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Neuraxial Block and Low–Molecular-Weight Heparin: Balancing Perioperative Analgesia and Thromboprophylaxis

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The efficacy and safety of low-molecular-weight heparins (LMWH) as postoperative venous thromboembolism prophylaxis has been demonstrated in more than 60 clinical trials, including more than 20,000 patients (1). However, recent reports of spinal hematoma occurring spontaneously and in association with regional anesthesia (2,3) have generated concern regarding the safety of spinal or epidural anesthesia in patients receiving LMWH. This review will discuss the chronology of events leading to the current situation, as well as examine the possible factors contributing to the increased risk of spinal hematoma in patients receiving LMWH.

Pharmacology of LMWH

The management of patients receiving regional anesthesia in combination with standard subcutaneous or intravenous heparin has been reviewed previously (4–6). However, these guidelines cannot be extrapolated to the use of LMWH because the biochemical and pharmacological properties of LMWH differ from those of standard heparin. LMWH has a more than 90% bioavailability after subcutaneous administration and a very predictable and reproducible anticoagulant response when dosed on a weight-adjusted basis. Consequently, neither laboratory monitoring of the anticoagulant response to LMWH (anti-Xa levels) nor dose adjustment is necessary. Peakanti-Xa activity occurs 3 to 4 hours after a subcutaneous LMWH injection. Because the half-life is 3 to 4 times that of standard heparin, significant anti-Xa activity is still present 12 hours after injection. The clearance of LMWH is primarily renal. The plasma half-life of LMWH is approximately two to four times longer than that of standard heparin and increases in patients with renal failure. The anticoagulant effects of standard heparin are neutralized by an equimolar dose of protamine. Because of the reduced protamine binding to LMWH fractions, only the anti-IIa activity of LMWH is completely reversed, whereas anti-Xa activity is not fully neutralized.Both anti-IIa and anti-Xa activity may return up to 3 hours after protamine reversal, possibly because of the release of additional LMWH from the subcutaneous depot (22).

LMWH Thromboprophylaxis in Europe

The administration of LMWH in patients undergoing spinal or epidural anesthesia was examined by Bergqvist et al. (7,8) in two reviews published in 1992 and 1993. These studies represent only the European experience with LMWH thromboprophylaxis, because no LMWH preparation had been approved for general use in the United States at that time. Bergqvist et al. (7,8) identified 19 reports involving 9,013 patients who safely received the combination of LMWH and spinal or epidural anesthesia. None of these studies were stratified on the basis of anesthetic methods, details of the regional anesthetic technique were not reported, and, with few exceptions, neurological complications related to spinal or epidural blocks were not included (9,10). The authors noted that pharmaceutical companies estimated an additional several million patients had received LMWH while undergoing regional anesthetic techniques with only one reported case of spinal hematoma (11). Based on these data, Bergqvist

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et al. (7,8) concluded that neurological complications after spinal or epidural anesthesia in patients receiving LMWH thromboprophylaxis are extremely rare, and the combination seemed safe. However, an accompanying editorial urged caution (12).

There have been 11 published and 2 unpublished case reports of spinal hematoma in foreign patients undergoing spinal or epidural anesthesia while receiving LMWH thromboprophylaxis (Table 1). Evaluation of patient and anesthetic factors associated with these cases subsequently led to guidelines for the practice of regional anesthesia in patients receiving LMWH.

European Practice Guidelines

A careful analysis of European literature in the early 1990s reveals that consistent practice guidelines among the European societies had been established (2,5,13). Recommendations included a delay in neuraxial needle placement of 8 to 12 hours after a LMWH injection (2,13). Subsequent administration of LMWH was postponed for 1 to 2 hours (2), or, more conservatively, 8 to 12 hours after needle placement (13). Traumatic needle placement might result in the additional delay in LMWH administration or an alternate method of thromboprophylaxis. Likewise, catheter removal was to occur 8 to 12 hours after LMWH administration (2,13) or 1 to 2 hours before the next dose (2). Formal guidelines for monitoring the patient's neurological function were also developed (21). These guidelines have apparently been effective in limiting an increase in the frequency of spinal hematoma in patients receiving the combination of regional anesthesia and LMWH. However, it is possible that European anesthesiologists have further altered anesthetic management of these patients by performing a spinal rather than continuous epidural anesthetic in those patients receiving LMWH.

LMWH Thromboprophylaxis in the United States

A recent review of the English language literature identified 215 articles in which LMWH was administered to surgical or obstetric patients (22). In 39 of these studies, representing 15,151 anesthetics, spinal or epidural anesthesia was used in combination with perioperative LMWH thromboprophylaxis. A single-dose spinal was performed in 7,400 cases, a continuous spinal in 20 cases, and an epidural anesthetic in 2,957 cases. The placement of an indwelling epidural catheter was specifically mentioned in 457 cases; however, it is impossible to determine the actual number of continuous epidural anesthetics. The anesthetic technique was recorded as spinal or epidural or regional anesthesia in 4,774 cases. LMWH thromboprophylaxis was initiated preoperatively in nearly 90% of cases and was typically administered once daily. Various LMWH preparations and dosages are represented. In more than half of the cases, the LMWH contained dihydroergotamine, a vasoconstrictor. There were no symptomatic spinal hematomas among the patients included in these studies. Because these studies were designed to analyze hemorrhagic and thromboembolic complications, it is unlikely that any serious neurological complications attributed to the anesthetic technique would remain unreported. However, limitations identical to those in reports by Bergqvist et al. (7,8) remain.

Currently, three LMWH formulations and one heparinoid are approved for general use in the United States (Table 2). However, additional fractionations are under investigation and will most likely be approved in the future. Enoxaparin, the first LMWH to be approved by the Food and Drug Administration (FDA) in the United States, was distributed for general use in May 1993. Approved dose scheduling was 30 mg every 12 hours, with the first dose administered as soon as possible after surgery. Within 1 year, two cases of spinal hematoma had been voluntarily reported through the MedWatch system. The warnings section of the drug label was revised in March 1995 to caution practitioners of the risk of spinal hematoma in patients with indwelling catheters or concomitant treatment with antiplatelet medications. In addition, the prescribing information was changed to recommend that the first dose be given 12 to 24 hours after surgery (rather than immediately postoperatively). By October 1995, 11 cases of spinal hematoma had been reported. A second revision of the drug label with expanded warnings and adverse reactions sections was requested in January 1996, and a "Dear Doctor" letter was issued by the manufacturer. However, despite efforts at relabeling and education, cases of spinal hematoma continued to occur. A total of 30 cases of spinal hematoma in patients undergoing spinal or epidural anesthesia while receiving LMWH perioperatively were voluntarily reported between May 1993 and November 1997. An FDA Health Advisory was issued in December 1997. In addition, the manufacturers of all LMWHs and heparinoids have been requested to revise the labeling of their respective products, specifically the placement of a "boxed warning." By

Table 1. Case Reports Outside the United States of Spinal Hematoma Associated With LMWH and Spinal or Epidural Anesthesia

Author* (Reference)	Regional Anesthetic Technique	LMWH/Dosage (Anti-Xa U)	Timing of LMWH Dose and Needle Placement	Timing of Catheter Removal	Onset of Symptoms	Neurological Outcome	Comments
1989							
Tryba (11)	Combined spinal/epidural, minimal bleeding during catheter placement	Nadroparin 5,000 U every 12 h	Unspecified	Unspecified	3 hours after third LMWH dose	Paralysis; epidural hematoma (T9–L4) decompressed	3 dosages of LMWH administered within 34 h
1992							
Unpublished	Unspecified	Enoxaparin 4,000 U every day	12 h preoperatively (2,000-U dose)		4 days postoperatively	Paresis and cauda equina syndrome; subarachnoid hematoma (T9) decompressed without improvement	
1993							
Tryba (13)	Continuous epidural	Unspecified	Unspecified	Unspecified	Unspecified	Paralysis; intervention unknown	Dextran and intravenous heparin administered
Tryba (13)	Continuous epidural	Unspecified	Unspecified	Unspecified	Unspecified	Paralysis; intervention unknown	Dextran and intravenous heparin administered
Choquet et al. (14)	Spinal	Nadroparin 4,000 U every day	16 h preoperatively (3,000-U dose)		40 h postoperatively	Laminectomy on sixth postoperative day, residual cauda equina syndrome	
1994							
Bent et al. (15)	Single-dose epidural	Mono-Embolex NM 3,000 U every day	8 h postoperatively		Fifth postoperative day	Back pain with radiation; L3-L4 epidural hematoma on MRI, spontaneous resolution	
1995							
Sternlo and Hybinnette (16)	Spinal (after failed/traumatic epidural)	Enoxaparin 4,000 U every day	12 h preoperatively		40 h postoperatively	Paralysis; spinal stenosis and epidural/subdural hematoma on MRI, laminectomy 30 h later, little improvement	Diclofenac administered

(continued)

Table 1. Case Reports Outside the United States of Spinal Hematoma Associated With LMWH and Spinal or Epidural Anesthesia (Continued)

Author* (Reference)	Regional Anesthetic Technique	LMWH/Dosage (Anti-Xa U)	Timing of LMWH Dose and Needle Placement	Timing of Catheter Removal	Onset of Symptoms	Neurological Outcome	Comments
1995							
Dahlgren and Tornebrandt (17)	Continuous epidural; 2 catheters placed in 5 days	Enoxaparin 4,000 U every day	Preoperatively (first procedure) for 7 days	24 h postoperatively (both catheters)	48 h after second procedure (back pain)	Paralysis; subdural hematoma (T11–L1) on CT, laminectomy performed 24 h later without improvement	
1996							
Christ et al. (18)	Continuous epidural, catheter replaced (blood noted)	Enoxaparin 4,000 U every day	12 h preoperatively	2 h postoperatively	Paralysis and incontinence 14 h postoperatively	Epidural oozing noted during laminectomy, but no significant hematoma noted	Dextran administered during surgery
1998							
Hetland et al. (19)	Continuous (thoracic) epidural	Enoxaparin 4,000 U every day	48 h postoperatively	72 h postoperatively, after blood aspirated from catheter	Evening of catheter removal	Back pain, progressed over 10 h to paraplegia, T10–T12 epidural hematoma on MRI, laminectomy 20 h after onset symptoms, ambulates with crutches	Preoperative aspirin, intraoperative hypotension, Dextran administered for first 48 h (before LMWH)
Hetland et al. (19)	Continuous (thoracic) epidural	Dalteparin 5,000 U single dose	?48 h before catheter placement	During neurosurgical decompression	Complete paralysis within 10 min of catheter placement	Surgery 18 h after onset subarachnoid hematoma evacuated; no improvement	Dual puncture noted during surgery
Christensen and Johnstad (20)	Spinal (cerebrospinal fluid bloody then cleared)	Dalteparin 2,500 U single dose	1 h preoperatively		Block never resolved, back pain noted 10 h postoperatively	Laminectomy performed to evacuate T9–L1 subdural hematoma, complete paralysis	History of multiple sclerosis with lower extremity weakness
Unpublished	Continuous (thoracic) epidural	Enoxaparin 6,000 U 12 h; started 5 days after catheter removal	5 h after 5,000 U standard heparin	72 h later (3 h after 5,000 U standard heparin)	2 days after LMWH initiated (back pain)	Paralysis 7 h later, MRI demonstrated T4–L1 epidural hematoma, patient died 3 days later	Patient received standard heparin 5,000 U twice a day while catheterized

* Eleven foreign reports of spinal hematomas have been published; references are included in the table.
Abbreviation: CT, computed tomography. LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging.

Table 2. Commercially Available LMWH

	Antifactor Xa:IIa Ratio	Plasma Half-Life (min)	General Surgery		Orthopedic Surgery	
			Dose	Initiation of Therapy	Dose	Initiation of Therapy
Enoxaparin (Lovenox and Clexane; Rhone-Poulenc Rorer, Collegeville, PA)	2.7:1	129–180	40 mg once daily	2 h preoperatively	40 mg once daily* 30 mg every 12 h	12 h preoperatively* 12–24 h postoperatively
Dalteparin (Fragmin; Kabi Pharmacia Piscataway, NJ)	2.0:1	119–139	2,500 U once daily	2 h preoperatively	5,000 U once daily 2,500 U every 12 h	12 h preoperatively 12–24 h postoperatively
Ardeparin (Normiflo; Wyeth-Ayerst Laboratories, Philadelphia, PA)	2.0:1	200			50 U/kg every 12 h	12–24 h postoperatively
Danaparoid (Orgaran; Organon, West Orange, NJ)	20:1	1,100			750 U every 12 h	2 h preoperatively

* The FDA recently approved a 40-mg once-daily dose of enoxaparin for patients undergoing total hip replacement. Initial dose is administered 12 h preoperatively.

Abbreviation: LMWH, low-molecular-weight heparin.

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April 1998, the reported number of spinal hematomas had risen to more than 40.

Although the actual frequency of spinal hematoma in patients receiving enoxaparin while undergoing spinal or epidural anesthesia is difficult to determine, estimates of the enoxaparin dosages administered and the prevalence of regional anesthesia in orthopedic patients places the frequency between 1:1,000 and 1:10,000 regional anesthetics (22). It is possible that the frequency of spinal hematoma reported to European manufacturers is significantly higher than estimates provided by published cases, and in fact approaches that encountered in the United States. However, this is unlikely, as evidenced by the lack of recent discussion in the European literature.

Several patient, surgical, and anesthetic factors may account for the difference in the frequencies of spinal hematoma between the United States and Europe. Perhaps the most important is the difference in dosing of enoxaparin, which is 30 mg (3,000 U) every 12 hours in the United States and 40 mg (4,000 U) once daily in Europe. The twice daily dosage regimen may deliver a more prolonged degree of anticoagulation and not result in the same trough of heparin activity required for the safe placement and removal of spinal and epidural needles/catheters as the once daily dosing regimen. The variation in dosing between the United States and Europe results from the interpretive differences of the clinical investigations available at the time of drug review and approval. Timing of the first dose of LMWH also varies. LMWH therapy is typically initiated 12 hours preoperatively in Europe. In the United States, product prescribing information for orthopaedic patients recommends the first dose be administered 12 to 24 hours after surgery. However, for general surgery patients, the first dose of dalteparin is to be administered 2 hours preoperatively; needle placement in these patients would occur at peak anticoagulant activity. Finally, regional anesthetic technique may affect the risk of spinal hematoma. Only 5 of the 45 patients with spinal hematomas associated with LMWH thromboprophylaxis in the United States had received a single-dose spinal anesthetic. The reported frequency of spinal hematoma in patients receiving LMWH is estimated to be approximately 33:100,000 continuous epidural anesthetics compared with 1:100,000 spinal anesthetics, once again suggesting that spinal anesthesia is a relatively "safer" neuraxial technique (24).

Description of Cases of Spinal Hematoma

As of April 1998, there have been 45 cases of spinal hematoma associated with LMWH, 40 of which occurred in patients undergoing neuraxial block. Two patients developed sponataneous spinal hematomas. The first was a 59-year-old man who underwent a cardiac allograft. Thromboprophylaxis with 40 mg enoxaparin every 12 hours was started 5 days postoperatively. A thoracentesis was performed uneventfully at that time. Twelve days after initiation of LMWH, the patient complained of back pain, which progressed to paralysis over 2 hours. An epidural hematoma extending from T3 to T7

was evacuated with little improvement in neurological function. The second patient was a 66-year-old woman who was treated with 1 mg/kg enoxaparin every 12 hours for unstable angina. Aspirin therapy was also reported. The patient complained of back pain 4 hours after the administration of LMWH. She was initially evaluated for aortic dissection. However, 17 hours later, a computed tomography scan demonstrated an extensive epidural hematoma from T9 to the sacrum. No surgery was performed, and the patient remained paraplegic.

There were also two patients who developed spinal hematomas after major spine surgery and LMWH thromboprophylaxis. One additional case identified by the MedWatch System seems on review to be unilateral lower extremity weakness caused by peroneal nerve palsy after total knee arthroplasty, rather than spinal hematoma.

Identification of Risk Factors

Examination of the 40 spinal hematomas associated with neuraxial block demonstrates several possible risk factors (Table 3). However, evaluation is incomplete; only patients with spinal hematomas are described and there are no data regarding the patient, anesthetic, and surgical factors of the several million patients who uneventfully received the combination of LMWH and spinal or epidural anesthesia (7). In addition, although two of the cases have been published as case reports that include a complete description of the event, the remaining cases exist as MedWatch reports. Although every effort is made by the FDA to obtain complete information and perform follow-up interviews, this is often not possible, and critical data are missing on some cases.

It is interesting to note that approximately 75% of patients were elderly women. This may either be representative of the orthopedic patient population, or, alternatively, may identify a population at increased risk.

Spinal hematomas were associated with both single-dose and continuous neuraxial techniques. Three patients received general anesthesia after attempted or failed neuraxial block. Two patients received epidural steroid injections. Six patients underwent spinal anesthesia, including one continuous spinal technique. Twenty-three patients underwent continuous epidural anesthesia, whereas an additional two patients underwent unspecified (spinal vs. epidural) continuous techniques. In the remaining four patients, the regional technique was unspecified.

Patients with single-dose or attempted (unsuccessful) neuraxial techniques are evaluated as a single group, because any trauma to the spinal canal vasculature would occur during actual or attempted needle placement (Table 4). All patients in Table 4 had at least one risk factor for spinal hematoma, such as difficult needle placement, concomitant administration of an additional drug affecting coagulation, or early administration of LMWH. In addition, the report of spinal hematoma in three patients with attempted and abandoned neuraxial technique again identifies difficult technique as a risk factor for spinal hematoma. The total number of patients who undergo failed needle placement is historically very small. In a prospective study of 1,000 consecutive spinal and epidural anesthetics, the attempt at needle placement was abandoned in only 9 cases (27). Therefore, it would seem that this group is overrepresented among our 40 total cases of spinal hematoma and suggests that prolonged needle trauma places the patient at increased risk. In addition, although needle placement was unsuccessful in these three patients, two of three patients developed subarachnoid hematomas, implying that the needle was at some point within the dural sac.

The remaining 26 patients with an identified neuraxial technique received a continuous spinal (1 patient), continuous epidural (23 patients), or unspecified continuous (2 patients) technique (Table 5). Fifteen of 20 patients in whom the timing of the initiation of LMWH therapy was specified received the first dose of LMWH preoperatively (4 patients) or within 12 hours of catheter placement (11 patients). Seven patients were administered concomitant antiplatelet medications, whereas two patients received warfarin. The onset of symptoms occurred while the catheter was indwelling in only four patients; seven patients became symptomatic within hours of catheter removal. However, 10 patients did not report neurological deficits for at least 12 hours after the removal of the indwelling catheter. Timing of catheter removal and onset of neurological symptoms was unknown in five patients. Importantly, the timing of administration of LMWH and catheter removal was specified in only six patients with indwelling catheters. Thus, it is difficult to estimate the level of anti-Xa activity at the time of catheter removal. Theoretically, it could be presumed that the morning dose of LMWH was administered within several hours of catheter manipulation, resulting in increasing (or peak) anti-Xa activity at that time. The lack of this crucial information regarding the dosing of LMWH and catheter removal makes it impossible to determine whether the increased incidence of spinal hematoma in patients with indwelling catheters is because of the

Table 3. Cases of Spinal Hematoma Associated With Enoxaparin* and Spinal or Epidural Anesthesia Reported to MedWatch Program

Year, Age/Gender Indication	Anesthetic Technique	Initiation of Enoxaparin	Timing of Catheter Removal	Onset and Presentation of Symptoms	Neurological Outcome	Comments
1993						
Unknown	Continuous epidural	Unknown	Unknown	When epidural catheter removed, there was an increase in bleeding	Neurological outcome not specified and may be localized bleeding only	Unspecified LMWH dosing
73/F THA	Continuous epidural	4 h after catheter placement	Catheter remained indwelling 24 h	24 h postoperatively while catheter indwelling (numbness)	Epidural hematoma decompressed and permanent paralysis	
1994						
84/F THA	Spinal	Operative day		14 days postoperatively (paralysis)	Subarachnoid hematoma (T11–T12) evacuated without improvement	Symptoms occurred 11 days after stopping LMWH, aspirin and ketorolac administered perioperatively
76/F TKA	Continuous epidural (2 attempts, 1 "wet" tap)	Postoperatively, timing unknown	Unknown	5 days after LMWH initiated (numbness and weakness)	Subdural hematoma, T7–T10 evacuated and residual sensory and motor loss	
Hynson et al. (25)† 78/F Hip fracture	Continuous epidural	12 h preoperatively and 30 min after catheter placement	Immediately postoperatively, 1 h after LMWH dose	14 h postoperatively and 3 h after third LMWH dose (leg pain and paresis)	Epidural hematoma (T5–L3) on MRI and laminectomy with fair recovery	3 dosages of LMWH administered in 12 h
74/F TKA	Continuous epidural	24 h postoperatively	48 h postoperatively	6 days postoperatively (paresis and bowel bladder dysfunction)	Epidural hematoma (T11–L2) decompressed and residual numbness	
1995						
77/M THA	Continuous epidural	8 h postoperatively	Left indwelling overnight, timing of removal unknown	24 h postoperatively and 3 h after second LMWH dose (paralysis)	Epidural hematoma on MRI, laminectomy performed within 6 h of onset and residual numbness	
28/M THA	Continuous epidural, multiple attempts	12 h postoperatively	48 h postoperatively	After catheter removal, 48 h postoperatively (paralysis)	Epidural hematoma, intervention unknown and permanent paralysis	

(continued)

Table 3. Cases of Spinal Hematoma Associated With Enoxaparin* and Spinal or Epidural Anesthesia Reported to MedWatch Program (Continued)

Year, Age/Gender Indication	Anesthetic Technique	Initiation of Enoxaparin	Timing of Catheter Removal	Onset and Presentation of Symptoms	Neurological Outcome	Comments
1995						
75/F TKA	Continuous epidural	First dose at 1,300 on operative day	24 h postoperatively and 1 h after LMWH, ketorolac	48 h postoperatively (sensory/motor loss)	Paralysis; epidural hematoma evacuated, outcome unknown	Ketorolac also administered
Unknown spine surgery	Continuous epidural	Unknown	Unknown	Unknown	No permanent paralysis	Unspecified LMWH dosing
80/F TKA	Continuous epidural	24 h postoperatively	48 h postoperatively	48 h postoperatively (cauda equina syndrome)	Epidural hematoma T12–L3 on MRI, laminectomy performed with partial recovery	
1996						
82/F THA	Continuous epidural	Postoperatively (on operative day)	96 h postoperatively	7 days (unilateral paresis and bowel/bladder dysfunction)	Epidural hematoma L2-L3 on MRI, and laminectomy performed with fair recovery	
79/F TKA	Continuous epidural	9 h postoperatively	72 h postoperatively and 5 h after LMWH dose	After catheter removal (paralysis and cauda equina syndrome)	Epidural hematoma T12 to sacrum on MRI, no surgical intervention, and poor neurological recovery	Patient also received ketorolac for 48 h postoperatively
83/M TKA	Continuous epidural	24 h postoperatively	48 h postoperatively and <1 h before LMWH dose (numbness and inability to void)	Acute paralysis 30 min after catheter removal	T8–L4 epidural hematoma on MRI and laminectomy with little recovery	Ketorolac administered concomitantly
73/F TKA	Continuous epidural, three catheters over 3-week period	Initiated after first procedure, continued for 3 weeks	48 h postoperatively	Before third surgical procedure/epidural (back pain and fever)	Abnormality at L1-L3 noted on MRI, laminectomy performed, and no deficits	Aspirin and persantine administered Infected epidural hematoma (pseudomonas)
74/F THA	Continuous epidural	Immediately postoperatively	36h postoperatively when patient c/o of minor and neurological symptoms	Complete paralysis developed on removal of catheter	Paralysis; epidural hematoma evacuated and permanent paralysis	
Unknown TKA	Continuous epidural	Postoperatively	Unknown	24 h postoperatively	Laminectomy performed to evacuate epidural hematoma and good neurological recovery	

(continued)

Table 3. Cases of Spinal Hematoma Associated With Enoxaparin* and Spinal or Epidural Anesthesia Reported to MedWatch Program (Continued)

Year, Age/Gender Indication	Anesthetic Technique	Initiation of Enoxaparin	Timing of Catheter Removal	Onset and Presentation of Symptoms	Neurological Outcome	Comments
1996 70/F Chronic pain	Continuous epidural	LMWH intitiated 5 days earlier, dose given 6 h before catheter placement	Unknown	5 days after LMWH therapy inititated (unilateral weakness)	Laminectomy performed to evacuate epidural hematoma and fair recovery	Unspecified LMWH dosing and naproxen administered
83/F THA	Continuous technique	24 h postoperatively; therapy continued for 9 days after paralysis noted	Immediately postoperatively	48 h postoperatively (numbness and incontinence)	MRI performed 72 h after paralysis; large epidural hematoma; complete paralysis present until death 7 months later	Warfarin 5 mg administered in PACU
72/M TKA	General after attempted spinal (2 bloody taps)	Evening of surgery		48 h postoperatively (weakness)	T12–L1 subarachnoid hematoma evacuated and permanent paralysis	
1997 68/F TKA	Continuous epidural	9 h postoperatively	48 h postoperatively and 4 h after LMWH dose	4 days postoperatively and weakness progressed to paraplegia over next 48 h	Epidural hematoma, T11–L3 (10 mL of blood) evacuated, and ambulates with walker	Platelet count 62,000 and INR 1.25 on day of catheter removal
Porterfield and Wu (26)† 60/F Arthroscopy	Continuous epidural	90 min before catheter insertion	2.5 h after placement	2 h after hospital discharge (8 h after LMWH dose)	Back pain to paralysis in 90 min; laminectomy within 6.5 h of onset and full recovery	Aspirin and naproxen given preoperatively
Unknown/F THA	Continuous spinal	Unknown	Unknown	Unknown	Permanent paralysis (?laminectomy)	Patient developed blood in the CSF after spinal catheter was removed and unspecified LMWH dosing
81/F TKA	Continuous epidural	24 h postoperatively	48 h postoperatively and 2 hr after LMWH dose	72 h postoperatively (weakness); 3 additional LMWH dosages given and symptoms progressed for 24 h	MRI showed large T12–L3 hematoma, surgery performed 96 h postoperatively, and walks 4–5 steps unaided	

(continued)

Table 3. Cases of Spinal Hematoma Associated With Enoxaparin* and Spinal or Epidural Anesthesia Reported to MedWatch Program (Continued)

Year, Age/Gender Indication	Anesthetic Technique	Initiation of Enoxaparin	Timing of Catheter Removal	Onset and Presentation of Symptoms	Neurological Outcome	Comments
1997 88/F THA	General after attempted spinal and epidural	Operative day, timing unknown		72 h postoperatively (weakness)	Transferred for neurological evaluation/ evacuation of epidural hematoma and near complete paralysis remains	Ketorolac administered immediately postoperatively
Elderly/F THA	Spinal	24 h postoperatively		Third postoperative day (paralysis)	Paralysis resolved (?laminectomy)	
76/M TKA	General after attempted spinal	10 h postoperatively		72 + h postoperatively (numbness)	Surgery 10–12 days after initial surgery for L2 to sacrum subarachnoid hematoma (MRI), residual numbness, weakness, and incontinence	Patient also received intravenous heparin between 72 and 96 h postoperatively, paraplegia developed while on intravenous heparin
89/F Bed rest	Epidural steroid injection	1 h before epidural injection		72 h, 2 additional dosages LMWH given after onset	Laminectomy performed and residual weakness	
75/F ?Indication	Spinal, bloody CSF which cleared	24 h postoperatively, single dose	Unknown	48 h postoperatively (weakness)	Progression to paralysis over several hours, laminectomy for epidural hematoma 24 h later, and still paralyzed	
82/F TKA	Continuous epidural; traumatic	12 h postoperatively	24 h postoperatively after c/o back pain; ketorolac given	Progression over 36 h, additional LMWH and ketorolac given	Epidural hematoma shown on MRI and decompressed with fair neurological recovery	Warfarin and ketorolac also administered
87/F Hip fracture	Continuous epidural	Intra- or postoperatively	Unknown	12 h postoperatively	Epidural hematoma on computed tomography scan; patient died ~3 weeks later	Unspecified LMWH dosing
68/F Bed rest	Epidural steroid injection	Unknown timing		48 h after epidural injection (numbness, urinary retention)	Epidural hematoma L2-L5 on MRI and laminectomy with residual paralysis	Enoxaparin 2,000-U twice-daily dosing and ibuprofen also administered
81/F Hip fracture	Spinal	24 h postoperatively		On day 6 of LMWH therapy	Spinal hematoma	

(continued)

Table 3. Cases of Spinal Hematoma Associated With Enoxaparin* and Spinal or Epidural Anesthesia Reported to MedWatch Program (Continued)

Year, Age/Gender Indication	Anesthetic Technique	Initiation of Enoxaparin	Timing of Catheter Removal	Onset and Presentation of Symptoms	Neurological Outcome	Comments
1997 Unknown THA	Unknown	Unknown	Unknown	Unknown	Epidural hematoma	
81/F THA	Continuous epidural	Unknown	Approximately 3 days	Unknown	Epidural hematoma, no mention of laminectomy, bowel/bladder dysfunction for 1 month *postoperatively, and* residual foot numbness remains	Consumer report unspecified LMWH dosing
1998 Unknown	Unknown	Unknown	Unknown	Unknown	Epidural hematoma after enoxaparin	Unspecified LMWH dosing
Unknown/F	Continuous technique	12 h after catheter removed	Postoperatively	Unknown	Neuraxial hematoma resulting in permanent paralysis	
88/F Hip fracture	Spinal, 2 levels attempted	12 h postoperatively		48 h postoperatively (numbness/weakness and difficulty voiding)	Progressed to paraplegia over approximately 12 h; L2-L3 blockage on myelogram, surgery declined	
Unknown/F	Unknown	Unknown	Unknown	Unknown	Paralysis	Consumer report, paralysis with use of enoxaparin unspecified LMWH dosing
80/? Bed rest	Unknown	Started on day of hospital admission	Unknown	3–4 days after admission (paralysis)	MRI revealed epidural hematoma; residual paralysis after laminectomy	Consumer report, some information provided may be incorrect; unspecified LMWH dosing

* All enoxaparin dosages were 3,000 U (30 mg) every 12 h, unless otherwise specified.

† Two spinal hematomas have been published as individual case reports; references are included in the table.

Abbreviations: CSF, cerebrospinal fluid; LMWH, low-molecular-weight heparin; THA, total hip arthroplasty; TKA, total knee arthroplasty; MRI, magnetic resonance imaging; PACU, postanesthesia care unit.

Table 4. Patients With Single Dose/Attempted Neuraxial Techniques

	Spinal (n = 5)	Epidural Steroid (n = 2)	Unsuccessful/ Attempted (n = 3)
LMWH administered on operative day	2	1	3
Traumatic or difficult needle placement	2	0	1
Antiplatelet therapy	1	1	1
Other anticoagulant	0	0	1 (intravenous heparin)

Abbreviation: LMWH, low-molecular-weight heparin.

level of anticoagulation achieved with the twice-daily dosing of LMWH, or the timing of catheter removal, or both.

Variability in the presenting signs and symptoms of spinal hematoma may have delayed the diagnosis. Severe radicular back pain was rare in our series. Most patients complained of new onset numbness, weakness, or bowel and bladder dysfunction. This is similar to Vandermeulen et al.'s (2) series, where muscle weakness and sensory deficit were reported as the first neurological symptom of spinal hematoma by 46% and 14% of patients, respectively. Finally, the median time interval between the initiation of LMWH therapy and neurological dysfunction was 3 days, whereas median time to onset of symptoms and laminectomy was more than 24 hours. It is not surprising that less than one-third of the patients reported fair or good neurological recovery.

Table 5. Patients With Continuous Epidural Anesthesia/Analgesia (n = 26)

	No. of Patients
Initiation of LMWH dosing	
Preoperative	4
≤12 h postoperatively	11
24 h postoperatively	5
Unknown	6
LMWH administered with catheter indwelling *	17
Concomitant antiplatelet/anticoagulant medications	
Antiplatelet therapy	7
Warfarin	2
Multiple medications	3
Onset of symptoms †	
Catheter indwelling	4
Within hours of catheter removal	7
More than 12 h after catheter removal	10
Undetermined	5

* A minimum of 17 patients received LMWH with an indwelling neuraxial catheter. Only two patients had documented catheter removal occur before initiation of LMWH, including one patient who received warfarin in the postanesthesia care unit.

† Four patients reported minor deficits before catheter removal, including two patients who became acutely paraplegic on catheter removal. Although paralysis occurred shortly after catheter removal in at least seven patients, 24 h or more often elapsed between catheter removal and the onset of neurological dysfunction.

Abbreviation: LMWH, low-molecular-weight heparin.

Recommendations for Patients Receiving LMWH and Neuraxial Anesthesia

The decision to perform a neuraxial block on a patient receiving perioperative LMWH must be made on an individual basis by weighing the risk of spinal hematoma with the benefits of regional anesthesia for a specific patient. Anesthesiologists in the United States can draw on the European experience to develop their own practice guidelines for the management of patients undergoing spinal and epidural blocks while receiving perioperative LMWH. Although it is impossible to devise recommendations that will completely eliminate the risk of spinal hematoma, we believe:

1. Monitoring of anti-Xa level is not recommended. The anti-Xa level is not predictive of the risk of bleeding and is, therefore, not helpful in the management of patients undergoing neuraxial blocks.
2. Antiplatelet or oral anticoagulant medications administered in combination with LMWH may increase the risk of spinal hematoma. Concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin, or dextran, represents an additional risk of hemorrhagic complications perioperatively, including spinal hematoma. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects.
3. Presence of blood during needle and catheter placement does not necessitate postponement of surgery. However, initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively. Traumatic needle or catheter placement may signify an increased risk of spinal hematoma, and it is recommended that this consideration be discussed with the surgeon.
4. Patients on preoperative LMWH can be assumed to have altered coagulation. A single-dose spinal anesthetic may be the safest neuraxial technique in patients receiving pre-

operative LMWH. In these patients, needle placement should occur at least 10 to 12 hours after the LMWH dose, whereas patients receiving higher doses of LMWH (e.g., enoxaparin 1 mg/kg twice daily) will require longer delays (24 hours). Neuraxial techniques should be avoided in patients administered a dose of LMWH 2 hours preoperatively (general surgery patients), because needle placement would occur during peak anticoagulant activity.

5. Patients with postoperative initiation of LMWH thromboprophylaxis may safely undergo single-dose and continuous catheter techniques. The first dose of LMWH should be administered no earlier than 24 hours postoperatively and only in the presence of adequate hemostasis. In addition, it is recommended that indwelling catheters be removed before initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight and removed the following day, with the first dose of LMWH administered 2 hours after catheter removal.
6. The decision to implement LMWH thromboprophylaxis in the presence of an indwelling catheter must be made with care. Extreme vigilance of the patient's neurological status is warranted. An opioid or dilute local anesthetic solution is recommended in these patients to allow frequent monitoring of neurological function. If epidural analgesia is anticipated to continue for more than 24 hours, LMWH administration may be delayed (in selected cases) or an alternate method of thromboprophylaxis may be selected (e.g., external pneumatic compression), based on the risk profile for the individual patient. These decisions should be made preoperatively to allow optimal management of both postoperative analgesia and thromboprophylaxis.
7. For any LMWH prophylaxis regimen, the timing of catheter removal is of paramount importance. Catheter removal should be delayed for at least 10 to 12 hours after a dose of LMWH. A true normalization of the patient's coagulation status could be achieved if the evening dose of LMWH was not given and the catheter was removed the following morning (24 hours after the last dose). Again, subsequent dosing should not occur for at least 2 hours after catheter removal.

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