Central nerve block and thromboprophylaxis—is there a problem?

Postoperative thromboembolic complications continue to be one of the leading causes of morbidity and mortality in hospital patients; one autopsy study found that 10% of all inpatient deaths were caused by pulmonary embolism. Thus there is increasing awareness of the need for effective methods of reducing the incidence of deep venous thrombosis (DVT) and pulmonary embolism in the UK, Europe and North America. The UK Thromboembolic Risk Factors (THRIFT) Consensus Group reviewed methods of prophylaxis in 1992 and made specific recommendations for medical and surgical patients. The consensus group stratified patients into low-, moderate- and high-risk groups using the well recognized risk factors for DVT and recommended that local thromboprophylaxis procedures should be drawn up. This recommendation has now been implemented in most regions, the Scottish Intercollegiate Guidelines Network publication being an example, and prophylaxis with unfractionated heparin, low molecular weight heparin (LMWH) or warfarin is advised for patients in the moderate- and high-risk categories.

However, thromboprophylaxis has risks as well as benefits. For the anaesthetist, the main concerns are: first, increased bleeding during or after surgery; and second, the possibility of an increased predisposition to vertebral canal haematoma. The particular problem is the large overlap between those patients for whom spinal or epidural anaesthesia is considered appropriate and those in the moderate- to high-risk DVT groups for whom it is prudent to consider thromboprophylaxis, usually with subcutaneous unfractionated heparin or LMWH. The anxiety about this combination is a large part of the broader concern that has been growing for almost a decade about performing spinal or epidural anaesthesia in a patient with any factor interfering with normal coagulation. Abnormal bleeding within the vertebral canal may result in the formation of a haematoma which may compress the theca and result in irreversible neurological injury and paraplegia.

Fortunately, this disastrous complication is extremely rare, but the actual incidence is unknown. Tryba attempted to estimate the risk after central nerve block by reviewing all of the published series: 13 series of epidural block (comprising 850 000 patients, three of whom developed a haematoma) and seven series of spinal block (comprising 650 000 patients, none of whom developed a spinal haematoma). He calculated the upper 95% confidence interval of the risk of spinal haematoma after central nerve block to be very low: 1 in 150 000 after epidural block and 1 in 220 000 after spinal block. Clearly these data give no more than a rough estimate of the overall level of risk and are weakened further by a lack of information regarding the proportion of patients who had received anticoagulants, had a coagulopathy or received traumatic punctures, all of which are factors considered to be associated with an increased risk of haematoma. It is also unlikely that every vertebral canal haematoma occurring after central nerve block was reported.

It is important to remember that vertebral canal haematoma occurs spontaneously, and that it is seen more commonly in this presentation than after central nerve block. Holtas, Heiling and Lomntoft reported 13 cases at a single institution over a 9-yr period and estimated the incidence of spontaneous vertebral canal haematoma as 1 per 1 000 000 population per year. Interestingly, four of these patients had received anticoagulant drug therapy and five had sustained minor trauma, but there were no obvious risk factors in the other four. Other authors have reviewed the literature and found far more reports of spontaneous spinal or epidural haematoma than the numbers (see below) which now cause such anxiety in anaesthetic circles. However, it is clear that a large proportion of vertebral canal haematomas (25% in one study) are associated with a clotting disorder which may be drug induced, acquired or congenital. Thus it is necessary to consider the impact of these factors on the decision to use central nerve block in such patients, particularly because there are no hard data on the relative risk.

In 1994, Vandermeulen, Van Aken and Vermylen published a wide ranging review of all reports of vertebral canal haematomas occurring after central nerve block, between 1906 and 1994. There were only 61 such cases and, in 42 of these, the patient had some type of coagulation ‘disorder’. Twenty-five patients had received heparin (four LMWH and 21 unfractionated heparin—18 i.v., three s.c. and one both), and it was probably used in another five patients who underwent major vascular surgery. A variety of factors were present in the remaining 12 patients, such as chronic alcohol abuse, chronic renal failure or therapy with antiplatelet or oral anticoagulant drugs. Four patients had anatomical abnormalities of the spinal cord or vertebral canal. The block was technically difficult in 15 (25%) patients, bloody in 15 (25%) and required multiple punctures in 12 (20%). Spinal anaesthesia was used in 15 of the 61 patients, and an epidural in 46, 32 of these receiving a catheter. The haematoma occurred immediately after catheter removal in 15 of these patients and nine had therapeutic plasma concentrations of heparin at the time.

The message from this review seems clear: coagulopathy and ‘traumatic’ puncture are the main risk factors, and
Vertebral canal haematoma seems to be a complication associated more with epidural catheter use than with any other central nerve block technique. This delineates the problem more clearly than was previously the case, but there is nothing to alter previous advice to clinicians. However, the whole issue has come under the spotlight again with increasing reports of vertebral canal haematoma in patients who had received enoxaparin, one of the newer ‘heparins’, and there is such a report from Australia in this issue of the journal. There has been particular concern about the problem in the USA where a Public Health Advisory Message was issued in December 1997 by the Food and Drug Administration (FDA) after more than 30 reports to the manufacturers of enoxaparin, of vertebral canal haematoma associated with central nerve block. Unfortunately, many of these patients had significant neurological impairment or permanent paralysis and the FDA issued a ‘black box warning’ of the risk which has to be included in the data sheet of all LMWH marketed in the USA.

Prior to these events, the combination of central nerve block and prophylaxis with enoxaparin was thought to be ‘safe’: Bergqvist, Lindblad and Matzsch reviewed controlled studies of more than 10 000 patients who had received both LMWH and central nerve block without sequelae. They also estimated that a further 1 million patients had received the combination without formal studies, with only one vertebral canal haematoma being reported at the time of writing (1992). What has emerged since that review is a striking difference in the number of cases being reported in the USA and Europe. Tryba and Wedel compared the European and American experience by examining all cases reported in either continent, and attempted to estimate the incidence in patients undergoing central nerve block while receiving enoxaparin using data supplied by the manufacturers (Rhone Poulenc Rorer Pharmaceuticals). They calculated that 4.5 million patients had received enoxaparin and central nerve block in Europe between the drug’s launch in 1987 and the end of 1995. Only two cases of vertebral canal haematoma had been reported, giving a ‘European’ incidence in the region of 1 in 2 250 000. It was estimated that 100 000 patients had received enoxaparin and central nerve block in the USA between drug release in May 1993 and the end of 1995. Eight cases of vertebral canal haematoma were reported in that time, seven involving central nerve block, and an ‘American’ incidence of 1 in 14 000 was estimated.

This much greater incidence of vertebral canal haematoma would seem to be confirmed by the total number of reports to the FDA, which reached 43 by the end of February 1998. Two patients developed haematoma spontaneously, and two had undergone spinal surgery, but the other 39 involved central nerve block; this has been the cause of much concern in North American anaesthesia circles recently. Twenty-six of the patients had epidural catheters inserted, six a spinal anaesthetic, three an epidural steroid injection and no technique was specified in four patients. The mean age of the unfortunate patients was 74 yr, and 75% were female. The haematomas became apparent a median of 3 days (range 0–12 days) after the LMWH was started and the diagnosis was made a median of 24 h after the onset of symptoms. Typically, the initial complaint was of lower limb weakness or numbness and not severe radicular back pain, as is traditionally taught. In 16 cases, drugs known to affect coagulation (e.g. NSAID, aspirin, warfarin or heparin) were administered concomitantly.

It was believed previously that NSAID and aspirin therapy did not increase the risk of vertebral canal haematoma after central nerve block, but there is now a consensus opinion in the USA that NSAID and LMWH should not be given together in patients undergoing surgery under central nerve block (T. T. Horlocker, personal communication). The FDA has instructed LMWH manufacturers to include a statement regarding the potential additional risk of antiplatelet drugs in the ‘black box’ warning with the data sheet literature. This may limit the scope for central nerve block techniques in orthopaedic patients undergoing joint replacement therapy, most of whom are receiving NSAID. It remains unclear if concomitant NSAID administration actually increases the risk of vertebral canal haematoma associated with central nerve block in patients receiving LMWH thromboprophylaxis. More than one-third of case reports occurred in elderly, orthopaedic patients, most of whom would be receiving NSAID anyway, and the association may be coincidental not contributory.

Several American patients received warfarin and LMWH. Warfarin is not used widely in the UK for DVT prophylaxis, but coumarins are the most popular thromboprophylactic drugs used in the USA. Earlier work by several authors suggested that coumarin use, if monitored closely (mean INR approximately 1.5 at epidural catheter removal), does not significantly increase the risk of vertebral canal haematoma after central nerve block. However, case reports have appeared sporadically and the combination with LMWH may further increase the risk, although to what extent remains unknown at present.

With such a catalogue of catastrophe it is hardly surprising that the FDA has issued stringent warnings about the combination of central nerve block and LMWH, but there is a need to look beyond the data and explain the transatlantic difference in incidence of vertebral canal haematoma. The obvious starting point is enoxaparin dose regimens. In the USA, the current recommended thromboprophylactic dose is 30 mg twice daily starting 1 h after surgery, whereas in Europe it is 40 mg once daily (20 mg once daily in low and medium-risk patients) starting 12 h before surgery. Thus the American dose is 50% greater than the European, and 90 mg is administered within 24 h of surgery. LMWH dose is not adjusted for body weight and it is interesting that 75% of cases of vertebral canal haematoma occurred in elderly females, so it is possible that this group were relatively ‘overdosed’ because of their relative frailty.
LMWH are potent antithrombotic agents with half-lives of 3–6 h, and approximately 50% of peak anti-Xa activity is present 12 h after s.c injection.\(^\text{21}\) When a twice-daily regimen has been started, there may never be a ‘safe’ time in the day to either perform the block or remove the catheter. This may well be the major factor explaining the alarming number of haematomas reported in North America and it is interesting that the FDA has now approved the European dose schedule of enoxaparin 40 mg once daily.

Problems with communication may also have contributed. In the USA, patients commonly undergo even major surgery on the day of admission to hospital. This means that it is not usually possible to give the first dose of LMWH 12 h before surgery as is standard European practice. The surgeon who prescribes LMWH shortly before the procedure may not realize the importance of informing the anaesthetist before spinal or epidural block is attempted, and this places the patient at increased risk. In at least one instance, central nerve block was performed shortly after LMWH administration, but the anaesthetist was unaware of this and gave another dose after the block was established.\(^\text{22}\) It is vital that there is good communication between all members of the health care team with regard to the timing of thromboprophylactic medication and it is up to the anaesthetist to personally establish the position before performing a central nerve block. It is also vital that nursing staff are given clear instructions regarding the timing of epidural catheter removal in relation to heparin administration. The health care team must also be aware of the typical presenting symptoms of vertebral canal haematoma as late diagnosis makes neurological recovery unlikely. It is unfortunate that it took a median of 24 h from onset of symptoms until definitive diagnosis in the series of cases reported to the FDA.

Another factor that may be related to the transatlantic difference is that practice guidelines on central nerve block and LMWH were published in Europe as long ago as 1991, and have been reinforced by several subsequent authors.\(^\text{5, 6, 14, 23}\) Thus increased awareness among European anaesthetists may have been partly responsible for the lower incidence of haematoma. However, this should not lead to complacency. There have been fewer cases of vertebral canal haematoma after LMWH in Europe, but the number reported has now reached 11\(^\text{24}\) and each is a tragedy for both patient and anaesthetist. Nor should the American experience be ignored because there are lessons that can be learned, notably about drug interactions and timing of catheter removal.\(^\text{10, 25}\)

Why are there more cases of vertebral canal haematoma associated with LMWH than unfractionated heparin, even in Europe? Several studies suggest that LMWH may differ from unfractionated heparin in their action on the fibrinolytic pathway, platelet function and fibrinogen binding. LMWH exhibits a dose-dependent in vivo fibrinolytic activity which can be compared with clinically effective doses of urokinase, and this activity is not evident with unfractionated heparin.\(^\text{26}\)

In addition, binding of fibrinogen to platelets is inhibited more by LMWH than unfractionated heparin,\(^\text{27}\) as is platelet binding to endothelium.\(^\text{28}\)

So what conclusions can we draw? First, vertebral canal haematoma after central nerve block is extremely rare in the absence of coagulopathy or thromboembolic prophylaxis. Second, there is extensive clinical experience with s.c unfractionated heparin for thromboprophylaxis and central nerve block, and this combination seems safe provided that sensible guidelines are followed.\(^\text{10, 25}\) Third, the cluster of unfortunate cases of vertebral canal haematoma in the USA associated with enoxaparin were probably caused by a significantly higher and more frequent recommended dosing schedule compared with Europe. If European guidelines\(^\text{14}\) are adopted in the USA, we may see a reduction in the incidence of this tragic complication. It would be most unfortunate if European patients were denied the benefits of either central nerve block or optimum thromboprophylaxis because of that experience.

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Further reading
The American Society of Regional Anesthesia have recently published consensus statements on central nerve block and anticoagulation. Regional Anesthesia and Pain Medicine 1998; Supplement 2.

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