Expensive anaesthesia complications

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Abstract

The major, costly, and catastrophic adverse consequences of anaesthesia are reviewed. The American Society of Anesthesiologists' closed claims registry yields valuable insights. The size and success of claims is determined by the standard of care, and extent of injury. Ongoing assessment of the pattern of claims allows determination of high-risk patients and interventions, as well as the formulation of protocols or practice guidelines to reduce risk. Injuries to previously healthy individuals are inevitably more costly. Respiratory mechanisms still account for the majority of serious adverse events. However, the focus has shifted from intubation problems to extubation and the recovery room. Emerging areas of concern are claims that relate to nerve injury, with or without regional anaesthesia, postoperative visual loss, and monitored anaesthesia care and sedation. An area of particular concern, namely spinal-epidural haematoma associated with central neuraxial blockade, is a typical example of the closed claims registry/taskforce/protocol approach. Specific risk factors, such as use of anticoagulants close to the time of performance of the neuraxial block, traumatic technique, elderly patients, and renal dysfunction, have been identified. Protocols have been devised for risk reduction.

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Introduction: data from closed claims

For many years, most data relevant to anaesthesia safety were derived from closed legal claims, rather than from peer review and internal or external audits. This trend is changing in the developed world, but South Africa lags well behind in this regard. The American Society of Anesthesiologists (ASA) closed claim project extracts information from the closed claims of 35 medical malpractice insurance carriers, in order to detect recurring patterns of injury, or high risk practice. Problem areas are then allocated individual registries and task teams, in order to define the problem, and produce advisories or protocols, for avoidance thereof. Areas in which this approach has already yielded success (less injuries, claims and cost; and innovations in equipment and techniques) include basic monitoring standards and difficult airway management. The result is an ever-changing pattern of claims, highlighting new safety concerns.

Here are some observations regarding recent closed claims:

- The bulk of claims pertain to alleged injury to healthy elective adults, with a preponderance of claims in female ASA I or II patients undergoing general anaesthetic. Claims in medically or surgically compromised patients are less frequent, and smaller.
- The two big determinants of claim success and size are standard of care and extent of injury.
- There is an approximate 50:50 split between claims where the standard of care is judged to be appropriate, and those where the care is deemed to be suboptimal.
- The frequency of claim success is greatest where care has been suboptimal, irrespective of the extent of the injury.
- The amounts paid out for successful claims are proportional to the extent of the injury, and inversely proportional to the standard of care.
- Thirty-two per cent of assessed claims would be avoidable with better monitoring. These produce very costly payouts.
- The severity of the injury has a profound impact on the expert assessment of standard of care (peer bias). This has been confirmed in a trial in which scenarios of identical provocative events produced very different outcomes with respect to severity. Table I lists the distribution and median cost of major adverse anaesthesia outcomes in the 2006 ASA closed claims registry.

Table I: Major adverse outcomes leading to closed claims. (ASA closed claims registry, 2006)

Adverse outcome	% of cases	Median payment
Death	29	US$338 000
Nerve damage	19	US$87 700
Permanent brain damage	10	US$1 198 000
Visual injury	4	US$95 688

Certain recurring patterns of injury are evident when current claims are examined.

Adverse respiratory events

These remain the single largest source of injury.They have the highest frequency of adverse outcomes of all injurious processes (85% rate of death or brain damage), and are the most costly.

Three quarters are judged preventable through better assessment, monitoring, or protocol adherence. Three quarters are due to inadequate ventilation, oesophageal intubation, or difficult intubation. The primary task of the anaesthesiologist is to oxygenate the patient.

Nerve injury

There were 400 closed claims in the 1990s.They involved the major peripheral nerve injuries, namely ulnar, brachial plexus, lumbosacral roots. Seventy-five per cent of ulnar nerve injuries occurred in males, and happened despite appropriate positioning and padding.

The biggest increase in claims was for spinal cord damage (25% of all nerve injury claims, and five per cent of total claims). Almost half of these were for spinal-edpidural haematoma (SEH), and three quarters of patients had clear contraindications to central neuraxial block (CNB), in the form of coagulopathy or anticoagulant therapy.

Sudden cardiac arrest with central neuraxial block

The rate is unchanged from previous closed claim analyses. It occurs in healthy patients undergoing minor procedures, and is associated with blocks to T_4 or higher. It is far more frequent with spinal, than epidural, blocks.

There is a sudden rapid onset of cardiac arrest, from a base of apparently normal haemodynamics and respiratory function. It virtually always leads to death or adverse neurological outcome. It is the single largest contributor to deaths in closed claims, and is responsible for one-third of high-severity injuries.

The mechanisms invoked include decreased coronary perfusion pressure; absent adrenergic response to cardiac arrest, leading to poor cardiac perfusion, even during effective cardiopulmonary resuscitation; delayed use of adrenalin or vasopressor; and vagal dominance.

Some new areas of concern have also emerged. Procedures for chronic pain now account for > 10% of all claims. Claims are usually for nerve damage or paralysis (usually temporary), and generally relate to epidural steroid injections. Usually, the standard of care is deemed to be appropriate, and the claims are small.

Monitored anaesthesia care (conscious or deep sedation)

Increased claim frequency may mirror an increase in use of monitored anaesthesia care (conscious or deep sedation). Claims relating to death or brain damage account for 40% of medical affirmative claims (MAC) (~ general anaesthesia rate). These outcomes are half as frequent with regional anaesthesia claims.

Twenty-five per cent of these outcomes are deemed to be due to respiratory depression, while 50% are considered preventable with better monitoring. Seventeen per cent of claims relate to neck and facial burns, due to a combination of MAC, facial surgery, alcohol-based cleaning solutions, diathermy, and oxygen supplementation.

The impact of the ASA closed claims task teams (especially the difficult airway and paediatric ones) is evident from the following observations. Claims for death and permanent neurological impairment have fallen from 56% of claims in the 1970s to 31% in the 1990s.

Respiratory mechanisms were invoked for 55% of such claims in the 1970s, and only 45% in the 1990s [with a reciprocal increase in the contribution of cardiac mechanisms (24% in the 1990s vs. 12% in the 1970s)].

With regard to residual respiratory-related claims, hypoventilation claims have fallen by two-thirds, oesophageal intubation claims have declined by one-third, and claims related to failed airway management on induction are down by a half, but there has been no change with regard tosuch claims at other times, both intra- and postoperatively.

The standard of care was judged to be inadequate in 51% of claims in the 1990s vs. 65% in the 1970s. A corollary of this is that plaintiff success has fallen from 74% to 40% over this time period. Many challenges still exist in reducing adverse outcomes, and reducing medico-legal risk. These include an extension of reduced respiratory risk to the post-induction and postoperative period, greater focus on elucidating “grey areas”, e.g. nerve injury, and improving peer reviews and the elimination of “outcome bias”.

Postoperative visual loss

There has been a sharp rise in reports of postoperative visual loss (POVL) in the last two decades, possibly as a result of increased awareness of the entity; awareness that

it is not necessarily, or even frequently, related, to globe compression, and hence not medico-legally indefensible; an increase in the frequency, and extent, of spinal surgery, especially fusion (sixfold in the last decade); and an increasingly aging population, with more co-morbidities, presenting for spinal surgery.

We remain constrainedby the absence of a suitable animal model to research human POVL, and by an inability to monitor the optic nerve in real time. The ASA initiated a POVL registry in 1993, and 131 cases were reported in the first decade of its existence. Ninety-five were associated with spinal surgery, and 12 with cardiac surgery. Others related to major vascular, major orthopaedic, and various miscellaneous procedures.

The incidence of POVL is estimated to be0.003-0.0008%, rising to 1:500 for prolonged spinal fusion surgery. Ischaemic optic neuropathy (ION) accounts for 80% of POVL in spinal surgery. Two-thirds of this is posterior ischaemic optic neuropathy (PION), and the remainder, the anterior form (AION).

The differential diagnosis of POVL includes ION, central retinal artery occlusion (CRAO), cortical blindness, and direct eye injury. These may all have subtypes, and are differentiated from one another based on onset time, clinical scenario, presence or absence of pain, and uni- or bilaterality (see Table II).

Ischaemic optic neuropathy

Ischaemic optic neuropathy is the most commoncause of POVL (posterior > 2/3 ; anterior < 1/3). It is typically bilateral and painless. There is a variable degree of visual loss. Forty per cent may improve somewhat. There is a 75% male preponderance, with increased susceptibility to nerve injury, in general. This disease results from physiological perturbations of an at-risk optic nerve, during prone major spinal surgerymainly. There is no evidence of ischaemia of any other organs. It is not related to embolism or direct globe pressure.

Associated risk factorsinclude surgery > 450 minutes, blood loss > 1 l, and physiological risk factors, such as hypovolaemia, hypotension, and anaemia. Patient risk factors in AION, and often PION in well, young patients, include hypertension, diabetes, atherosclerosis, dyslipidaemia, smoking, sleep apnoea syndrome, and hypercoagulability. There is a high volume of colloid infusions and the use of vasoconstrictors. The mechanism provides inadequate oxygenation of the at-risk optic nerve. The precise pathogenesis is unknown.

Postulates include anatomical variants in the optic nerve blood supply, physiological aberration in the autoregulation of the optic nerve blood supply, oedema or compartment syndrome of the optic nerve, due to fluid shifts and orbital venous engorgement, and a tight scleral canal.

Treatment of ION is unsatisfactory. Steroids have been proposed for early limitation of extent, but evidence of efficacy is minimal. The focus is on prevention, but ION occurs across a wide range of physiological and haematological parameters, so it is difficult to identify a specific “safe” blood pressure or haemoglobin range. The head should always be in a neutral position, and not elevated, or dependent with regard to the heart. Important issues include proper informed consent, and considering staging surgery if it is likely to exceed six hours, or if blood loss is likely to exceed 1 l.

Central retinal artery occlusion

Central retinal artery occlusion is the most common cause of unilateral blindness after spinal or cardiacsurgery. Bilateral blindness after cardiac surgery is usually ION, or cortical, in origin. CRAO is associated with embolism in cardiac and vascular surgery, and direct globe compression in prone surgery. Up to 20% of cardiopulmonary bypass (CPB) patients may have features of retinal injury, and 2.5% demonstrate fundoscopic evidence of embolism. It is unilateral, complete, painless, and irreversible. Seventy per cent show features of globe compression such as

Table II: Features of the major categories of post-operative visual loss

Type Subtype	Onset of POVL[a]	Nature of POVL	Pain	Clinical scenarios
ION[b] Anterior Posterior	 Delayed Immediate	 Bilateral Bilateral	No	Spinal surgery Cardiac surgery Not high ASA
CRAO[c] Central Branch	Immediate and progressive	 Unilateral Unilateral	No/minimal	High ASA Cardiac surgery Globe compression
Cortical True Visual pathways	 Immediate Immediate	 Bilateral Homonymous hemianopia	No	Global ischaemia or anoxia Neck surgery CABG[e] or valve surgery
Direct injury	Immediate	Unilateral	Yes	Direct compression or perforation or abrasion

a = postoperative visual loss, b = ischaemic optic neuropathy, c = central retinal artery occlusion, e = coronary artery bypass graft

ophthalmoplegia, bruising, periorbital oedema, and proptosis.

Prevention can be achieved through obsessive, regular eye checks, and avoidance of compression. Treatment is unsatisfactory, and includes intravenous acetazolamide, 5% CO_2 inhalation, thrombolytics, and local cooling. Retrochiasmal visual pathways and cortical blindness may result from embolism, e.g. carotid endarterectomy (CEA), watershed ischaemia, global anoxia (typically associated with CPB, especially CABG and valve surgery, and even more so if combined), or from cervical vascular injury in neck surgery.

Central retinal artery occlusion is rare, but the rate may reach 6% with CEA, and 7.5% with combined CABG and valve surgery. Presentation depends on the level of injury. It is often homonymous hemianopia, if unilateral, and cortical blindness, if bilateral. Once again, as with closed claims in general, the absence of evidence of a specific mechanism, ignorance, and outcome bias, weigh against the anaesthesiologist in the event of an adverse outcome.

Below are transcripts of expert opinions:

- "The anaesthesiologist clearly caused this patient's vision loss by letting the MABP drop below 60 mmHg for more than five minutes." *Mea culpa!*
- "This patient is now blind because the anaesthesiologist let the patient's haematocrit level decrease to less than 24% during the case." *Mea culpa!*
- "The person providing the patient's anaesthesia failed to avoid prolonged pressure on the eye, leading to the patient's (bilateral) ischaemic optic neuropathy and blindness." Expert?

Nerve injuries

Nerve injuries, including spinal injuries, constitute a significant component of closed claims.

The majority do not relate to regional anaesthesia. It is suggested that nerve injuries are due to positioning in at-risk patients (males, obesity, and extreme underweight) with at-risk nerves (diabetics, peripheral vascular disease, peripheral neuropathy, and inflammatory neuritis or plexitis), undergoing at-risk procedures (requiring non-neutral positioning and extension or rotation of the neck and joints). Nerve injuries often occur, despite documentation of careful positioning and appropriate padding. The majority are judged to have occurred despitean acceptable standard of care.

However, nerve injuries related to regional anaesthesiamay lead to severe and long-term disability. The incidence of regional anaesthesia-related neuropathy is dependent on the intensity of screening and reporting. Prospective studies indicate that minor or subclinical neuropathies occur in 10-15% of blocks, relatively irrespective of the method of nerve location. Retrospective studies place this figure at 0.5-1%, and probably select for more symptomatic injuries. Ninety-five per cent of injuries resolve in four to six weeks, and 99% within a year. Permanent neuropathies are observed in 1:5 000 regional anaesthesia procedures. Cauda equine or spinal cord injuries are associated with 1:14 000 neuraxial blocks. Generally, neuropathies present as residual motor or sensory deficits, or as the generation of new neuropathic pain.

Should regional anaesthesiabe abandoned then? The response of Andre Boezaart is perhaps most apt: "Despite the risk of nerve injury, blocks and peripheral nerve catheters are still valuable, and the only modality providing dynamic analgesia". It is likely that the majority of reversible injuries are neuropraxic in nature. In this regard, the myelin sheath is damaged, with disruption of nerve action potentials (AP), but universal recovery occurs once myelin repair is complete. The likely underlying mechanisms of neuropraxia are compression (haematoma, prolonged tourniquet, high-volume subepineurial injections, and surgical oedema) and stretch injury. Most permanent and incompletely reversible injuries relate to axon loss. In this regard, recovery depends on collateral re-innervation (sprouting) in incomplete injuries,and axonal regrowth in complete injuries. The usual mechanisms of axonal loss are blunt and sharp trauma with nerve transection (complete or incomplete), toxic injury from local anaesthesia, additives (especially subperineurial injection), and prolonged ischaemia.

After regional anaesthesia, what is it that causes neuropathy exactly? There are many proposed mechanisms.

Direct nerve trauma

While it is beyond question that complete or incomplete nerve transaction, due to needle trauma, will cause neuropathy, it is less clear whether nerve puncture, without fascicular injury, produces any deleterious effects. Between 50-90% of nerve volume is occupied by extrafascicular connective tissue. This amount is greatest where nerves cross joints, an apparent protective adaptation.The whole nerve is surrounded by an epineurium, whereas the axonal fascicles are covered by a tough perineurium. In the 1970s, Selander showed that large nerves in unconfined spaces, approached by a blunt needle, were almost impossible to penetrate. In confined spaces, e.g. the olecranon fossa and fibular head, this protective mechanism does not apply.

Ultrasound studies of blocks performed, using the parasthesia technique, reveal nerve penetration in up to 85% of regional anaesthesia, and intraneural injection in 80%. The overwhelming majority of these injections are subepineurial, but outside the perineurium. The latter appears to be acritical barrier in avoiding axonal injury. Large-volume, and pressure subepineurial injections, may be associated with transient neuropraxias. High-volume, or pressure saline injections, even in excess of capillary

perfusion pressure, produce no anatomical, or functional, nerve damage. This points to the likely influence of the injected local anaesthesiaon nerve injury.

Traditionally, intraneural injection is taught to be intensely painful, and to require high pressures. Incidences of permanent nerve injury, without pain on injection, are proposed, to relate to an instantaneous anaesthetic effect of injected local anaesthesia. This phenomenon can be avoided by preceding all local anaesthesia injections with 1 ml of saline. This will produce pain without anaesthesia, in the event of intraneural placement. However, motor response to peripheral nerve stimulation (PNS) will be lost due to charge dissipation. In terms of pressure, subperineurial deposition of an equivalent volume of local anaesthesia to that delivered suepineurially, will produce or require a six- to tenfold greater pressure. Safe injection pressure has been estimated at < 11 psi (75kPa). Pressures of 20 psi are exceeded in 80% of blocks, and 30 psi, in 10%. It remains uncertain as to whether or not use of PNS reduces the risk of nerve penetration or intraneural injection, but logic dictates that it should. The impact of ultrasound, while theoretically beneficial in terms of visualisation of intraneural injection, is still to be determined.

Local anaesthesia toxicity

Local anaesthetic toxicity is related to the drug (esters > lignocaine > bupivacaine) proximity of injection to the nerve, and the duration and concentration of exposure. Sensory nerves are most sensitive.

Numerous mechanisms of local anaesthetic neurotoxicity have been proposed. These include:

- Nerve oedema, due to absorption of water from the local anaesthesia into the hyertonicendoneural fluid
- Impairment of neural blood flow, due to pressure effects of injected local anaesthesia or consequent haematoma, oedema, the effect of added vasoconstrictor, and inhibition of the endothelial process regulating the microvascular flow or tone. Lignocaine directly inhibits peripheral nerve blood flow. Bupivacaine inhibits at low concentrations, but vasodilates and promotes flow at higher concentrations. (See below with regard to the pathophysiology of nerve ischaemia).
- The direct neurolytic effect of intrafascicular local anaesthesia injection.

Ischaemia

Aside from the ischaemic effect of the local anaesthesia, mechanical, compressive and stretching forces tend to produce ischaemia. Adrenalin 5µg/ml can lead to nerve degeneration, even without intraneural injection. Nerves with good blood supply are protected, but those at vascular watersheds are at risk, e.g. sciatic.

Tourniquets, especially if > 3 hours, and hypotension, increase risk. Large diameter nerves are most at risk. Up to six hours of ischaemia may be tolerated without permanent structural or functional impairment, but oedema and fibre degeneration lasting one to two weeks is likely.

Failure of blood flow leads to metabolic stress. The initial response is depolarisation, with spontaneous nerve activity and parasthesiae. Later, calcium accumulation leads to loss of sensation, and may trigger the final common pathway to cell death, if perfusion is not restored.

Final common pathway of nerve injury

Several mechanisms are likely to be implicated, including:

- Disruption of cytoplasmic calcium signalling, with cellular calcium overload and cell death, or triggering of apoptosis
- Mitochondrial damage
- Direct nerve membrane injury
- Inhibition of axonal transport, through loss of microtubules
- Generation of oxygen-free radicals.

Approach to post-regional anaesthesia neuropathy

A detailed history should reveal the likely anatomical locations of the injury, the presence of a pre-existing neuropathy, and the presence of risk factors, such as diabetes, obesity, cachexia,and prolonged surgery. A thorough examination should permit localisation of the likely site of the lesion (single nerve, multiple nerves, plexus, nerve roots, or cord), and determination of its severity.

Should the patient report mild or resolving symptoms, and exhibit no signs, reassurance and reassessment is probably all that is required. The presence of signs of neuropathy indicates additional investigations in the case of peripheral nerves, and urgent neurosurgical assessment and decompression, in the event of suspected compressive cord lesions.

There are two types of special investigations, namely neurophysiological and electrophysiological (EP) studies (electromyogram and nerve conduction studies are frequently combined), and radiological imaging. The latter allows precise localisation of the nerve injury. Magnetic resonance imaging (MRI) is most accurate, but computed tomography scanning is acceptable for suspected spinal lesions.

Electrophysiological (EP) studies allow accurate localisation and quantification of the injury, and also provide an indication of pre-existing nerve status and underlying pathology. They only become definitive two to three weeks after the injury, and false negatives can reflect within the first seven to ten days, due to the recruitment of axons (not yet degenerated) distal to a transection (pseudo conduction block).

By two to three weeks, there will be two major findings. The first is a conduction block. There will be a decrease in action potential amplitude, when stimulating proximal to the injury site, as compared to distal stimulation. This method is only accurate with motor nerves. Conduction block is a hallmark of neuropraxia, and indicates a good prognosis.

The second is non-conduction. No distal AP is observed with proximal or distal nerve stimulation. This indicates complete transaction and a poor prognosis.

Identification of a severe or progressive lesion may be an indication for acute nerve exploration. However, this is not the norm. In most instances, EP studies are performed between two to three weeks, to assess the extent of axonal damage, and to determine a likely prognosis. This could be that incomplete lesions are managed expectantly with follow-up EP after two to five months, or that the complete lesions require neurosurgical opinion and possible exploration.

Central neuraxial blockade: defining the risk

Assessment of any therapeutic intervention requires examination of the real clinical benefit of the technique.

This includes evidence of outcome benefit, or survival advantage, associated with the intervention; the failure rate of the technique, which is not inconsiderable with postoperative epidural analgesia (5-14%); and the incidence of complications.

A recent national audit by the Royal College of Anaesthetists revealed the following. There were in excess of 700 000 CNBs performed per annum in the UK [46% spinals; 41% epidurals; 6% combined spinal-epidural (CSE) and 7% caudals]. It showed the relative safety of CNB, with an adverse event rate of not > 4.2:100 000, and a rate of major adverse events (paraplegia or death) of not more than 1.8:100 000 interventions. There was an increased rate of adverse events with epidural anaesthesia or analgesia (EA) (up to 17:100 000), and CSE: approximately double that of CNB as a whole. Over 60% of CNB-related adverse neurological events were completely reversed by one year after injury, but this did not apply to spinal cord ischaemia, or SEH. Deaths were related to cardiovascular system collapse, inadvertent wrong site, or wrong drug administration, and CNB-associated abscesses. Paralysis was most commonly associated with SEH.

Protocols for dealing with prolonged or exaggerated blocks, or new neurological deficits, were absent in 50% of institutions. Of all of the patient groups (obstetric, general surgical, chronic pain, paediatric, and non-anaesthetic CNB, e.g. radiological procedures), the general surgical population had substantially the highest risk (40% of cohort, and 83% of complications). There was a cluster of low-to-moderate severity reversible injuries in the chronic pain population (transient "ischaemic" or inflammatory symptomatology, related to volume or constituents of the injectate in an inherently litiginous population). There were no reports of adverse events in the paediatric population, and very few in obstetrics. Virtually the only obstetric patents in whom adverse events were reported were those with HELLP syndrome [H: haemolysis (the breakdown of red blood cells); EL: elevated liver enzymes; LP: low platelet count].

Examination of UK closed claims for the 10 years from 1995-2005, has revealed that 251 claims were settled for CNB-related adverse events. The average settlement was £129 000. Pathologies ranged from unnecessary pain to paraplegia.

An associated editorial in the *British Journal of Anaesthesia* (BJA) recommended the following steps to avoid litigation:

- Four-hourly observations, for at least 24 hours after removal of the catheter
- Guidelines for CNB procedures and catheter removal in patients with altered haemostasis
- Discontinuation of local anaesthesiainfusion, if a new neurological deficit presents
- MRI within four hours, if the deficit persists
- Surgical decompression within 12 hours of the onset of symptoms.

The remainder of this lecture will concentrate on the issue of SEH.

Safety of central neuraxial block when combined with anticoagulants

CNB is employed extensively for anaesthesia and analgesia, for major orthopaedic and general surgery. Despite much emotional attachment and anecdotal reports of benefit, Level 1 evidence reveals that the only overall benefits compared with general anaesthesia and multimodal analgesia, are a better quality of analgesia and enhanced rehabilitation. Many of the analgesic benefits can be replicated with peripheral and plexus nerve blocks and infusions. Nonetheless, over 700 000 CNBs are performed annually in the UK, with epidurals and spinals each accounting for in excess of 40% of these, and the remainder being combined spinal-epidurals.

There is incontrovertible Level 1 evidence that the incidence of silent and symptomatic venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary thromboembolism (PTE), is prohibitive in the major orthopaedic surgery patient group. VTE prophylaxis is mandatory, and needs to be prolonged to five weeks, or more, in many cases. The most effective option for VTE prevention is chemical prophylaxis. A range of agents are effective in this respect, including warfarin, unfractionated

heparin (UFH), low-molecular-weight heparins (LMWH), fondaparinux, and the new oral agents: rivaroxaban (an oral factor Xa inhibitor) and dabigatran (an oral direct thrombin inhibitor). There is compelling evidence for the inefficacy of aspirin in this regard.

SEH is a rare, but catastrophic, consequence of CNB and lumbar puncture. The estimated incidence under various circumstances is tabulated below in Table III. It has been suggested that the rate may be higher than quoted in the table, because of underreporting. Of necessity, the rates are estimates, as the relative infrequency of the complication makes adequately powered prospective studies logistically impossible.

Table III: Estimated rates of spinal-epidural haematoma, with different modalities of central neuraxial block and concurrent risk factors

	Spinal	Epidural	Epidural catheter
Normal haemostasis	1:220 000	1:150 000	
Traumatic CNB[a]	1:150 000	1:70 000	
UFH[b] alone	1:32 000	1:32 000	
UFH + aspirin	1:8 500		
LMWH[c] (North American dosing)	1:40 800	1:6 600	1:3 100
LMWH (European dosing)	1:156 000	1:18 000 (Frail patients: 1:3 600)	

a = central neuraxial block, b = unfractionated heparin, c = low-molecular-weight heparins

The consequence of SEH is irreversible paraplegia in over 50% of patients, even with optimal detection and management techniques. In the presence of anticoagulation, and in the absence of precautions, the SEH rate increases 15-fold or more. Eighty-seven per cent of cases of SEH in the literature had a readily identifiable haemostatic abnormality. SEH is often insidious in onset, and tends to occur between 15 hours to three days after CNB, following subsequent doses, and possible accumulation, of the anticoagulant. Presentation is usually as a new, or intensifying neurological sign. Although higher levels of anticoagulant activity would logically predispose to SEH, no clear correlation has been shown between absolute levels of such activity, and the occurrence of SEH. This may be as a result of the absence of prospective trials. The incidence of SEH with removal of an epidural catheter is equal to that following CNB itself. Surveillance for SEH, in the form of neurological monitoring, should continue at least four hourly, for up to three days after the last neuraxial intervention. Suspicion of SEH on the basis of severe back pain, or any new neurological abnormality, mandates discontinuation of local anaesthesia infusion, and, failing rapid complete resolution, a MRI scan. If positive, this mandates emergency laminectomy within 8-12 hours of the onset of symptoms.It appears that a SEH-related neurological deficit becomes irreversible by about 15 hours after onset. It is not clear why the relatively small volumes of blood found when many SEH are drained produce paralysis, while similar or larger volumes injected (rapidly) during an epidural blood patch, do not.Thoracic SEH require far lower volumes of blood to produce paralysis than low lumbar lesions. Outcome appears proportion to rate of bleeding. The source of the bleeding is presumed to be from the epidural venous plexus, based on the insidious nature of the onset of symptoms. However, this isan incomplete explanation, as a venous bleed should tamponade before exceeding spinal perfusion pressure, and therefore not produce spinal cord ischaemia. It is likely that SEH only occurs in patients with at-risk anatomy: bony or vascular.

The differential diagnosis of SEH includes:

- Surgical neuropraxia
- Prolonged or exaggerated local anaesthesia effect
- Anterior spinal artery syndrome
- Exacerbation of pre-existing neurological disorders, or development of a new, unrelated neurological disorder.

The relevant issues in the safe combination of CNB with anticoagulation, relate to patient, drug and technical factors.

Patient factors

Patient factors include advanced age, low lean body mass, renal (especially) and liver dysfunction, acquired or congenital coagulopathy or defect inlatelet number or function, spinal abnormalities, and osteoporosis. These all increase the risk.

Drug factors

Critical factors are choice (potency) of drug, dose, proximity of dose to CNB, and the drug pharmacokinetics in the individual patient, e.g. half-life ($t_{1/2}$) may increase almost twofold in an elderly patient with renal dysfunction, as compared with a healthy control. Half-life and time to maximal plasma concentration (C_{max}) are the critical pharmacokinetic considerations. The goal is to provide effective VTE prophylaxis, while performing CNB interventions (insertion or removal) at times of acceptable haemostasis. A recurring theme in cases of SEH is the combination of two or more drugs or natural remedies with anti-haemostatic effects, e.g. aspirin and LMWH.

Technical factors

Multiple punctures, traumatic puncture and bloody tap, or the presence of blood in the catheter, are all associated with increased risk of SEH. As can be seen in Table III, attempts to quantify a universal risk for CNB, in the presence of anticoagulants, are impossible. There was only one SEH associated with LMWH and CNB in eight years of combined use in Europe, prior to the release of enoxaparin in North America. This contrasts starkly with 43 cases in five years in North America, after its release there.

The striking difference in risk relates to two major factors:

The absence of guidelines for CNB in patients receiving LMWH in North America (guidelines were in place in Europe *de novo*)

Drug and pharmacokinetic issues: LMWH are administered twice daily in North America, and the total daily dose is 50% higher (60 mg vs. 40 mg for enoxaparin). Given that the average $t_{1/2}$ for LMWH is about six hours, and the average C_{max} is four hours, it is not surprising that a reasonable nadir in anticoagulant levels cannot be achieved with this *bd* protocol for neuraxial interventions, e.g. removal of epidural catheters. Douketis showed that, while no patients on a once-daily protocol had anti-Xa activity approaching the therapeutic range, a quarterof North American patients had activity compatible with high bleeding risk.

Therefore, it is clear that the use of a higher dose of a potent agent, at a time close to the performance of a CNB, is associated with an exponential increase in risk of SEH. Guidelines have been formulated for concurrent use of anticoagulants and CNB, based largely on the pharmacokinetics of the drugs and consensus of experts, in the unavoidable absence of randomised, controlled studies. These guidelines are designed to allow efficacious use of anticoagulants and safe CNB practice, but do not guarantee absence of risk of SEH in each individual patient.

Guidelines for central neuraxial blockade in the presence of anticoagulation

The algorithm proposed by Rosencher can be applied to CNB and epidural catheters utilised in the presence of drugs directly, or indirectly, inhibiting clotting factors (UFH, LMWH, fondaparinux, rivaroxaban, and dabigatran), but not those altering the synthesis of these factors (warfarin). This states that no neuraxial intervention (insertion or removal) should be performed until a minimum of two half-lives have elapsed from the last prophylactic dose of anticoagulant (four half-lives if on therapeutic doses). Subsequent doses of anticoagulant should be active, only once stable primary haemostasis can reasonably be expected to be present. This should occur by eight hours in most patients, but the dose of drug does not have to be delayed this long. Drugs achieving their C_{max} rapidly should be withheld longer than those with a longer C_{max}. In effect, the subsequent dose can be administered eight minus C_{max} hours after the CNB or catheter removal.

There are some common-sense provisos to this algorithm. In calculating the delay before CNB or catheter removal, it seems prudent to use a $t_{1/2}$ appropriate to the particular patient, or default to the maximum $t_{1/2}$ quoted for a frail patient population. The passage of two half-lives should ensure that anticoagulant activity is no more than 25% of peak activity. With drugs available in lower dosage formulations, e.g. LMWH and dabigatran, acceptable levels of anticoagulant activity may be achieved before the passage of two half-lives. However, as stated previously, routine monitoring of anticoagulant activity at the time of neuraxial intervention is not recommended in normal patients, in whom guidelines are followed. It may become difficult to properly time catheter removal in drugs with long half-lives to ensure an adequate haemostatic state at time of removal, but not lose anticoagulant efficacy as a result of excessive delays, or neglect to reinstitute therapy.

Further caution should be exercised in the presence of other coagulation defects, related, for instance, to low platelet count or function, other concurrent anti-haemostatic drugs, e.g. aspirin, NSAIDs, or intra-procedural thrombolytics, and renal dysfunction. Active bleeding or prohibitive bleeding risk mandates a delay in administration of subsequent doses of the anticoagulant.

Since most centres only institute thromboprophylaxis postoperatively, single-shot CNB can be employed safely with all agents, provided no other contraindications exist.

It is of medico-legal importance that the absence of evidence of safe use of epidural catheters with the newer agents, fondaparinux, rivaroxaban and dabigatran, may weigh heavily in the event of a SEH with one of these agents, despite adherence to a pharmacokinetically logical regimen. The manufacturers of dabigatran state in their package insert that the agent cannot be used concurrently with epidural catheters.

Table IV: Kinetics and predicted safe intervals for central neuraxial block and subsequent anticoagulant administration

	Half-life	Delay before CNB[a]	C_{max}	Delay to next dose
UFH[b]	1-2 hours	4 hours	< 1 hour	7 hours[c]
LMWH[d]	4-7 hours	12-16 hours	4 hours	4 hours
Fondaparinux	17-22 hours	At least 36 hours[e]	1 hour	7 hours
Rivaroxaban	8-3 hours	At least 20 hours[e]	2-4 hours	6 hours
Dabigatran	10-15 hours	At least 24 hours[e]	1-4 hours	6 hours

a = central neuraxial block, b = unfractionated heparin, c = theoretical value: practically unfractionated heparin often given within one hour of central neuraxial block, with a low risk of spinal-edpidual haematoma, d = low-molecular-weight heparins, e = Agents generally commenced postoperatively and post-central neuraxial block. Therefore, delays are only applicable to epidural catheter removal

Typical pharmacokinetic data and safe intervals are tabulated in Table IV.

In the case of warfarin, thrombolytics and anti-platelet drugs, intervals before safe CNB, are determined by the duration of clinical effect of the drug, many multiples of, and unrelated to, their plasma $t_{1/2}$. With these agents, monitoring of clinical effect [international normalised ratio (INR), fibrinogen level, or thromboelastography (TEG) and platelet function tests] is indicated prior to CNB,where CNB is contemplated before the recommended interval has passed.

Guidelines for anticoagulation in the presence of central nuraxial block

Patients with indwelling epidural catheters, or recent CNB, may require anticoagulation or thrombolysis for vascular emergencies (acute coronary syndromes and threatened limbs). This poses substantial problems regarding risk of continuing local anaesthesia infusions, timing of catheter removal, and incidence of SEH, although these risks have not been defined. It seems prudent to avoid any CNB in patients presenting for procedures related to advanced peripheral vascular disease, or with a history of unstable angina. This is despite the possible outcome benefit of emergency anaesthesiain these patients, because of the low threshold of surgeons and physicians who administer potent and multiple anticoagulants in these settings. Should such drugs be required in patients with recent CNB, or those with indwelling epidural catheters, prolonged intense monitoring becomes mandatory, until three days after cessation of the anticoagulants.

Ideally, catheter removal should be carried outat a nadir of anticoagulant effect, if feasible. Temporary interruption of anticoagulants for this purpose must be assessed by a multidisciplinary team, and individualised based on risk-benefit in the particular patient.

Catheters can be left indwelling for up to 72hours before risk of infection starts to rise. Catheter removal should be performed shortly thereafter, but the haemorrhagic risk must be assessed against risk of infection.

Conclusion

Millions of patients have received concurrent CNB and anticoagulants without problems. However, the occurrence of a SEH is a disaster for both patient and anaesthesiologist. Guidelines are in place to maximise the efficacy of both interventions, and to promote safe practice, but these are not guarantees of safety. The use of CNB, and particularly epidural catheters,in the presence of anticoagulation, must be a carefully considered therapy. Each patient's bleeding risk should be assessed individually by means of a careful history, and selected special investigations. It is advisable to err on the side of caution in applying guidelines or algorithms, especially where bleeding risk may be increased.

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