	Preventing early post-operative pain	Comfort	Ia
	SPA	Reduced need for anaesthetics and analgesics	Morbidity	Ia
Severe obstetric pain	EDA/ CSE/ SPA	Optimal pain relief	Comfort	Ia
		Improved neonatal Apgar and pH	Morbidity	Ia
Post-operative pain relief (after CNB or CNB+GA for surgery)	EDA	Reduced post-operative pain, especially on moving	Comfort	Ia
			Morbidity	Ia
		Early mobilization and gastrointestinal-recovery	Morbidity/mortality	Ia
		Reduced incidence of cardiovascular events and renal failure	Morbidity/mortality	Ia
		Reduced risk of respiratory failure	Morbidity	Ia
		Reduced risk of chronic pain after surgery	Morbidity	III
Caesarean section	SPA/ EDA	Avoidance of airway complication in the mother	Morbidity	IIb
		Maternal mortality reduced	Mortality	III
Hysterectomy	SPA	Less risk of chronic post-operative pain	Morbidity	III
TUR-Prostate	SPA	Early detection and treatment of TURP syndrome	Mortality	IIb
Vascular surgery – abdominal aortic and lower extremity	EDA/ SPA	Reduced risk of graft occlusion, cardio-pulmonary and renal complication	Morbidity	Ia
Alternative to (or combined with) GA in selected patients with intermediate-to-high risk non-cardiac surgery‡	SPA/ EDA	Reduced risk of cardiopulmonary complication	Morbidity	Ia
		Reduced 30 days mortality	Mortality	IIa
Tetraplegia+operation in the pelvic region	SPA/ EDA	Inhibition of sympathetic hyper-reflexia	Morbidity	III
			Mortality	IV

*SPA And EDA are not uniform terms: low dose local anaesthetic drugs combined with an opioid and an α_2-receptor agonist, and with EDA continued after major surgery may entail more benefits on post-operative morbidity than single shot SPA or EDA.
†Evidence category I–IV (see Table 1).
‡Examples: major orthopaedic surgery, large bowel surgery, liver resection, liver transplantation, Whipple procedure, pneumonectomy, lobectomy, gastrectomy, oesophagectomy, nephrectomy, cystectomy.
In the text, a 'strong indication' implies an indication with at least likelihood of reduced peri-operative morbidity.

SPA. More recent controlled trials and reviews confirm reduced morbidity, but not always reduced mortality.[6–8] The latter may reflect an improvement in post-operative care, with closer surveillance and more aggressive anti-thrombotic prophylaxis.[7]

However, data from an administrative database showed that patients who received thoracic epidural analgesia during and after segmental lung resection had significantly lower mortality than patients who did not receive this form of analgesia.[11] A recent, large, population-based cohort study documented a statistically significant lower 30-day mortality in patients undergoing an intermediate-to-high risk non-cardiac surgery under epidural compared with non-epidural techniques.[12] Furthermore, maternal mortality from a caesarean section (CS) is reduced with spinal or EDA compared with GA.[13] (see below)

EDA, or CSE, for labour pain. There is strong evidence that epidural analgesia provides more effective pain relief in labour than other analgesic techniques, and that it does not increase the risk of CS,[14] but it may be associated with a longer second stage of labour and an increase in instrumental delivery.[14]

CSE analgesia or low-dose EDA started in early labour may decrease the incidence of instrumental delivery and reduce the duration of labour, compared with systemic opioid analgesia or higher concentrations of epidural local anaesthetics.[15,16] However, there are no randomized studies comparing CSE or low-dose epidural analgesia with 'natural childbirth' without pharmacologic pain relief.

Epidural analgesia is increasingly recommended in diabetic and obese women who are presumed to have a greater risk of complicated labour, including CS.[17] Thus, the early insertion of an epidural catheter may also facilitate management when there is a sudden need for regional anaesthesia for CS.

Why benefits of EDA vary: epidural analgesia is not a uniform technique. Optimal epidural analgesia is a technically demanding and labour-intensive technique. Conflicting outcomes of studies are most likely due to wide variations in establishing, maintaining, and monitoring of the effects and adverse events of EDA.[18] The segmental level of catheter placement, and types and doses of drugs used, all significantly influence the effects and safety of EDA. The lack of a protocol for urgent management of intraspinal bleeding or infection is a serious threat to the safe outcome of EDA.[18–20]

We are convinced that the full benefit is more likely to be achieved if segmentally optimized epidural analgesia is started before surgery and prolonged throughout the most painful post-operative period. Using epidural analgesia, rather than epidural anaesthesia, the benefits are maximized and the risks of adverse effects are minimized. A high degree of preparedness is extremely important for discovering and treating adverse effects early, before an irreversible damage is established.[18–20]

An acute post-operative pain service (team) (APS)

An APS with sufficient resources for education and training of ward nurses and other personnel taking care of post-operative and obstetric patients, for quality assurance and monitoring of epidural practice, is a decisive success factor.[18–21]

Important differences between thoracic and lumbar epidurals

A low lumbar EDA causes motor block and interferes with post-operative mobilization, spontaneous urination, and monitoring of spinal cord functions. Lumbar epidural anaesthesia and CSE for surgery of the lower part of the body is good clinical practice, but lumbar EDA may not be the optimal post-operative pain management strategy because of urinary retention and leg weakness (Table 3).

Table 3

Differences between the effects of thoracic and low lumbar epidural analgesia.[18,19]

	Epidural anaesthesia/analgesia with low doses of local anaesthetic and opioid		
Effect on	Thoracic	Lumbar	Evidence category
Coronary arteries	Dilatation	Constriction (compensatory)	Ib
Myocardial oxygen supply/demand ratio	Up	Down	Ib
Post-operative myocardial ischemic events	Decreased	May be increased	IIa
Post-operative lung function	Improved	Unaffected	Ib
Leg mobility and bladder function	Unaffected	Impaired	Ia

Benefits of spinal anaesthesia (SPA)

Alternative to GA in high-risk cardio-pulmonary patients. SPA has been regarded a favourable alternative to GA in patients with severe cardiovascular disease, pulmonary disease, or severe airway problems. The practice of adding an opioid and reducing the dose of local anaesthetic, resulting in less sympathetic blockade, has strengthened this indication. However, new general anaesthetic agents with favourable cardiovascular profiles, improvements in airway management, and improved monitoring have reduced the importance of this indication of SPA.[6]

Caesarean section (CS) under SPA or CSE anaesthesia–analgesia. The Confidential Enquiries into Maternal Deaths in UK have identified and analysed the causes of maternal mortality and morbidity during more than 50 years. A majority of the anaesthesia-related deaths in these reports have been associated with GA for CS and were mostly due to intubation difficulties. GA is still associated with a mortality ratio of 1 : 20,000,[22] and maternal morbidity and mortality is significantly reduced with regional anaesthesia. Thus, neuraxial blocks remain the standard of care in anaesthesia for CS.[13,22]

SPA for transurethral resection of the prostate (TURP). For a long time, regional anaesthesia has been the gold standard for TURP, mainly because it enables an earlier and more reliable detection of the TURP syndrome than with GA, but also because regional anaesthesia has a more favourable haemodynamic profile.[23] In a recent study, it was demonstrated that a saddle block, with low doses of bupivacaine and fentanyl, was the most favourable anaesthetic technique for TURP when compared with EDA or conventional SPA.[24]

Miscellaneous indications for SPA. For intrapelvic operations in patients with a spinal cord lesion above T6, SPA (in combination with GA when needed) is the gold standard, in order to prevent sympathetic overflow, which may result in serious cardiovascular incidents, or even death.[25]

In major orthopaedic surgery of the lower limbs, especially hip surgery, important benefits of SPA are reduced blood loss and reduced post-operative thromboembolism.[26] However, blood-saving techniques and post-operative thromboprophylaxis have reduced these differences, and more recent studies have not been able to fully reproduce these results.[6,27]

Risk factors for spinal haemorrhage

A SH can have three different locations: epidural, subdural, or subarachnoid. In the following, the term spinal haematoma or spinal haemorrhage (SH) will be used, regardless of the location.

Controlled studies to evaluate the causes of SH are not feasible. Therefore, estimates of the risks of SH and published guidelines for CNB in the presence of likely or possibly increased risk of SH are all based on knowledge of pharmacodynamics, pharmacokinetics, and known interactions between drugs that have effects on primary haemostasis (formation of a platelet plug), secondary haemostasis (development and stabilization of a fibrin mesh), and fibrinolysis.

Studies of drug effects on haemostasis and surgical bleeding, as well as interpretation of case reports, are also important sources of information. When available data are insufficient to provide for clinical evidence, 'experts' opinions' serve as a basis for our recommendations (Table 1).

Because of the low incidence of complications from SH, and because there are often several possible causes, exact risks are not possible to estimate. Furthermore, the number of unpublished cases is large. Thus, of 33 cases of SH identified from administrative databases in Sweden in the 1990s,[1] only six were published in the literature.[28–33]

Three different kinds of risk factors for the development of post-CNB SH can be distinguished: procedure, drug, and patient related. These will be further discussed below. It should be noted, however, that haemorrhage may also occur in patients without any known risk factors.[34,35]

Procedure related risk factors

Complicated punctures, i.e. difficulties in locating the epidural or the subarachnoid spaces, leading to several attempts to establish the block, and/or the appearance of blood in the needle or the catheter after entering the epidural space, are independent risk factors for SH, and are seen in a large number of case reports on SH.[1,32,33] Moen et al.[1] reported complicated punctures in 11/26 cases with post-CNB SH (42%), and Wulf[33] reported it in 21/51 cases (41%) in his review. In case reports published after Wulf's review, we have identified 23 cases with complicated punctures in 62 reports on post-CNB SH (37%).

Drugs that need special attention before a neuraxial block

In a patient with disturbed haemostasis, CNB carries an increased risk of spinal bleeding. This

risk has to be carefully evaluated against any possible benefits from a CNB at the pre-anaesthetic visit. In addition to a history of bleeding tendencies, any intake of antihaemostatic drugs should be carefully documented.

If a CNB is likely to be beneficial for a patient on antihaemostatic medication, the recommended time intervals between neuraxial puncture or manipulation (partial retraction or removal) of a CNB catheter and drug intake (Tables 4 and 5) will reduce, but not eliminate, the risk of spinal bleeding.

The recommended time limits from the last dose of a drug to CNB are generally based on the plasma half-life of the drug. The time limits from CNB to the next dose are based on the time from intake of the drug to its peak effect or maximum plasma concentration (T_{max}), taking into account that it takes at least 8 h for a platelet plug to solidify into a stable clot.[27]

When difficulties are encountered, requiring multiple attempts or causing a 'bloody tap', the need for the CNB should be re-evaluated. In case of a bloody tap, an extension of the interval to the next dose of an antihaemostatic drug should be considered.

Factors IIa and/or Xa inhibitors (Tables 4 and 8)

Unfractionated heparin (UFH). UFH inhibits factor IIa (thrombin) and factor Xa equally. It is mainly used for the treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE), and for intraoperative prophylaxis against thromboembolic complications during vascular surgery. The effects of prophylactic doses ($\leq$ 5000 U) of subcutaneous (s.c.) UFH are unpredictable, inasmuch as they do not exert measurable effects on clotting variables in most, but may reach therapeutic levels in a few patients.[36] Therefore, UFH is no longer recommended for thromboprophylaxis in the Nordic countries.

Higher doses ($>$5000 U) are administered intravenously (i.v.) for the treatment of DVT and PE and for intraoperative heparinization. After an i.v. bolus, the peak effect is reached immediately, and the half-life is 1–2 h, depending on the dose. Its effect is monitored by activated prothrombin time (APTT), which should be prolonged two to three times for a therapeutic effect. CNBs are rarely indicated in patients under heparin treatment. In those cases, it is generally appropriate to turn off the heparin infusion for 3–4 h until APTT is normalized. We recommend a 6-h delay after surgery before the infusion is restarted.

Heparinization with i.v. doses up to 100 U/kg, given at least 1 h after CNB, is routine in many hospitals in the Nordic countries and elsewhere during extracerebral vascular surgery.[37] This routine may, however, interfere with clot consolidation in the spinal canal after a recent CNB puncture, because clot consolidation may take at least 8 h.[27]

In a cohort study of 684 patients, Ruff and Dougherty[38] reported SHs in almost 2% of patients after diagnostic lumbar puncture with a 20 G needle, performed soon after systemic heparinization to treat acute cerebral ischaemia. They identified three risk factors for haematoma: concomitant use of acetylsalicylic (ASA), traumatic lumbar needle insertion, and heparinization within 60 min after puncture.[38] That study and the study by Rao and El-Etr[39]are behind the recommendations to wait 1 h from a CNB to heparinization.[40,41]

However, in the study by Ruff and Dougherty[38] spinal needles of 20 G were used, while in CNB for vascular surgery, epidural needles of larger size and catheter insertion are generally used. According to published series of neuraxial block for vascular surgery, patients receiving systemic heparinization during surgery, spinal–epidural haematoma is a rare complication if there are no other risk factors. In the study by Rao and El-Etr[39] in 4011 peripheral vascular surgery patients, heparin doses were carefully titrated (using activated clotting time) to an average dose of only 2600 U. In case of a bloody tap, the CNB attempt was interrupted, and the whole procedure was postponed to the following day.[39] Moen et al.[1] reported eight haematomas in vascular surgical patients during 1990–1999 in Sweden, yielding an estimated incidence of $>1:4000$ when combined with operation data of the Vascular Registry of Sweden. In the review of reported case series until 1995 (51 case reports), Wulf[33] concluded that full heparinization during vascular surgery does carry an increased risk. Tryba[40]concluded that intraoperative heparinization is not an absolute contraindication in patients with a recently inserted CNB catheter, but that it should be regarded as a major risk factor for SH, that a dose limit for heparin should be applied, and that the patients must be carefully observed in the post-operative period.

After prolonged use (more than about 5 days), UFH may cause a decrease of approximately 50%

Table 4

Recommendations on antihaemostatic treatment when central neuraxial block (CNB) is indicated: heparins, Xa-inhibitors, vitamin K-antagonists, and platelet inhibitors.

Recommended minimum time intervals between the last dose of a certain drug and CNB, and between CNB and first dose or iteration of the drug.
The same recommendations apply for manipulation or removal of a catheter.
Patients with delayed drug elimination (e.g., renal impairment) may require longer intervals.
Combinations of antihaemostatic drugs increase the risk of bleeding.

Antihaemostatic drug	Drug ⇨ CNB or cath. manipulation	RG	CNB or cath. manipulation ⇨ Drug	RG
Heparins/Xa-inhibitors				
Unfractionated heparin (UFH)				
≤ 5000 U (70 U/kg)/day	4 h, normal APTT and platelets*		1 h†,‡	
>5000 U (70–100 U/kg)/day	4 h, normal APTT and platelets*,†	D^P	6 h recommended, 1–2 h common practice‡	D
>100 U/kg/day	4 h, normal APTT and platelets*,†	D^P	6 h recommended,‡ start EDA evening before surgery†,‡	D
Low molecular weight heparin (dalteparin or enoxaparin)				
≤ 5000 U or ≤ 40 mg/day	10 h§	D^P	6 h recommended, 2–4 h common practice¶	D^P
>5000 U or >40 mg/day	24 h	D^P	6 h recommended, 2–4 h common practice¶	D^P
Fondaparinux				
≤ 2.5 mg/day (Xa+at)	36 h	D^P	6 h	D^P
Rivaroxaban (pi/oral) (Xa)	18 h	D	6 h	D
Apixaban (pi/oral-Xa-inh)	Data not available		6 h	D
Vitamin K antagonists				
Warfarin; phenprocoumon	(1–4 days, dose dependent) INR ≤ 1.4–2.2 – see Table 7 ‖	D	Restart after catheter removal ‖	D
Platelet inhibitors				
Acetyl salicylic acid (ASA)	12 h in patients on secondary prevention**	D	Resume as soon as possible after surgery	D
	3 days in others (1 week at doses >1 g/day)	D^P	Resume after surgery	
Dipyridamol	No interval required	D^P	No interval required	D
NSAID	See Table 6	D^P	2 h††	D
Clopidogrel	5 days‡‡	D^P	After catheter removal	D
Ticlopidin	5 days‡‡	D^P	After catheter removal	D
Prasugrel	Probably 5 days – insufficient experience for recommendations	D^P	After catheter removal	D

RG, Recommendation Grade (Table 1). RG are mostly based on experts' opinion, in some cases on pharmacokinetic data (indicated with a ^{P}).
*__After 5 days of UFH treatment__, follow daily platelet counts in order to rule out Heparin Induced Thrombocytopenia (HIT-II).
†__If surgery requires intraoperative UFH >5000 U__, consider inserting the epidural catheter in the evening before.
‡One to 2 h after CNB, an i.v. dose of 50–100 U/kg **is common practice during extracranial vascular surgery**. However, an increased risk of bleeding is possible with doses 70–100 U/kg.
§Emergency cases on LMWH 2500 U or 20 mg twice daily, and strong indication for SPA (because benefit/risk is high, seeTable 2; e.g., hip fractures, urgent Caesarean Section): **0 h**.
¶The balance between risk of bleeding and thrombosis is optimal when the first dose is given 6 h after the end of elective surgery in non-thrombogenic patients. Major cancer surgery, prolonged surgery in very ill patients, and those >75 years may need preoperative or intraoperative thromboprophylaxis.
‖Start LMWH prophylaxis when INR <2.0 in patients at high risk of a thromboembolic episode (e.g., mechanical mitral valve, aortic valve, recent (<6 months) arterial or venous thromboembolic episode – see Table 11B).
**In patients with unstable angina and after stroke/TIA, MI, PCI or CABG – see Table 11A.
††In a patient with an indwelling EDA catheter and simultaneous LMWH or other antihaemostatic treatment, non-selective NSAIDs should be avoided when catheter manipulations are indicated; COX-2 inhibitor preferable.
‡‡Five days after discontinuing clopidogrel or ticlopidin >50% of platelets have regenerated which is sufficient for primary haemostasis.

in the platelet counts because of heparin-induced thrombocytopenia type II (HIT-II)(Table 4). HIT-II is associated with a paradoxical increase in the risk of thromboembolic events and an increased bleeding tendency.[42,43] The more benign HIT-I can occur already after 2–3 days on UFH.[42]

The antihaemostatic effects of UFH can be completely reversed by protamine.

Recommendations

- ***In patients treated with a UFH infusion, we recommend that this is discontinued no less than 3–4 h before an intended CNB, and that a normalization of the APTT value is documented. The infusion may be restarted 6 hours after a CNB. (Recommendation grade D; evidence category IV).***
- ***In patients treated with UFH for more than 5 consecutive days, a platelet count is mandatory in order to monitor for HIT-II, before the initiation of a CNB. (Recommendation grade C; evidence category III).***
- ***If a procedure requires i.v. heparinization, we recommend a delay of no less than 1 h after a CNB before UFH is administered at a maximum bolus dose of 5000 U or 70 U/kg BW. (Recommendation grade D; evidence category IV).***
- ***Whereas higher doses, up to 100 U/kg, are commonly used in vascular surgery, pharmacological properties of the drug indicate that these doses may increase the risk of bleeding. Therefore, this practice requires a careful weighing of the risk/benefit ratio in each patient and vigilant monitoring for early signs of SH. (Recommendation grade D; evidence category IV).***
- ***At doses above 100 U/kg, based on the pharmacologic properties of the drug, the risk of bleeding is probably significantly increased and we recommend up to a 6 h delay after CNB before UFH is administered in such doses. (Recommendation grade D; evidence category IV).***

LMWHs (Table 4). In common with UFH, LMWHs inhibit factors IIa and Xa, but inhibit more selectively factor Xa, the ratio II/X inhibition being approximately 1:3. For thromboprophylaxis, the most commonly used LMWHs in the Nordic countries are dalteparin in s.c. doses up to 5000 U s.c. or enoxaparin up to 40 mg s.c. daily in adults. For treatment of DVT or PE the daily therapeutic doses are generally 100 U/kg (or 1 mg/kg) twice daily s.c.[42] Half-lives of LMWH are 3–7 h, depending on the dose, and the peak effect of a s.c. dose is reached within 3 h. LMWHs are excreted by the kidneys. In patients with creatinine clearance below 30 ml/min, the half-life is prolonged, increasing the risk of accumulation and major bleeding.[44,45] A dose reduction by 50% has been recommended in such patients.[27]

The bleeding tendency and risk of SH were reported to be more pronounced with LMWHs than with UFH.[2] However, this risk is highly dose dependent: in the United States, there was a cluster of 40 cases with post-CNB SHs after enoxaparin treatment reported to the FDA within 5 years of its release,[46] most of them elderly women. One possible reason for this high incidence of SH, much higher than in Europe, was the dose regimen of enoxaparin, 30 mg enoxaparin every 12 h. A twice-daily dose regimen may lead to accumulation of the drug after a few days, because the second dose is given while a significant part of the activity of the first dose is still present.[46] Notably, in a majority of these cases, the prophylaxis was started more than 6 h post-operatively, i.e. after initiation of the CNB, and many of the haematomas did not appear until more than 2–3 days after a CNB or catheter removal, especially in the elderly.[2,46] The high plasma concentrations of LMWH may lead to profibrinolytic effects, weakening the haemostatic clot.[2] In order to prevent overdosing of LMWH, kidney function should be monitored in the post-operative period in elderly patients with CNB.

HIT-II occurs in about two to three per 100 patients on UFH prophylaxis or treatment for more than about 5 days, but only in 1–2 per 1000 patients on LMWH.[43] Platelets should be monitored daily after 5 days of UFH administration, whereas a weekly platelet count may be reasonable during ongoing LMWH administration.[43]

The antihaemostatic effects of LMWH can be reduced by protamine.

Timing of the first dose of LMWH for thrompboprophylaxis after surgery

The common clinical routine in the Nordic countries has been to initiate thromboprophylaxis with LMWH in the evening of the day before surgery. In those cases, most guidelines recommend a waiting time of 10–12 h between the last dose of LMWH and a CNB.

In the last decade, several studies and meta-analyses have shown that a post-operative start of LMWH prophylaxis will reduce the amount of surgical bleeding without increasing the risk of post-operative thrombosis.[47,48] Today, most hospitals in the Nordic countries have adopted this routine, and usually administer the first LMWH dose 2–6 h after the end of surgery, in common with other European countries.[49]

The post-operative start of thromboprophylaxis has the obvious advantage that there is no haemostatic drug effect at the time of initiation of a CNB, or during or immediately after surgery.[47] This routine should therefore reduce the risk of spinal

or surgical bleeding from interactions with platelet inhibitors taken until the day before surgery.

Highly thrombogenic patients (e.g. patients with malignancy, hip fracture, advanced age) may require a preoperative start of thromboprophylaxis.

Recommendations

- ***In patients treated with LMWH prophylactically (≤ 5000 U dalteparin or ≤ 40 mg enoxaparin per day s.c.), we recommend that there should be a delay of no less than ten hours between the last LMWH dose and the initiation of a CNB. (Recommendation grade D; evidence category IV)***.
- ***At higher doses, the delay should be no less than 24 h. (Recommendation grade D; evidence category IV)***.
- ***In patients with severely reduced renal function (GFR <30 ml/min), these intervals should be prolonged. (Recommendation grade D; evidence category IV)***.
- ***Following a CNB (or manipulation of a catheter), a delay of no less than 6 h is recommended before the next dose of LMWH is administered. (Recommendation grade D; evidence category IV)***.
- ***Monitoring of post-operative kidney function (serum creatinine) is recommended in elderly patients (>75 years) with an indwelling epidural or a subarachnoid catheter during LMWH treatment. (Recommendation grade D; evidence category IV)***.
- ***The recommended time for the first dose of LMWH is about 6 h (2–6 h acceptable) after elective surgery in non-thrombogenic patients. (Recommendation grade C; evidence category IV)***.

Factor X selective inhibitors (Tables 4 and 8)

Fondaparinux. In Scandinavia, fondaparinux is licensed for the prevention of VTE in high-risk patients (post-operative and other). It is a pentasaccaride that acts indirectly on factor Xa via antithrombin III. It is highly selective, without any effect on factor IIa (thrombin) or platelets. Its half-life is 17–20 h in normal individuals, but this may be significantly prolonged in patients with renal impairment. In the peri-operative setting, fondaparinux treatment should start 6 h post-operatively, provided surgical haemostasis is secured (manufacturer's recommendation). Kidney function should be monitored. There are no reports about spinal haemorrhage where fondaparinux has been implicated.

Recommendations grade D; evidence category IV. All are recommendation grade D; evidence category IV:

- ***The first dose is administered no less than 6 h after the completion of a CNB***.
- ***In patients with ongoing treatment, fondaparinux should be withheld at least 36 h before the initiation of a CNB***.
- ***In patients with renal impairment, a longer pause is needed***.

Rivaroxaban. Rivaroxaban is a direct inhibitor of factor Xa. It is an oral (and parenteral) formulation, licensed for post-operative thromboprophylaxis after hip or knee surgery in the Nordic countries since the autumn of 2008. The recommended dose is 10 mg once daily, starting 6 h after the end of surgery, and continued for 2–5 weeks. Its half-life is 7–11 h. There are no reports about SH where rivaroxaban has been implicated.

Recommendation

- ***Following a CNB, there should be a delay of no less than 6 h before rivaroxaban treatment is initiated (24 h if the procedure has been traumatic or bloody)***.
- ***In patients with ongoing treatment, there should be a delay of no less than 18 h between the last dose and the initiation of a CNB, or manipulation of an EDA catheter. (Recommendation grade D = Manufacturer's recommendations).***

Apixaban. Apixaban is a direct factor Xa inhibitor, with oral and parenteral formulations. It is in phase III development, waiting for registration in the Nordic countries. It is intended for post-operative thromboprophylaxis starting 6 h after the end of surgery, and lasting up to several weeks in high-risk patients.

There are no reports about SH where apixaban has been implicated, but, as of today, there are insufficient data to issue any recommendation with regard to CNB.

Thrombin inhibitors (Table 5)

Dabigatran. Dabigatran etexilate is an inactive pro-drug, which is converted to dabigatran in plasma. It is a direct thrombin inhibitor, which has been released on the Scandinavian markets in 2008. After an oral dose of dabigatran etexilate, the peak effect is reached within 2–4 h and the plasma half-life

Table 5

Recommendations on antihaemostatic treatment when central neuraxial block (CNB) is indicated – thrombolytics, activated protein C, thrombin inhibitors – all recommendations are based on experts' evaluation of pharmacokinetics ($RG = D^P$).

Recommended minimum time intervals between the last dose of a certain drug and CNB (left column), and between CNB and first dose or iteration of the drug (right column). The same recommendations apply for manipulation or removal of a catheter. **Patients with delayed drug elimination (e.g.,renal impairment) may require longer intervals. Combinations of antithrombotic drugs increase the risk of bleeding.**

Antihaemostatic drug	Drug ⇨ CNB or cath. manipulation	CNB or cath. manipulation ⇨ Drug
Thrombolytic drugs		
Streptokinase	24 h*	**At least 2 h, but clots** are not completely stabilized until about 10 days, and risk of bleeding is probably increased if any thrombolytic drug is given before 10 days
Alteplase	6 h*	
Reteplase	24 h*	
Tenecteplase	Data not available*	
Activated protein C		
Drotrecogin alfa	Data not available	12 h
Thrombin inhibitors (treatment of HIT-II and VTE-prevention)		
Dabigatran	Data not available	6 h
Bivalirudin	Data not available	Data not available
Argatroban	Data not available	Data not available
Lepirudin	Data not available	Data not available
Epoprostenol	Data not available	Data not available

*Monitoring of fibrinogen levels may be helpful.

ranges from 14 to 17 h after multiple dose administration.[27] Dose recommendations are 110 mg 1–4 h after surgery, and thereafter 220 mg/day for up to 35 days. Its elimination is largely dependent on kidney function, and dabigatran is therefore contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). In patients with creatinine clearance 30–50 ml/min, and in patients >75 years, the daily dose is reduced to 150 mg. It is licensed for post-operative thromboprophylaxis, with extended oral use after hip surgery. There are no reports about SH where dabigatran has been implicated. The manufacturer states that the first dose should wait a minimum of 2 h after removal of an epidural catheter.

Recommendation

- ***We recommend that the first dose of dibigatran should be given no less than 6 h after a CNB or catheter removal. (Recommendation grade D; evidence category IV).***

Other thrombin inhibitors (Table 5). These are intended for treatment of HIT, a situation in which CNBs are generally contraindicated.

Platelet inhibitors (Tables 4, 6 and 8; see also Table 12)

Acetyl salicylic acid (ASA). ASA was initially intended for treatment of pain and rheumatism. One important problem with ASA is bleeding complications, secondary to its platelet-inhibiting effects. Currently, its antiaggregatory effect is utilized in patients with an increased risk for a thromboembolic event. This is achieved with subanalgesic doses of ASA, 75–160 mg/day (analgesic dose >1 g/day). In low doses, ASA is rapidly deacetylated and thereby inactivated within 30 min. However, its platelet effects are irreversible and last for the entire life cycle of a platelet, i.e. 7–10 days. On the other hand, the regeneration of platelets is rapid, and the 'newborn' platelets are unaffected by ASA when the drug effect has disappeared. After 2–3 days, the number of healthy platelets is high enough to provide for a normal primary haemostasis.[50]

The main indications of low-dose ASA are prophylaxis in patients with an increased risk of an arterial thrombotic event, but without a history of angina pectoris, MI, or stroke, i.e.primary prevention, and prevention of a recurrent thrombotic event in patients with a history of angina pectoris, MI, or stroke, i.e. secondary prevention.

The risk of added bleeding because of low-dose ASA is negligible in most types of surgery. In a large meta-analysis of bleeding tendencies from ASA in various kinds of surgery,[51] it was found that this was slightly increased in TURP, but not in other forms of surgery (although analgesic doses increased bleeding after a tonsillectomy). However,

in intraocular, neurosurgical, and some plastic surgical procedures, even this minimally increased risk of bleeding from ASA may be significant.

We have found only one case report of spinal bleeding associated with CNB where ASA was the only recognized possible risk factor.[52] With regard to the widespread use of this drug, ASA is probably not an independent risk factor of spinal bleeding after neuraxial blocks.

However, the risk of SH may be increased if ASA is combined with another antihaemostatic drug (see below). Therefore, a careful analysis of the benefits of a CNB and the need to continue ASA treatment *vs* the risk of an SH is required if the patient has other antithrombotic medication or additional risk factors for bleeding; thus, many patients on ASA treatment also require venous thromboprophylaxis after major surgery (see above and Table 4).

Patients on secondary prevention have an increased risk of recurrent MI or stroke, and this risk may be aggravated by a rebound effect on platelets after ASA withdrawal.[53,54] In this group of patients, the drug-free interval should therefore be as short as possible. The benefits of primary prevention with ASA have recently been questioned,[55] and there is no report of any cardiovascular event shortly after its discontinuation. Therefore, ASA prescribed for primary prevention can and should be discontinued for at least 3 days before a CNB.

In emergency cases, the antihaemostatic effect of ASA can be rapidly reversed with desmopressin, if needed.[56]

Recommendations

- ***In patients on ASA for secondary prevention after a coronary event or stroke, we recommend that the treatment is continued up to the day before surgery and a planned CNB. ASA treatment should be restarted as soon as possible after the operation. (Recommendation grade C; evidence category III).***
- ***In patients on ASA for primary prevention of arterial thrombotic events, we recommend that treatment is interrupted 3 days before surgery and a planned CNB (or manipulation of a CNB-catheter). (Recommendation grade D; evidence category IV).***
- ***In patients on higher doses of ASA treatment for its analgesic or anti-inflammatory effects (>1 g/day), 7 days should be allowed to elapse between the last ASA dose and a CNB. (Recommendation grade D; evidence category IV).***
- ***In emergency cases, patients on ASA may receive a CNB, provided there is a strong indication for it (***Table 2***). In these cases, a single shot SPA is the preferred CNB technique. Reversal of the antihaemostatic effect with desmopressin (and tranexamic acid) should be considered. (Recommendation grade D; evidence category IV).***

Non-steroidal anti-inflammatory drugs (NSAIDs) (Tables 4, 6, 8). In common with ASA, NSAIDs are cyclo-oxygenase (COX) inhibitors, but while ASA acetylates and irreversibly inactivates COX, this is reversibly blocked by NSAIDs. In both cases, the formation of thromboxane A_2 is inhibited, resulting in reduced platelet aggregation. Because of its reversibility, the antihaemostatic effect of NSAIDs wears off simultaneously with the drug leaving the body, and it is independent of platelet regeneration. The platelet effect of various NSAIDs differs depending on the ratio between inhibition of the two forms of cyclo-oxygenase: COX-1 and COX-2. For instance, the effect on platelets of an i.v. dose of ketorolac or ketoprofen is more profound than that of diclofenac, which has a relatively more COX-2-inhibiting effect.[57] The NSAIDs with COX-2-specific inhibition do not have any effect on platelets.[58] However, even non-selective NSAIDs *per se* have only a minor effect on platelets and bleeding, and their clinical effect has dissipated before the drugs are completely eliminated from the body.

The impact of NSAID pharmacodynamics on the risk of a SH is a matter of controversy,[59] and there are differences between guidelines with regard to NSAIDs in various countries.[3] But in several case reports, an NSAID drug has been implicated in the cause of SH.[60–62] One meta-analysis concluded that non-selective NSAIDs increased post-tonsillectomy bleeding (higher incidence of reoperations due to bleeding),[63] although this could not be confirmed in two other meta-analyses.[64,65] Intraoperative use of ketorolac may worsen platelet function in patients under CNB,[66] but not in patients under GA,[67] possibly because GA does not reduce the general thrombogenicity caused by surgery.

NSAIDs, including selective COX-2 inhibitors,[68,69] have effects on kidney function, which are of clinical importance mostly by aggravating pre-existing renal impairment.[68] This may enhance the effect of drugs that are excreted by the kidneys, such as LMWH, fondaparinux, dabigatran, rivaroxaban, and less so apixaban.

NSAIDs have been used routinely for many years with pre-medication before surgery, with

the intention to reduce intra- and immediate post-operative pain. In the immediate peri-operative period, however, another analgesic may be safer, e.g. paracetamol or a selective COX-2 inhibitor.

Both non-selective NSAIDs and COX-2-specific inhibitors are associated with an increased risk of thrombotic cardiovascular events, and the higher the COX-2-selectivity, the higher this risk.[70] Even short-term, post-operative treatment with COX-2 inhibitors has been implicated.[71] Notably, one non-selective NSAID, ibuprofen, has been shown to interfere with the preventive effects of ASA.[72] All NSAIDs should be avoided if possible in patients with severe ischaemic heart disease, cerebrovascular, and peripheral vascular diseases, as well as in patients with a creatinine clearance <30 ml/min.

Intra-articular administration of NSAIDs can be used without regard to a recent SPA.

In common with ASA, the effect of NSAID on platelets can be reversed by desmopressin.[54]

Recommendations

- ***In patients treated with an NSAID, we recommend that the treatment is discontinued before a CNB. The drug-free intervals should be no less than those outlined in* Table 6. *(Recommendation grade D; evidence category IV).***
- ***In patients planned for CNB, we recommend that a non-selective NSAID is replaced by another analgesic in the immediate peri-operative period, e.g. paracetamol or a selective COX-2 inhibitor. (Recommendation grade D; evidence category IV).***
- ***In emergency cases CNB should be performed regardless of the interval, provided there is a strong indication for the CNB* (Table 2). *(Recommendation grade D; evidence category IV).***
- ***The same intervals as in* Table 6 *should be applied before manipulation or removal of an epidural catheter. NSAID can be started or restarted about one hour after CNB. (Recommendation grade D; evidence category IV).***

Table 6

Half-lives and recommendations regarding discontinuation of some NSAIDs.

Drug	$T_{1/2\beta}$ (h)	Recommended interval from last dose till CNB*
Diklofenac	1–2	12 h
Ibuprofen	2	12 h
Ketoprofen	2 h	12 h
Indomethacin	4.5 h	24 h
Ketorolac	4–6 h	24 h
Naproxen	10–17 h	48 h
Lornoxicam	4 h	24 h
Piroxicam	10–70 h	2 weeks
Tenoxicam	72 h	2 weeks
COX-2-specific inhibitors		No effects on platelets

*Recommendation grade D; evidence category IV.
In emergency cases no interval, provided there is a strong indication for the CNB.

Dipyridamol (Table 4). Dipyridamol is a weak platelet inhibitor, without any clinically important antihaemostatic effect. There is no need for discontinuation before a CNB.

Thienopyridines–adenosindiphospate (ADP) blockers (Tables 4 and 8)

Clopidogrel. Clopidogrel is a pro-drug that is converted in the liver into its active metabolite. This binds irreversibly to the platelet P2Y12 ADP-receptor, and thereby inhibits ADP-mediated activation and aggregation of the platelets.[73] Its half-life is longer (8–12 h), and it takes about 5 days for the platelet population to be restored enough after cessation of the drug to maintain a normal primary haemostasis.[73] ADP-blockers have two major indications: in place of ASA in patients with allergy or resistance to ASA, and together with ASA (dual therapy) for a limited period of time (1 month–1 year) after MI, stroke, or a percutaneous coronary intervention. As with ASA, the risk of a thrombotic event after discontinuation of clopidogrel is increased, and it is advisable to keep the drug-free interval as short as possible. In patients with no significant risk for thrombotic events (patients on primary prevention) clopido-

Table 7

Recommended levels of INR for neuraxial block at different levels of benefit from CNB.

	Potential benefit of neuraxial block (see Table 2)					
	Single-shot spinal anaesthesia			Epidural and combined spinal-epidural		
	Comfort	Morbidity	Mortality	Comfort	Morbidity	Mortality
INR (normal: 0.9–1.2)	≤ 1.4	<1.8	<2.2	≤ 1.2	<1.6	<1.8

Recommendation grade D; evidence category IV.

grel treatment should be discontinued at least 5 days before an operation.[74]

One major problem with clopidogrel is resistance to the drug. The prevalence of non-responders is about 15–25%.[75,76] In patients on dual therapy after stent implantation, the risk of stent thrombosis is imminent after cessation of treatment, and both drugs may have to be maintained up to the day of surgery.[53,77,78] Only surgery for vital indications is performed in patients on dual therapy,[53,79] and CNB is contraindicated.

There are four case reports where clopidogrel has been implicated in patients with SH, two spontaneous[80,81] and two after CNB.[82,83] The latter two patients had also received LMWH and clopidogrel was discontinued 7 days before the CNB. Both patients had renal impairment.

Ticlopidine. This ADP-blocker has more adverse effects (e.g. thrombocytopenia; aplastic anaemia) than clopidogrel. It is rarely prescribed in the Nordic countries, and its foremost indication is resistance to clopidogrel. Ticlopidine has a longer half-life than clopidogrel, and most guidelines recommend cessation of ticlopidine 10–14 days before a CNB in patients who do not need this potent antiplatelet drug.[3] However, the rate of platelet reproduction is fast enough to raise platelet numbers to about 50% of normal within 5 days after discontinuation of ticlopidine, which is sufficient for adequate primary haemostasis.[42]

Prasugrel. Prasugrel is a novel ADP receptor antagonist, which has been released on the European markets in 2009. In common with clopidogrel, it is a pro-drug, whose active metabolite binds irreversibly to the P2Y12 receptor, but prasugrel is more potent, has a faster onset, and, above all, patients seem to be less prone to developing resistance against prasugrel. Therefore, one important indication of prasugrel will probably be to replace clopidogrel in patients with resistance to the latter.[84] There seems to be more bleeding complications with prasugrel than with clopidogrel, especially in older (>75 years) and low-weight (<60 kg) patients.[85] The half-life of prasugrel is similar to that of clopidogrel. At this time, there are not enough data to issue any recommendations other than those valid for clopidogrel.

Novel antiplatelet drugs. Several new antiplatelets will be introduced in the future: ADP-inhibitors like ticagrelor (AZ6140) and cangrelor, nitric oxide-releasing aspirin (NCX-4016), a reversible tromboxane receptor antagonist (S18886), and also a couple of thrombin receptor antagonists.[85]

Platelet infusion is the only safe way of reversing the antihaemostatic effects of ADP-blockers,[86] but may be relatively ineffective in the presence of active drug.[53] Platelet infusion is not recommended as a routine prophylaxis before an invasive procedure in patients taking platelet inhibitors.[87]

Recommendations

- ***In patients treated with clopidogrel (or ticlopidine) alone for primary prevention of thrombotic events, we recommend that the treatment is discontinued no less than 5 days before surgery and an intended CNB. The treatment should be reinstituted as soon as surgical haemostasis is secured, or after removal of an epidural catheter. (Recommendation grade C; evidence category IV).***
- ***In patients treated with dual antiplatelet medication with a thienopyridine and ASA (Table 11A) after coronary stent implantation, the antiplatelet medication should not be interrupted and CNB is contraindicated. (Recommendation grade C; evidence category III).***
- ***In an emergency case, with intake of clopidogrel or ticlopidine within the last 5 days, CNB is contraindicated, except when a reduced mortality can be expected with reasonable certainty from a single-shot SPA in place of GA. (Recommendation grade D; evidence grade IV).***

Vitamin K antagonists (VKA) (Tables 4, 7, 8)

Warfarin. Warfarin is the most commonly used VKA drug. It inhibits all vitamin K-dependent factors: II, VII, IX, and X. Its major indications are thromboprophylaxis in patients with atrial fibrillation, with mechanical heart valves, and treatment of venous thromboembolism (DVT and PE). In some countries, but not in the Nordic countries, VKA drugs are also used for post-operative thromboprophylaxis. Its effect is monitored by INR, and the therapeutic level of INR aimed at is generally 2.0–3.0 for the prevention of venous thrombosis and 2.5–3.5 for the prevention of arterial thrombosis (e.g., mechanical mitral valve, after MI, some patients with cardiomyopathy). The reference value in untreated individuals is ≤ 1.2.[42,88]

In major surgery, the pre-operative INR aimed at is normally <1.5, which is considered satisfactory for surgical haemostasis.[79] This level is generally reached if treatment is discontinued for 4–5 days, provided the patient does not have a simultaneous

vitamin K deficiency (e.g., by food deprivation or malnutrition).

In patients at an increased risk of thromboembolic complications (Table 11B), initiation of LMWH prophylaxis (bridging) is recommended when the INR reaches subtherapeutic levels, i.e. INR < 2.0.[86]

We have identified three case reports with VKA as the only drug implicated as the cause of post-CNB SH.[89–91] One occurred 3 days after the insertion of an EDA catheter in a patient on VKA treatment, which had not been discontinued (INR = 4.1).[89] Two occurred after epidural catheter removal in patients receiving warfarin for post-operative thromboprophylaxis. INR was 6.3 at the time of catheter removal in one patient[90]; the other had a prothrombin time (PT) of 17.3 s (normal 10.9–12.8 s).[91]

On the other hand, there are four case series without any adverse events in patients on preoperative warfarin treatment.[92–95] Odoom and Sih[92] reported experiences from 1000 vascular surgical patients with EDA insertion at full anticoagulation, while the mean thrombin time was 19.3%, corresponding to INR 2.0. The patients were also heparinized intraoperatively. In a prospective study on patients undergoing total knee replacement, PT values ranged from 10.6 to 25.8 s (INR about 1.2–2.0) at epidural catheter removal ($n = 192$).[93] In a similar study on 1030 patients, in almost 40% of the patients, catheter removal occurred at INR between 1.5 and 4.25.[95]

These studies, and the relatively few case reports despite the wide usage of VKA therapy, indicate a relatively small, but undeterminable, risk for SH from CNB in patients under VKA treatment.[96]

Recommended upper INR levels before a CNB vary, depending on the technique and strength of indication (Table 7). Vitamin K is the primary antidote against VKA, but it has a slow onset and long lasting effect. In emergency situations, where a fast reduction of INR is necessary, the VKA effect can be reversed by prothrombin complex concentrate (factors II, VII, XI, and X). If this is not available, the less effective fresh-frozen plasma should be administered.

After resumption of warfarin therapy, it usually takes about 2 days before any increase in INR can be observed.

Other VKA, e.g. phenprocoumon. These are not in common use in the Nordic countries.

Recommendations

- ***In patients treated with warfarin, we recommend that treatment is temporarily discontinued 1–5 days before surgery in order to attain an INR value according to* Table 7. *(Recommendation grade D; evidence category IV).***
- ***We also suggest that INR be checked on the day before surgery, and, if the targeted value is not reached, the patient is given a low dose of vitamin K (1–2 mg orally), followed by a re-evaluation of INR on the morning of the operation day. (Recommendation grade D; evidence category IV).***

Table 8

Properties of some commonly used anti-haemostatic drugs.

Drug/class	Target factor(s)	Time to peak effect	Plasma half-life	Monitoring	Antidote	Antihaemostatic effect
Heparin (i.v.)	II and X (1/1)	< 30 min	1–2 h	APTT	Protamine	Moderate/severe*
LMWH (s.c.)	II and X (1/3)	3–4 h	4–7 h	Anti Xa activity	(Protamine)	Moderate/severe*
Fondaparinux	X	2–3 h	17–20 h	Anti Xa activity	-	Moderate/severe*
ASA	Platelets (irreversible)	~ 1 h	0.5 h†	Platelet Function Analyser® Multiplate®	Desmopressin	Mild
NSAID	Platelets (reversible)	Variable	See Table 6	Platelet Function Analyser®/Multiplate®	Desmopressin	Mild
ADP-receptor blocker (e.g., clopidogrel)	Platelets (irreversible)	3–7 days	8 h†	Platelet Function Analyser® / Multiplate®	Platelets	Moderate
VKA drugs (e.g., warfarin)	II, VII, IX, and X	5 days (oral intake)	Variable	INR	Vitamin K Factor concentrate Human plasma	Moderate at INR 2–3 Severe at INR > 3

*Prophylactic/therapeutic doses.
†Duration of haemostatic effects are more dependent on platelet regeneration than drug half-life.

- ***After single-shot SPA techniques, the VKA treatment can be resumed as soon as haemostasis is secured. In other techniques, treatment can be resumed immediately after catheter removal. (Recommendation grade D).***
- ***In emergency cases, where a fast reduction of INR is mandatory, this can be accomplished by the use of a prothrombin complex concentrate. If this is not available, fresh-frozen plasma can be given instead. (Recommendation grade D; evidence category IV).***

Thrombolytic drugs (Table 5). These drugs convert plasminogen in blood clots and thrombi to plasmin, which is the active enzyme that causes fibrinolysis. Thrombolytic therapy is indicated in patients with acute myocardial infarction (AMI), PE, and embolic occlusion of cerebral arteries (and other arteries). Fortunately, CNB is rarely indicated in patients recently subjected to fibrinolytic therapy.

We have found no published case report of post-CNB SH in patients receiving streptokinase, alteplase, or reteplase. There are five case reports of SH in patients receiving urokinase: in four patients after insertion of EDA catheters,[97–100] and in one patient after insertion of an intrathecal catheter (subdural haematoma).[101] All four patients were also heparinized, and drug treatments were started shortly after insertion of the catheters. Urokinase has not been used for several years in the Nordic countries.

There are three reports of spontaneous SH in patients treated with streptokinase and 12 reports of spontaneous SH in connection with alteplase treatment. In some of these cases, the patients also received UFH.

Owing to the fibrinolytic effects of these drugs, they cause increased risk of degradation of an organized clot in an epidural vessel, leading to the risk of haematoma formation for several days following a CNB. There is no clear information as to how long this risk will persist, but in some guidelines, 10 days has been suggested.[102]

Recommendations. For initiation of fibrinolytic therapy after CNB or epidural catheter removal:

- ***In most cases, fibrinolytic therapy is vitally indicated and has to be started within a short period of time even after a recent CNB or epidural catheter removal. The interval between the CNB procedure and the fibrinolytic treatment has to be determined from a risk/benefit analysis in each single case.***
- ***If possible, waiting 2 h may reduce the risk of bleeding* (Table 5). *(Recommendation grade D; evidence category IV).***

Streptokinase. Streptokinase has relatively long-lasting effects, and the risk of bleeding is increased for 24 h after its administration. During this period, CNB is strictly contraindicated.

Recommendations

- ***In a patient treated with parenteral streptokinase, we recommend that no less than 24 h is allowed to elapse before a CNB is initiated after cessation of streptokinase.***
- ***After small doses of locally applied streptokinase, there is no need for any restriction in the timing of a CNB. (Recommendation grade D; evidence category IV).***

Alteplase. Alteplase is a recombinant human plasminogen activator with a high affinity to fibrin. It is relatively inactive in the systemic circulation. It has a fast onset, and is eliminated rapidly: no more than 10% is left in the plasma 20 min after discontinuation of the infusion.

Recommendation

- ***In a patient treated with alteplase, we recommend that no less than 6 h is allowed to elapse before a CNB is initiated. (Recommendation grade D; evidence category IV).***

Reteplase. Reteplase is a recombinant human plasminogen activator with a high affinity to fibrin. However, its elimination rate is slow, similar to that of streptokinase.

Recommendation

- ***In a patient treated with reteplase, we recommend that no less than 24 h is allowed to elapse before a CNB is initiated. (Recommendation grade D; evidence category IV).***

Miscellaneous drugs

Antidepressants and health preparations. Specific serotonin reuptake inhibiting drugs (SSRI) can affect platelet aggregation, and there seems to be a slightly increased risk of peri-operative

bleeding.[103] This risk is even greater in patients with concomitant ASA or NSAID medication.[104] There are no case reports of either spontaneous or traumatic SH in patients taking SSRI, and we do not believe there is enough evidence for issuing specific recommendations regarding withdrawal of SSRI before a CNB. However, a history of any bleeding tendency should always be obtained.

Some herbal preparations and omega3 have mild antiplatelet effects. However, there is no evidence that they increase surgical bleeding, not even in combination with ASA or NSAID.[105]

Recommendations

- ***The antihaemostatic effects of SSRI antidepressants are not strong enough to warrant discontinuation of these drugs before neuraxial anaesthesia. However, in combination with other antihaemostatic drugs, their effects may contribute slightly to an increased risk of spinal bleeding during CNB. (Recommendation grade D, evidence category IV).***
- ***Herbal preparations and omega3 are drugs without clinically important antihaemostatic effects, but should be discontinued before surgery and CNB because of unknown and unnecessary risks of interactions with prescribed medications. (Recommendation grade D, evidence category IV).***

Plasma expanders. Plasma-expanding solutions may decrease the concentration of coagulation factors through haemodilution. Apart from a relative decrease in the amount of coagulation factors and blood viscosity, blood flow characteristics tend to move platelets away from their normal position close to the vessel wall at haematocrits below about 30%, reducing their ability to create a platelet plug on an injured endothelium.

Dextran also inhibits von Willebrand's factor and seems to have a profibrinolytic effect on thrombi, which may explain its thromboprophylactic effect. In recommended doses, these effects are mild, and dextran *per se* does not seem to have any significant antihaemostatic effects.[106] However, additive effects with other platelet inhibitors and anticoagulants may occur.

There are three case reports on post-CNB SH in patients receiving dextran infusions, where other drugs could also have contributed: one with intraoperative heparinization in an isolated leg,[34] one with ASA and heparin,[107] and one with chronic prednisolone therapy.[108]

Recommendations

- ***There are no restrictions on the use of plasma expanders in patients with a planned or an active CNB, as long as recommended dose limits are respected (<1.5 g/kg BW) and the haematocrit is maintained above 30%. (Recommendation grade D; evidence category IV).***
- ***Dextran infusion should be avoided in patients with an indwelling catheter and simultaneous treatment with other antihaemostatic drugs. (Recommendation grade D; evidence category IV).***

Combinations of drugs with effects on haemostasis. In a majority of case reports over post-CNB SH, more than one risk factor is implicated as possible causes of the complication. Most frequently, two or more drugs are implicated, and, in the aging population, patients frequently receive antiplatelet or VKA therapy on a daily basis, at the same time as more and more patients are heparinized (with UFH or LMWH) in the peri-operative period. Virtually every patient >50 year undergoing an operation that requires post-operative epidural analgesia will receive concomitant LMWH prophylaxis.

ASA alone increases the risk of spinal bleed only slightly, and the risk is of the same magnitude as that of thromboprophylactic doses of heparin. In combination, however, ASA and UFH may increase the risk significantly.[36] A synergistic fibrinolytic effect of ASA or an NSAID in combination with LMWH has been suggested.[109] There are several case reports of post-CNB SHs implicating the combination of antiplatelet drugs and LMWH as a causative factor.[83,84,110] Spontaneous SH in four patients treated with LMWH and ASA, one also with warfarin, should remind us that in patients with a high risk of bleeding complications, SH can occur even without a spinal puncture or epidural catherization.[111]

Pharmacodynamic interactions. Theoretically, combinations of anticoagulants with different pharmacodynamics have an additive effect on haemostasis and coagulation, with increased bleeding tendency.

Pharmacokinetic interactions. There are in particular two types of pharmacokinetic interactions that may affect the elimination rate of anticoagulants: competition of metabolic pathways in the liver, and reduction of renal clearance. Typically, drugs like phenytoin, dextropropoxiphene, and ciprofloxacin increase the effect of VKA drugs by competitive interaction. Barbiturates may induce

warfarin metabolism and decrease its plasma concentration.

The approximate additive effects on the risk of bleeding by different combinations of antihaemostatic drugs are illustrated in Table 9.

Emergency cases. In emergency cases, an ideal timing of a CNB after antihaemostatic drug intake is often impossible. The following suggestions, based on the above considerations, may help in these often difficult dilemmas.

Recommendations

- ***In patients with a low or a moderate risk of thromboembolic complications who have ongoing ASA or NSAID treatment, CNB may be administered, timing determined by surgery, provided there is a strong indication for the CNB, and the first dose of LMWH should be delayed until 6 h after surgery. Single-shot SPA is to be preferred in these situations. (Recommendation grade D; evidence category IV).***
- ***Desmopressin (0.3 μg/kg) may be given in combination with tranexamic acid if a haemostatic disorder is suspected (e.g., by oozing in the surgical field). A platelet function test before and after the desmopressin can provide valuable information. (Recommendation grade D; evidence category IV).***
- ***In patients at a high risk of thromboembolic complications, LMWH should be started as soon as possible after admission to the hospital, with half the daily dose (i.e. 2500 U/20 mg s.c.), repeated every 12 h. In these patients, SPA may be administered without delay when the patient requires immediate surgery, provided there is a strong indication for the CNB. (Recommendation grade D; evidence category IV).***
- ***In emergency CSs, SPA may be considered without regard to the last dose of dalteparin or enoxaparin up to 2500 U or 20 mg every 12 h, provided platelet count is $>50\times10^9$/l. (Recommendation grade D; evidence category IV).***

Table 9

Bleeding tendency with various antihaemostatic drugs and combinations.

UFH	1*–3					
LMWH	2*–3	3				
VKA	2†	3	3			
Low dose ASA	1	2	2	3		
NSAID	1	2	2	3	2	
Clopidogrel	2	3	3	3	3	3
Other drug:	None	UFH	LMWH	VKA	ASA	NSAID

1 = mild; 2 = moderate; 3 = severe.
*Prophylactic doses (≤ 5000 U/day s.c.).
†Therapeutic dose (INR 2–3).
Evidence category IV.

Patient-related risk factors

Haematological diseases. All conditions listed in Table 10 increase the risk of developing a post-CNB spinal haemorrhage. This risk should be evaluated by a specialist, preferably by the patient's own physician.

Recommendation

- ***The decision to perform a CNB in a patient with a haematological disorder listed in* Table 10 *should be based on a careful individual risk/benefit analysis, after consultation with a specialist.***

Renal and hepatic failure. Patients with chronic renal failure (CRF) may suffer from haemorrhagic as well as thromboembolic complications.[112] The antihaemostatic effects of CRF may have several reasons. Platelet disorders (thrombocytopenia and platelet inhibition) and abnormal platelet–vessel wall interactions seem to be the most important causes, but anaemia (altered blood rheology, especially when haematocrit declines below 30%), erythropoietin deficiency, and abnormal production of nitric oxide have also been implicated.[112] The platelet dysfunction is in part due to uraemic toxins, which are dialysable. Haemodialysis will therefore diminish, but not eliminate, the risk of bleeding, although the haemodialysis process itself may contribute to bleeding.[113] Desmopressin, or conjugated oestrogen, may have beneficial effects on uraemic bleeding.[113]

Thus, CRF is a definite risk factor for spinal haemorrhage,[3] illustrated by two case reports of post-CNB SHs, where CRF was the only recognized risk factor.[114,115] There are also two cases of CRF with clopidogrel medication, interrupted 1 week before the CNB, and given LMWH peri-operatively,[82,83] and one additional case with aspirin medication, intraoperative heparinization, and dextran infusion, apart from his renal disease.[116] Although only parts of clopidogrel and rivaroxaban are eliminated by the kidneys, LMWH, fondaparinux, and dabigatran are fully excreted by the kidneys; these drugs may accumulate in patients with CRF, contributing to a higher risk of spinal

Table 10

Some conditions associated with increased bleeding tendency.[42]

	Platelet disorder	Coagulation factor deficiency
Start of haematoma formation	Immediate (min)	Delayed (h, days)
Locus of spontaneous bleeding	Mucous membranes (nose, GI- and/or urogenital tract), skin	Muscles, joints, skin, retroperitoneal
Manifestation	Petecciae, ecchymosis	Haematoma, haemarthrosis, ecchymosis
Inherited conditions	von Willebrand's disease (1 : 50–1 : 500) [autosomal, recessive (mild, common) or dominant (severe, rare)]*	FVIII deficiency (1 : 5000) boys (X-linked, recessive)
	Ehlers–Danlos syndrome (1 : 5000?)†	FIX deficiency (1 : 30,000) boys (X-linked, recessive)
	Storage Pool Disease (rare)	FVII deficiency (1 : 500,000) boys/girls (autosomal, recessive)
	Cyclooxygenase deficiency (rare) Bernard–Soulier (extremely rare) Glanzmann's trombasthenia (extremely rare)	
Acquired conditions	Immunologic thrombocytopenic purpura (ITP), autoimmune diseases, amyloid, sepsis, drug dependent deficiency, uraemia, cancer, DIC, HIV	Hepatic disease, vitamin K deficiency, celiac, DIC
Drug-induced	ASA, NSAID, dipyridamole, ADP inhibitors, GP IIb/IIIa inhibitors, heparin or other drug-induced thrombocytopenia (HIT-I and HIT-II)	Vitamin K antagonists, thrombin inhibitors, unfractionated heparin (UFH), low molecular weight heparins (LMWH), pentasacharides

*Individuals with von Willebrand's disease have normal platelets, but reduced amount of von Willebrand's disease factor in plasma and in platelets, which affects adhesion of platelets to the injured vessel wall.
†Individuals with Ehlers–Danlos syndrome have normal platelets, but have deficient collagen, leading to vessel fragility and decreased platelet function.

bleeding from CNB.[113]

NSAIDs, including COX-2-selective inhibitors, have profound effects on the kidneys in patients with highly prostaglandin-dependent renal function, e.g. in patients with CRF, hypovolaemia, left ventricular failure, cirrhosis,[117,118] and also in patients on ACE inhibitors,[119]in elderly patients, and possibly patients on β-blockers.[119] NSAIDs including COX-2 inhibitors should be avoided in such patients, especially during thromboprophylaxis with LMWH, fondaparinux, or dabigatran.

Recommendation

- ***In patients with CRF, CNB should be avoided unless a strong indication exists. (Recommendation grade D; evidence category IV).***

Hepatic dysfunction can increase the risk of an SH by a decreased synthesis of coagulation factors, especially those that are vitamin K dependent (factors II, VII, IX, and X), causing an increase in INR. Many patients also have thrombocytopenia. In patients with portal hypertension, blood may be diverted to the epidural veins, which are devoid of valves, and therefore become dilated and prone to bleeding.[120] There are, five case reports where liver disease was implicated.[121–125] One SH occurred after a lumbar puncture,[124] and one in a patient who had thrombocytopenia and a recent fracture of the vertebra at the level where an EDA catheter was inserted.[125] Two obstetric cases with HELLP (Haemolsis, Elevated Liver enzymes, and Low Platelet syndrome) were reported by Moen et al.[1] The cause of SH was multifactorial, with hepatic failure being a tentative factor.

Table 11A

Thromboprophylactic medication that should not be interrupted before surgery.[53]

Patients treated with platelet inhibitors for secondary prevention of thromboembolic events
ASA and clopidogrel (or ticlopidin) should be interrupted *only* during the day of surgery in patients with*
- Myocardial infarction
- Coronary intervention:
  - CABG
  - Mechanical dilatation
  - Bare metal stents
  - Drug eluting stents
- Stroke/TIA /intracranial intravascular stents

*Recommendation grade D; evidence category IV

Recommendation

- ***CNB is usually contraindicated in patients with severe hepatic dysfunction with elevated***

Table 11B

Prophylactic medication for thromboembolic events that cannot be completely interrupted before surgery.

Patients treated with vitamin K antagonist (VKA) need INR reduced from 2.5–3.5 to 1.8–2.2, depending on type (and urgency) of surgery.[79]
Patients with high or moderate risk of thromboembolic events require bridging with LMWH when INR falls <2.0.

Risk for thromboembolic events	Indication for vitamin K antagonist therapy		
	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism (VTE)
High risk	Any mitral valve prosthesis Older aortic valve prosthesis Stroke or TIA within 6 months	$CHADS_2$ score $\geq$ 5 pts* Stroke or TIA within 3 months Rheumatic valvular heart disease	VTE within 3 months Severe thrombophilia (e.g., APC (activated protein C resistance)
Moderate risk	Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke/TIA, hypertension, DM, congestive heart failure, age >75 yr	$CHADS_2$ score 3 or 4 pts*	VTE within the past 3–12 months Nonsevere thrombophilic conditions Recurrent VTE Active cancer
Low risk†	Bileaflet aortic valve prosthesis without any other risk factor	$CHADS_2$ score $\leq$ 2 pts (without a history of stroke/TIA)*	Single VTE occurred >12 months ago and no other risk factor

*$CHADS_2$ = **C**ardiac failure, **H**ypertension, **A**ge >75 years, **D**iabetes and **S**troke. Each one is 1 pt except for stroke (= 2 pts).
†Bridging is not required in low risk patients.

INR and/or platelets below 100×10^9/l. (Recommendation grade D; evidence category IV).

Spinal deformities and vascular malformations. Ankylosing spondylitis is a risk factor for SH.[3] This condition was suggested as a possible contributing factor in five of 51 cases in the review by Wulf.[33] Three more case reports of SH associated with a CNB and ankylosing spondylitis have been published.[126–128] Ankylosing spondylitis is often associated with difficult and often traumatic CNB needle insertion. Furthermore, narrowing of the spinal canal, renal dysfunction, and a need for potent NSAIDs may be implicated.[33,129] However, in a case series of 613 mostly spontaneous SHs,[130] only 0.5% had ankylosing spondylitis, which is within the range of the prevalence of this disease (0.1–1.4%).[131] Thus, the disease *per se* does not seem to be the risk factor, but rather the anatomical abnormalities of the spine, leading to an increased number of traumatic attempts.

SH after CNB or lumbar puncture has also been reported in three patients with spinal stenosis,[132–134] one patient with non-symptomatic spina bifida oculta,[135] two cases of spinal angiomas,[136,137] one case of epidural lymphoma,[138] and one case of a lumbar ependymoma.[139]

There are no case reports of post-CNB SH where a metastatic vertebral tumour has been implicated.

Recommendations

- ***In patients with ankylosing spondylitis or other severe spinal disorders, such as symptomatic spinal stenosis or osteoporosis, the number of CNB attempts should be limited to three, and, in the case of a bloody tap, the procedure should be abandoned. (Recommendation grade D; evidence category IV).***
- ***In patients with known intraspinal vascular abnormalities, CNBs should be avoided. (Recommendation grade D; evidence category IV).***

Gender and age. Female gender has been pointed out as an independent risk factor for the development of SH after CNB.[3] In a population of 40 patients reported to the FDA with SH after LMWH prophylaxis in the United States, approximately 75% were elderly women, after major orthopaedic surgery.[44] We have identified altogether 105 cases of SH after epidural anaesthesia (obstetric cases excluded) reported in the literature from 1952 to 2008. Between 1952 and 1992, 22 of 35 patients were men (63%), and the median age was 68 years in both gender groups[1,33] whereas between 1993 and 2008 (70 cases), only 37% were men with median age 70 years, whereas the female patients had a median age of 77 years.[1,33] (Lagerkranser, personal communication).

Possible explanations for this trend towards a higher risk of SH among elderly women may be that these have more major orthopaedic surgery in

recent years, at the same time as they have a high prevalence of osteoporosis of the spine, generally have a smaller body mass than men, and a high prevalence of renal impairment due to advanced age. Since LMWH became routine post-operative thromboprophylaxis in the early 1990s, dose recommendations of enoxaparin or dalteparin have not taken weight and age into consideration. Therefore, a recommended prophylactic dose may be close to or equivalent to a therapeutic dose, and this may increase bleeding tendency in a small patient.[44,140,141] There also seem to be pharmacokinetic gender differences. Campbell et al.[142] reported higher plasma levels in elderly women than in men after a weight-adjusted dose of heparin. A similar increase in sensitivity to LMWH was reported by Oldgren et al.,[143] who found higher levels of anti-Xa in women than in men after weight-adjusted doses of dalteparin.

Recommendations

- ***Elderly patients, especially women, commonly have several risk factors for SH. They have a high risk for thromboembolic complications, but also a high risk for haemorrhagic complications.***
- ***Carefully conducted CNB may reduce morbidity and mortality after major surgery and may still be the best anaesthetic and analgesic techniques for these patients. (Recommendation grade D; evidence category IV).***
- ***For major orthopaedic surgery, single-shot spinal analgesia is the most appropriate technique when CNB is indicated. (Recommendation grade D; evidence category IV).***
- ***In the post-operative setting, a reduced dose of LMWH should be considered in patients with body weight <55 kg. (Recommendation grade D; evidence category IV).***

Recommended screening for the risks of bleeding before CNB. The choice of anaesthetic technique is always a matter of risk/benefit evaluation in a patient at risk. Patient history is the most important means to discover patients with increased risk of bleeding.[144] Screening by specific history and appropriate laboratory tests should be undertaken and documented in the patient records.

Patient history

- Family: Any coagulation disorder or abnormal bleeding after surgery or tooth extraction among relatives?
- Bruises: Spontaneous or easily acquired after a mild blow?
- Gum bleedings: Spontaneous or severe after brushing of teeth?
- Nose bleed: Frequency? Severity?
- Bleeding after pinches/needle punctures: At sewing, shaving, or blood tests?
- Joint bleedings: Localization? Residual joint disorders?
- Bleedings from the GI tract: Frequency? Severity? Underlying diseases?
- Urological bleeding: Frequency? Severity? Underlying diseases?
- Gynaecological or obstetric: Menorrhagia? Haemorrhages at childbirth?
- Surgery: Severity of haemorrhage; amount of blood transfused?
- Conditions with pathologic vessels, e.g. severe arteriosclerosis, complicated diabetes mellitus, and long-term steroid medication.
- Medication, such as ASA, NSAID, potent platelet inhibitors, warfarin, UFH, LMWH, steroids, SSRI.

Recommendation

- ***If patient history indicates a haemostatic disorder, this should be carefully documented and further examination should be undertaken. (Recommendation grade D, evidence category IV).***

Laboratory tests. Only two tests are recommended for screening in order to detect patients with haematological disorders: *Hb* and *serum creatinine*. A low *Hb* without an obvious reason may indicate a concealed bleeding, and an increased creatinine level may indicate kidney impairment, which in turn may cause platelet inhibition and increased effects of some antihaemostatic drugs.

Specific laboratory tests. If history or a low Hb indicates a disturbed haemostasis, further examinations are indicated:

Platelet count (normal range 150–350 $\times 10^9$/l). The number of functioning platelets for adequate haemostasis is 100×10^9/l.

Recommendation

- ***The minimum number of platelets required for various CNB techniques is indicated in Table 12. (Recommendation grade D; evidence category IV).***

Devices such as a platelet function analyzers (PFA) can detect the effects of the platelet inhibitors ASA, clopidogrel, and GpIIb/IIIa antagonists, and also the newer direct ADP receptor antagonists. The PFA can, e.g., be used for assessment of the optimal timing of epidural catheter removal,[145] and requires trained personnel. it has a poor prediction of surgical bleeding with sensitivity and a positive predictive value similar to those of the platelet count.[146]

Specific tests for von Willebrand's disease.

Bleeding time (BT): The value of BT has been seriously questioned because of a large interobserver variability, and a poor prediction of surgical bleeding. Therefore, BT is not recommended as a screening test.

APTT (test of all coagulation factors, except for VII and XII). It is generally used for monitoring the effect of UFH. The APTT should be within the normal range. However, there are conditions with a prolonged APTT without an increased risk of haemorrhage, e.g. factor XII disturbance.

The prothrombin complex INR (test of the vitamin K-dependent factors II, VII, IX, and X). INR is mandatory in all patients on VKA treatment, and the values should not exceed those outlined in Table 8. INR is also mandatory in patients with a suspected vitamin K deficiency, and in liver failure. In these cases, an increased INR is associated with a greater risk for bleeding than during VKA treatment to the same INR level.

Activated factor X (Xa). This is a test for evaluating the efficiency of LMWH or fondaparinux but is not routinely used in clinical practice.

Thromboelastography with specialized laboratory equipment can test the integrity of coagulation, platelet function, fibrinolysis, and reversal of heparin effects.

Reducing the risk of complications during CNB

Pre-requisites for safe CNB practice

- All hospitals with surgical activities requiring neuraxial blocks should have *protocols* and a *robust monitoring regime for detecting the early signs and symptoms of intraspinal bleeding* and a high alert for verification of diagnosis and evacuation of the haematoma.[18–21,147,148]
- A *single-shot SPA with a small calibre spinal needle carries a lower risk* of SH than insertion of an epidural catheter. Therefore, lower platelet counts and higher INR levels are accepted for single-shot SPA than other CNB techniques (Tables 8 and 12).
- During continuous epidural analgesia, the *detection of early signs of a haematoma is essential* in order to reduce the the risk of permanent neurological damage.

Recommendations. All are recommendation grade D, evidence category IV:

- ***Make sure that the catheter position is in the segmental epicentre of the operation area.***
- ***Use the lowest possible concentration of a local anaesthetic in the post-operative setting. Combinations with opioids and adrenaline reduce dose requirements and dose-related side effects. Adrenaline also promotes platelet aggregation and may reduce risk of bleeding.***
- ***Assess leg weakness every 4 h during ongoing epidural analgesia, and for 24 h after removal of an epidural catheter.***
- ***Inform the patient of the significance of leg weakness, a new backache, and loss of sensation in the perineum.***
- ***Do not manipulate the epidural catheter when the patient has a haemostatic abnormality* (Tables 4 and 5).**
- ***All hospitals need an updated protocol for the diagnosis and treatment of a SH.*[147,148]**

Recognition of early symptoms and signs is crucial[18–21]*. Four symptoms should alert all medical personnel of the possibility of a developing SH:*

- New, severe back pain, often radiating.
- Leg weakness → paraparesis.

Table 12

Number of normally functioning platelets acceptable for CNB.

	Potential benefit of neuraxial block (see Table 2)					
	Single shot spinal anaesthesia			Epidural and combined spinal-epidural		
	Comfort	Morbidity	Mortality	Comfort	Morbidity	Mortality
Platelet count $\times 10^9$ (normal: 150–350)	>100	>50	>30	>100	>80	>50

Recommendation grade D; evidence category IV.

- Sensibility disturbances unrelated to the block itself.
- Bladder or bowel disturbances.

The symptoms may start shortly after a puncture, or removal of an epidural catheter, but there may be a delay.[149] In some cases, an MRI has revealed a SH without the patient being paraparetic (only back pain was present). Too often are symptoms mistaken for an ongoing epidural by nurses and doctors. This delays effective treatment (laminectomy) and may cause a permanent disability in a patient.[147,148]

With suspicion of a SH, the attending physician must take immediate action

- *Request an MRI (CT is less sensitive) and urgently consult a neurosurgeon or an orthopaedic surgeon.*
- *In case of an indwelling epidural catheter: try to evacuate as much blood as possible via the catheter.*
- *Leave the catheter in place: manipulations/extraction may increase bleeding.*
- *Try to reverse any possible haemostatic disorder, in order to reduce an ongoing bleeding.*
- *Avoid unnecessary patient transport and loss of time. The most effective treatment is decompressive laminectomy within about 12 h of the appearance of symptoms of intraspinal bleeding.*

Concluding remarks

Are guidelines and protocols for preventing and treating SHs worthwhile?

The alarmingly high prevalence of SHs reported during the 1990s when thromboprophylaxis was being accepted as the standard of care of surgical patients[1,44] led to numerous national and international guidelines intended to reduce the risk of spinal bleeding when both thromboprophylaxis and CNBs were indicated. The 2009 report from the Royal College of Anaesthetists of UK now indicates that focused attention to this problem has reduced the risk to an acceptable level.[147,148]

This is very encouraging for all of us who still believe that CNBs often are beneficial for our surgical and obstetric patients, most of whom also need optimal thromboprophylaxis. We hope this report will result in a common and improved understanding of these often complex challenges in everyday clinical practice in the Nordic countries.

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