REVIEW ARTICLE

Low Molecular Weight Heparin: Biochemistry, Pharmacology, Perioperative Prophylaxis Regimens, and Guidelines for Regional Anesthetic Management

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Multiple randomized clinical trials have established the efficacy of standard heparin (SH) anticoagulation for venous thromboembolism prophylaxis. However, for high-risk populations, such as patients undergoing total hip or knee replacement, SH is relatively ineffective and may be associated with significant bleeding complications (1). Initial animal model studies suggested that low molecular weight fractions of heparin, when administered at equivalent antithrombotic doses, caused less bleeding than SH (2). These early studies raised the exciting possibility of separating the antithrombotic from the bleeding effects of heparin. The efficacy and safety of low molecular weight heparins (LMWH) as postoperative venous thromboembolism prophylaxis subsequently has been demonstrated in more than 60 clinical trials including more than 20,000 patients (3). However, reports of spinal hematoma occurring spontaneously and in association with regional anesthesia (4,5) have generated concern regarding the safety of spinal or epidural anesthesia in patients receiving LMWH. In this review, we focus on the biochemistry and pharmacology of LMWH compared with SH, current LMWH prophylaxis regimens, and the implications of perioperative LMWH prophylaxis for anesthesia, particularly among patients receiving regional anesthesia and analgesia. Guidelines will be provided for minimizing the risk of spinal hematoma in patients undergoing regional anesthesia while receiving perioperative anticoagulant-based prophylaxis.

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Biochemistry and Pharmacology of SH and LMWH

SH is a mixture of linear polysaccharide molecules of variable chain lengths (45–50 sugar units) and molecular weights (5,000–30,000 daltons). The mean molecular weight of SH ranges from 12,000 to 15,000 Daltons. Heparin acts as an anticoagulant by binding and catalyzing antithrombin III, a plasma serine protease inhibitor. The heparin-antithrombin III complex inhibits several procoagulant serine proteases, including factors IIa (thrombin), IXa, Xa, XIa, and XIIa (Figure 1).

Heparin catalytic activity is dependent on both the polysaccharide chain length as well as a specific pentasaccharide sequence within the heparin molecule, which is a high-affinity binding site for antithrombin III. Approximately 30% of SH molecules contain the pentasaccharide high-affinity binding sequence and can catalyze antithrombin III. Heparin chain length partially determines antithrombin III substrate specificity. For example, to efficiently catalyze antithrombin III inhibition of factor IIa (thrombin), a heparin molecule must contain both the pentasaccharide high-affinity binding sequence as well as a chain length of at least 13 additional sugars. Conversely, only the pentasaccharide high-affinity binding sequence is required for heparin to catalyze antithrombin III inhibition of factor Xa.

Commercial LMWH is produced by either chemical or enzymatic depolymerization of SH and has a mean molecular weight of 4000–6500 Daltons and a chain length of 13–22 sugars. Consequently, LMWH retains full anti-Xa activity with relatively less anti-IIa (thrombin) activity. The concentration of LMWH is referenced to an international standard and usually expressed as anti-Xa U/mL.

The bioavailability and anticoagulant effect of SH is reduced due to binding of SH by plasma and platelet proteins, endothelial cells, and vascular wall matrix proteins (5). Many of these plasma proteins increase with illness as acute phase reactants (especially factor

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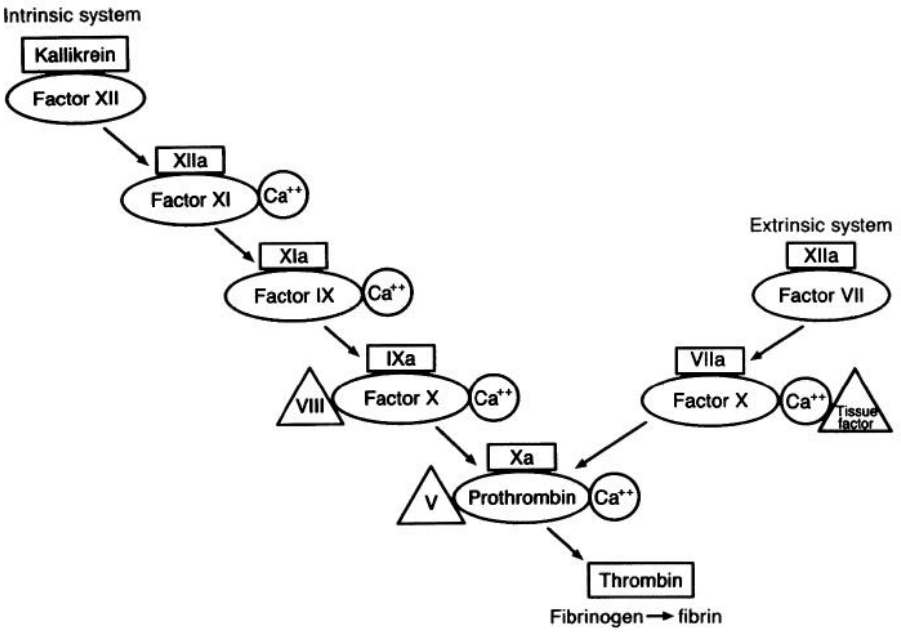

Figure 1. Schematic of the procoagulant system. Circulating procoagulants are shown in ellipses, and activated coagulation factors are shown in rectangles. Heparin catalyzes antithrombin III inhibition of all procoagulant factors enclosed in the rectangles except factor VIIa. Vitamin K-antagonist drugs reduce the plasma activities of factors II (prothrombin), VII, IX, and X. (Reproduced with permission from Horlocker TT, Wedel DJ. Anitcoagulants, antiplatelet therapy, and neuraxis blockade. In: Batra MS, ed. Anesthesiology clinics of North America. Vol 10. Philadelphia: WB Saunders, 1992:3.)

VIII and von Willebrand factor), which accounts in part for the large interpatient variability in the anticoagulant response to SH. In contrast, LMWH has a much lower affinity for plasma and matrix proteins (6), which results in greater 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.

Peak anti-Xa activity occurs 3–4 h after a subcutaneous LMWH injection, and 12-h anti-Xa levels are approximately 50% of peak levels. The clearance of SH is dose-dependent and occurs through a saturable mechanism due to binding by plasma proteins and endothelial cells, and a slower nonsaturable renal clearance. Because LMWH is not highly protein- or endothelial cell-bound, the saturable mechanism is minimal, and clearance is primarily renal. Therefore, the plasma half-life of LMWH is approximately 2–4 times longer than that of SH and increases in patients with renal failure (5,7). A comparison of the biochemistry and pharmacology of SH and LMWH is shown in Table 1.

Five LMWHs and one heparinoid (heparan and dermatan sulfate) are currently marketed or under development (Table 2). Low molecular weight heparin drugs vary both biochemically and pharmacologically, including molecular weight, anti-IIa and anti-Xa activities, and plasma half-life. Therefore, each drug must be administered based on the drug-specific dose and dosing schedule that have been determined in clinical trials to be safe and effective for the specific prophylaxis indication.

Administration, Monitoring, and Reversal of LMWH Anticoagulant Effect

To avoid bleeding and optimize convenience, most North American LMWH prophylaxis regimens for hip or knee replacement surgery administer the first dose from 12 to 24 h postoperatively and on a once- or twice-daily dosing schedule (dalteparin 5000 U once daily or enoxaparin 30 mg twice daily) (1). In contrast, European regimens typically administer the first dose 6 h preoperatively and use a once-daily schedule (enoxaparin 40 mg once daily). Neither regimen requires laboratory monitoring or dose adjustment. Several additional issues regarding the optimal LMWH prophylaxis regimen are unresolved, including fixed versus weight-adjusted dosing and the duration of prophylaxis (inpatient versus extended outpatient prophylaxis) (8,9). Because there are no adequate trials comparing the efficacy and safety of one LMWH with another, it is impossible to recommend one specific LMWH drug over another.

When LMWH is administered at prophylaxis doses, the activated partial thromboplastin time is a relatively insensitive measure of LMWH activity. The anti-Xa level, as measured by either clot-based assays, such as the Heptest, or amidolytic assays, is a more sensitive measure of LMWH anticoagulant effect. Peak anti-Xa levels of 0.1–0.2 U/mL provide safe and effective venous thromboembolism prophylaxis after hip or knee replacement surgery (10,11).

The anticoagulant effects of SH are neutralized by an equimolar dose of protamine. Because of reduced protamine binding to LMWH fractions, only the anti-IIa activity of LMWH is completely reversed, whereas anti-Xa activity is not fully neutralized. A dose of 1 mg

Table 1. Biochemical and Pharmacologic Properties of Standard Heparin and Low Molecular Weight Heparins

	Standard (unfractionated) heparin	Low molecular weight heparin
Mean molecular weight	12000–15000	4000–6500
Saccharide units (mean)	40–50	13–22
Anti-Xa/Anti-IIa activity	1:1	2:1 to 4:1
Affinity for plasma protein binding	High	Low
Binds to endothelium	Yes	Weakly
Dose-dependent clearance	Yes	No
Bioavailability at small doses	Poor	Good
Inhibits platelet function	Strong	Moderate
Increases vascular permeability	Yes	No

Adapted from reference 3.

Table 2. Commercially Available Low Molecular Weight Heparins

	Anti-factor Xa/IIa ratio	Mean molecular weight (range)	Saccharide units	Plasma half-life (min)	Recommended dose[a]	
					General surgery	Orthopedic surgery
Enoxaparin (Lovenox®, Clexane®; Rhône-Poulenc Rorer, Collegeville, PA)	2.7:1	4500 (3000–8000)	10–27	129–180	4000 U once daily	4000 U once daily or 3000 U twice daily
Dalteparin (Fragmin®; Kabi Pharmacia, Piscataway, NJ)	2.0:1	5000 (2000–9000)	7–30	119–139	2500 U once daily	2500 U twice daily or 5000 U twice daily
Nadroparin (Fraxiparin®; Sanofi Winthrop, New York, NY)	3.2:1	4500 (2000–8000)	7–27	132–162	2500 U once daily	
Tinzaparin (Logiparin®; Novopharm, Schaumberg, IL)	1.9:1	4500 (3000–6000)	10–20	111	3500 U once daily	75 U/kg once daily
Ardeparin (Normoflo®; Wyeth-Ayerst Laboratories, Philadelphia, PA)	2.0:1	6000 (2000–15,000)	7–50	200		50 U/kg twice daily
ORG 10172 (Lomoparan®; Organon, West Orange, NJ)	20:1	6500		1100		750 U twice daily

From reference 7, with permission.
[a] Converted into international anti-Xa units.

protamine/100 LMWH anti-Xa units reverses 90% of anti-IIa and 60% of anti-Xa activity. The clinical significance of the residual anti-Xa effect is unknown. Both anti-IIa and anti-Xa activity may return up to 3 h after protamine reversal, possibly due to release of additional LMWH from the subcutaneous depot (12).

LMWH for Venous Thromboembolism Prophylaxis

A comprehensive review of venous thromboembolism prophylaxis is beyond the scope of this article. We have restricted our review to the current Food and Drug Administration (FDA)-approved indications for LMWH as venous thromboembolism prophylaxis. For a more comprehensive review, the reader is referred to another publication (1).

Orthopedic Surgery Patients

In the absence of prophylaxis, the prevalence of deep venous thrombosis as detected by venography among patients undergoing major orthopedic surgery ranges from 50% for total hip replacement to 80% for total knee replacement patients (1). LMWH provides safe and effective prophylaxis in patients undergoing total knee or hip replacement. However, the efficacy varies by type of orthopedic procedure. For patients undergoing total hip replacement, LMWH is as effective as

adjusted-dose subcutaneous SH and low-intensity oral anticoagulation (international normalized ratio 2.0–3.0) (13,14). However, for patients undergoing total knee replacement, LMWH is significantly more effective than all other anticoagulant-based methods of prophylaxis (15–19). The risk of major bleeding among patients receiving LMWH is similar to that with other anticoagulant-based methods of prophylaxis (20,21). Currently, dalteparin and enoxaparin are FDA-approved and are marketed for prophylaxis after lower extremity joint replacement surgery, and ardeparin will be marketed for the same indication in the near future. LMWH prophylaxis is more effective and is as safe as low-dose SH prophylaxis after major trauma (22).

General Surgery Patients

Several large studies and meta-analyses report a modest decrease in venous thromboembolism prevalence among general surgery patients receiving LMWH compared with low-dose SH prophylaxis (20,21,23,24). In one study, the incidence of major bleeding was significantly less among LMWH patients compared with SH patients (24). Prophylaxis with LMWH may be appropriate for general surgery patients at especially high risk, such as those patients undergoing abdominal or pelvic surgery for malignancy. However, due to the greater LMWH cost and lower risk for postoperative deep venous thrombosis, LMWH is unlikely to replace SH as standard prophylaxis for other general surgery patients. Currently, dalteparin and enoxaparin are FDA-approved and are marketed for prophylaxis after general surgery.

Bleeding and heparin-induced thrombocytopenia and thrombosis (HITT) are the major complications associated with SH or LMWH prophylaxis. HITT, which is characterized by the presence of heparin-dependent, platelet-activating antibodies, typically occurs 7–10 days after initiation of heparin prophylaxis and may be associated with both venous and arterial thrombosis. In a clinical trial randomizing total hip replacement patients to either LMWH or SH prophylaxis, the incidence of HITT and heparin-dependent antibodies was significantly greater among patients receiving prophylaxis with SH (2.7%) compared with those receiving LMWH (0%) (25). However, HITT associated with LMWH therapy has been reported (26). Furthermore, antibody cross-reactivity between SH and LMWHs occurs in 40%–90% of patient sera with known heparin antibodies (27). Therefore, LMWH should be avoided in patients with established HITT. Heparinoids such as danaparoid, which contain no heparin, have minimal cross-reactivity and have been used successfully in patients with HITT (28).

Spinal and Epidural Anesthesia in the Patient Receiving Standard or Low Molecular Weight Heparin

Neurologic dysfunction due to bleeding after neuraxial blockade is rare, with an estimated incidence of less than 0.5 per 100,000 spinal anesthetics and less than 0.7 per 100,000 epidural anesthetics (29). A review of clinical studies involving patients undergoing regional anesthesia while receiving anticoagulants, as well as case reports of spinal hematoma after neuraxial block, is helpful in evaluating potential risk factors for spinal bleeding. Vandermuelen et al. (4) reported 61 cases of spinal hematoma associated with spinal or epidural anesthesia. In 42 (68%) of the patients, there was evidence of a hemostatic abnormality. Twenty-five patients had received intravenous (IV) heparin (18 patients), subcutaneous heparin (3 patients), or LMWH (4 patients), whereas an additional 5 patients presumably received heparin during a vascular surgical procedure. Timing of needle placement relative to heparinization was not reported. A spinal anesthetic was performed in 15 patients, whereas the remaining 46 patients received an epidural anesthetic, including 32 patients with an indwelling catheter. In 15 of these 32 patients, the spinal hematoma occurred immediately after removal of the epidural catheter. These results are noteworthy, as they suggest that both catheter removal and the patient's coagulation status at the time of removal are critical factors in the development of spinal bleeding. A more recent investigation of 8501 spinal and 9232 epidural anesthetics performed from 1991 to 1994 reported three spinal hematomas, which all occurred in anticoagulated patients receiving postoperative epidural analgesia (30). Two patients received an anticoagulant before catheter placement (one patient was chronically anticoagulated with dicoumarol and one patient received LMWH); the third patient received dextran intraoperatively and IV heparin postoperatively.

IV and Subcutaneous Heparin

Several large studies have demonstrated that spinal or epidural anesthesia followed by systemic heparinization is relatively safe (31,32). Rao and El-Etr (31) reported no spinal hematomas in over 4000 patients undergoing lower extremity vascular surgery under continuous spinal or epidural anesthesia. However, patients with preexisting coagulation disorders were excluded, heparinization occurred at least 60 min after catheter placement, the level of anticoagulation was carefully monitored, and the indwelling catheters were removed at a time when heparin activity was low. Surgery in patients with frank blood noted in the needle was canceled and was performed the following

day under general anesthesia. Subsequent investigations (4) of patients undergoing complete heparinization during cardiopulmonary bypass after subarachnoid or epidural needle/catheter placement typically followed the techniques described by Rao and El-Etr, including exclusion of patients with preexisting coagulapathies, a minimum of 1 h between needle placement and heparinization, close monitoring of clotting times, and postponement of surgery should a bloody tap occur. These methods were also substantiated in a subsequent report in the neurologic literature. Ruff and Dougherty (33) noted spinal hematomas in 7 of 342 (2%) patients who underwent lumbar puncture and subsequent heparinization for evaluation of cerebral ischemia. The presence of blood during needle or catheter placement, concomitant aspirin therapy, and heparinization within 1 h were identified as risk factors for spinal hematoma (33).

The safety of subcutaneous administration of SH also is well documented. A review by Schwander and Bachman (34) reported no spinal hematomas in more than 5000 patients undergoing spinal or epidural anesthesia while receiving varying doses of low-dose SH. Only three cases of spinal bleeding after subcutaneous SH have been reported in the literature, two of which involved a continuous epidural technique (4).

LMWH

The administration of LMWH in patients undergoing spinal or epidural anesthesia was examined by Bergqvist et al. (35,36) in two reviews published in 1992 and 1993. These studies represent 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. identified 19 articles involving 9013 patients who had safely received the combination of LMWH and spinal or epidural anesthesia. None of the studies were stratified on the basis of anesthetic methods, details of the regional anesthetic technique are not reported, and, with few exceptions, neurologic complications related to spinal or epidural blockade are not included (37,38). 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 (39). Based on these data, Bergqvist et al. concluded that neurologic complications after spinal or epidural anesthesia in patients receiving LMWH thromboprophylaxis are extremely rare, and that the combination seemed safe. However, an accompanying editorial urged caution (40).

In a MEDLINE search of the literature in English, we identified 215 studies in which LMWH had been administered to surgical or obstetric patients. In 39 of these studies, spinal or epidural anesthesia had been used in combination with perioperative LMWH thromboprophylaxis (Table 3). These studies represent 15,151 spinal or epidural anesthetics. A single-dose spinal was performed in 7400 cases, a continuous spinal in 20 cases, and an epidural anesthetic in 2957 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 4774 cases. LMWH thromboprophylaxis was initiated preoperatively in nearly 90% of cases and was typically administered once daily. A variety of LMWH preparations and doses 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 neurologic complications attributed to the anesthetic technique would remain unreported. However, limitations identical to those of the reports by Bergqvist et al. remain.

The ongoing trauma associated with the presence of an indwelling intrathecal catheter (22-gauge) was investigated by Lindgren et al. (64). Erythrocyte counts in the cerebrospinal fluid (CSF) of 66 orthopedic, vascular, and urologic patients were monitored. Twenty arthroplasty patients received enoxaparin 2000–4000 U, 22 vascular patients (many of whom admitted to regular aspirin therapy) received IV heparin 100 U/kg intraoperatively, and 24 prostatectomy patients had no anticoagulant or antiplatelet medications administered perioperatively and served as controls. Samples of CSF were collected immediately after catheter placement, 1 h after heparinization (vascular patients), or 3 h after catheter placement (arthroplasty and urologic patients), in the recovery room (vascular patients only), and before catheter removal 24 h later. A total of 17 patients, 5 each in the arthroplasty and vascular patients and 7 control (urologic) patients had more than 100×10^6/L erythrocytes and macroscopically blood-tinged CSF in at least one of the samples. There was no difference in CSF erythrocyte counts among patient groups. No patient exhibited signs of spinal hematoma. The authors concluded that the indications for the placement of an intrathecal catheter should be carefully weighed against the risk of spinal bleeding, and that the perioperative administration of SH and LMWH does not increase the risk of subarachnoid hemorrhage associated with continuous spinal anesthesia.

There have been eight published case reports of spinal hematoma in patients undergoing spinal or epidural anesthesia while receiving LMWH thromboprophylaxis (Table 4). The first five were published in non-English journals, reflecting the patient population

Table 3. Case Series with Combined Use of Low Molecular Weight Heparin (LMWH) and Spinal or Epidural Anesthesia

Author (reference)	Type of surgery	Type of LMWH	LMWH Dose (anti-Xa units)	Timing of first LMWH dose	Number of patients on LMWH	Number of patients on LMWH with epidural or spinal anesthesia
Avikainen et al. (41)	Orthopedic	Enoxaparin	4000 U once daily	12 h preoperatively	83	65 spinal
Baumgartner et al. (42)	Abdominal	Unspecified[a]	1500 U once daily	2 h preoperatively	87	37 epidural
Bergqvist et al. (43)	Abdominal	Dalteparin	5000 U once daily	12 h preoperatively	505	101 epidural
Bergqvist et al. (44)	Abdominal	Dalteparin	2500 U or 5000 U once daily	12 h preoperatively	2070	621 epidural
Borghi et al. (45)	Orthopedic	Unspecified	Unspecified	Unspecified	231	~78 spinal or epidural
Christiansen et al. (46)	Orthopedic	Tinzaparin	50 U/kg once daily	2 h preoperatively	105	29 spinal or epidural
Colwell and Spiro (47)	Orthopedic	Enoxaparin	1000 U or 4000 U once daily or 3000 U twice daily	12–48 h postoperatively	1348	~225 spinal or epidural
Colwell and Spiro (48)	Orthopedic	Enoxaparin	4000 U once daily or 3000 U twice daily	<24 h postoperatively	398	136 spinal or epidural
Danish Enoxaparin Study Group (49)	Orthopedic	Enoxaparin	4000 U once daily	12 h preoperatively	108	79 spinal or epidural
Dulitzki et al. (50)	Obstetric	Enoxaparin	2000–8000 U daily	Prepartum; LMWH continued to postpartum period	41	9 continuous epidural
Eriksson et al. (51)	Orthopedic	Dalteparin	5000 U once daily	12 h preoperatively	67	57 epidural
Eriksson et al. (52)	Orthopedic	Dalteparin	2500 U twice daily	2 h preoperatively	49	45 epidural
Eriksson et al. (53)	Orthopedic	Dalteparin	5000 U once daily or 2500 U twice daily	12 h preoperatively, 2 h preoperatively	116	99 epidural
Fauno et al. (54)	Orthopedic	Enoxaparin	4000 U once daily	12 h preoperatively	92	82 spinal or epidural
Fauno et al. (55)	Orthopedic	Enoxaparin	4000 U once daily	12 h preoperatively (2000-U dose)	186	49 epidural; some patients also on NSAIDs
Haas and Flosbach (56)	General surgical	Enoxaparin	2000 U once daily	2 or 12 h preoperatively	9919	1894 spinal or epidural
Hamulyak et al. (57)	Orthopedic	Nadroparin	60 U/kg once daily	12 h preoperatively	330	149 spinal, 30 epidural
Heit et al. (19)	Orthopedic	Ardeparin	25–50 U/kg twice daily	12–24 h postoperatively	554	85 spinal, 101 epidural
Hull et al. (16)	Orthopedic	Tinzaparin	75 U/kg once daily	18–24 h postoperatively	715	330 spinal
Jorgenson et al. (58)	Orthopedic	Dalteparin	5000 U once daily	2 h preoperatively (2500-U dose)	30	10 spinal
Koppenhagen et al. (59)	Abdominal	Mono-Embolex NM® (Sandoz AG, Germany)	3000 U once daily	2 h preoperatively	323	18 continuous epidural; catheters left indwelling 24–48 h
Lassen et al. (60)	Orthopedic	Heparin-NM-Dihydergot®[a] (Sandoz A/S, Denmark)	6000 U once daily	Preoperatively	53	11 epidural
Lassen et al. (61)	Orthopedic	Heparin-NM-Dihydergot®[a] (Sandoz A/S, Denmark)	6000 U once daily	2 h preoperatively	107	12 epidural
Lassen et al. (62)	Orthopedic	Tinzaparin	50 U/kg once daily	2 h preoperatively	93	26 spinal or epidural
Leclerc et al. (17)	Orthopedic	Enoxaparin	3000 U twice daily	Day of surgery or 24 h postoperatively	66	4 epidural
Leclerc et al. (18)	Orthopedic	Enoxaparin	3000 U twice daily	24 h postoperatively	336	43 spinal or epidural
Levine et al. (63)	Orthopedic	Ardeparin	50 U/kg twice daily	12–24 h postoperatively	122	12 spinal or epidural
Lindgren et al. (64)	Orthopedic	Enoxaparin	2000–4000 U daily	2 or 12 h preoperatively	20	20 continuous spinal; catheters indwelling 24 h
Matsch et al. (65)	Orthopedic	Tinzaparin	35 U/kg once daily	2 h preoperatively	47	45 spinal or epidural
Ockelford et al. (66)	General surgical	Dalteparin	2500 U once daily	2 h preoperatively	95	3 epidural
Oerlti et al. (67)	Orthopedic	Sandoparin	3000 U once daily	Preoperatively	113	96 spinal or epidural
Planes et al. (37)	Orthopedic	Enoxaparin	4000 U once daily	1 h after spinal (2000-U dose) or 12 h postoperatively	188	126 spinal
Pham et al. (68)	Unspecified	Enoxaparin	4000 U once daily	12 h preoperatively (2000-U dose)	1025	751 spinal, 274 continuous epidural
RD Heparin Group (15)	Orthopedic	Ardeparin	50 U/kg twice daily or 90 U/kg once daily	12 h postoperatively	770	216 spinal, 89 epidural
Sturridge et al. (69)	Obstetric	Enoxaparin	2000 or 4000 U once daily	Prepartum; LMWH continued to postpartum period	18	3 continuous epidural
Torholm et al. (70)	Orthopedic	Dalteparin	5000 U once daily	2 h preoperatively (2500-U dose)	58	6 spinal, 1 epidural
Warwick et al. (71)	Orthopedic	Enoxaparin	4000 U once daily	12 h preoperatively	78	78 spinal or epidural
Wolf et al. (72)	Orthopedic, trauma, urologic, gynecologic	Mono-Embolex NM® (Sandoz AG, Germany)	3000 U once daily	Unspecified	5765	632 spinal, 135 epidural
Wolf (73)	Orthopedic, general, urologic, gynecologic	Embolex NM®[a] (Sandoz AG, Germany)	3000 U once daily	2 h preoperatively	43,526	5030 spinal, 1105 single-dose epidural, 153 continuous epidural, 1951 spinal or epidural

NSAIDs = nonsteroidal antiinflammatory drugs.
[a] LMWH preparation containing dihydroergotamine 0.5 mg.

Table 4. Case Reports of Spinal Hematoma Associated with Low Molecular Weight Heparin (LMWH) and Spinal or Epidural Anesthesia

Author, year (reference)	Regional anesthetic technique	Timing of catheter removal	Type of LMWH	LMWH Dose (anti-Xa units)	Timing of LMWH dose and needle placement	Onset of symptoms	Neurologic outcome	Comments
Tryba, 1989 (39)	Combined spinal/epidural, minimal bleeding during catheter placement	Unspecified	Nadroparin	5000 U twice daily	Unspecified	3 h after third LMWH dose	Paralysis; epidural hematoma (T9-L4) decompressed	3 doses of LMWH administered within 34 h
Tryba, 1993 (29) (two reports)	Continuous epidural	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Paralysis; intervention unknown	Dextran and intravenous heparin also administered
Choquet et al., 1993 (74)	Spinal		Nadroparin	4000 U once daily	16 h preoperatively (3000-U dose)	40 h postoperatively	Laminectomy on sixth postoperative day, residual cauda equina syndrome	
Bent et al., 1994 (75)	Single-dose epidural		Mono-Embolex NM® (Sandoz AG, Germany)	3000 U once daily	8 h postoperatively	6 days postoperatively	Back pain with radiation; L3-4 epidural hematoma on MRI, spontaneous resolution	
Sternlo and Hybbinette, 1995 (76)	Spinal (after failed epidural with blood present in catheter)		Enoxaparin	4000 U once daily	12 h preoperatively	40 h postoperatively	Paralysis; spinal stenosis and epidural/subdural hematoma on MRI, laminectomy 30 h later, little improvement in symptoms	Diclofenac also administered postoperatively
Dahlgren and Tornebrandt, 1995 (30)	Continuous epidural—two catheters placed in 5 days	24 h postoperatively (both catheters)	Enoxaparin	4000 U once daily	Preoperatively (first procedure) for 7 days	48 h after second procedure	Paralysis; subdural hematoma (T11-L1) on CT, laminectomy performed without improvement	
Hynson et al., 1996 (77)	Continuous epidural	Immediately postoperatively (1 h after LMWH dose)	Enoxaparin	3000 U twice daily	12 h preoperatively and 30 min after catheter placement	14 h postoperatively (3 h after third LMWH dose)	Paralysis; epidural hematoma (T5-L3) on MRI, laminectomy performed with fair recovery	Patient had received 3 doses LMWH in 12 h

MRI = magnetic resonance imaging, CT = computed tomography.

to which LMWH was administered at that time. Evaluation of patient and anesthetic factors associated with these five cases subsequently led to guidelines for the practice of regional anesthesia in patients receiving LMWH. Tryba (29) recommended that needle and catheter placement should be delayed for at least 10–12 h after the last dose of LMWH. Likewise, catheter removal should occur at least 10–12 h after the last dose, with subsequent dosing of LMWH delayed for at least 2 h after catheter removal. Similar recommendations were made by Vandermeulen et al. (4) in their review. These guidelines have apparently been effective in reducing 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, for example by performing a spinal rather than a continuous epidural anesthetic.

Enoxaparin was released for general use by the FDA in May 1993. Since that time, there have been 16 cases of spinal hematoma in the United States associated with LMWH thromboprophylaxis reported to the manufacturer (Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, PA) (Tables 4 and 5). Only one of these has been published as a case report (77) (Table 4). 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 doses administered and the prevalence of regional anesthesia in orthopedic patients places the frequency between 1 in 1,000 and 1 in 10,000 regional anesthetics. It is possible that the frequency of spinal hematoma reported to European manufacturers is significantly greater 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 frequencies of spinal hematoma between the United States and Europe. Perhaps the most important factor is the difference in dosing of enoxaparin, which is 30 mg (3000 U) twice daily in the United States and 40 mg (4000 U) once daily in Europe. The twice-daily dose regimen may provide a greater 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. The variation in dosing between the United States and Europe results from 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 often initiated preoperatively (or intraoperatively by the anesthesiologist) in Europe. In the United States, product prescribing information

Table 5. Cases of Spinal Hematoma Associated with Enoxaparin and Spinal or Epidural Anesthesia Reported to Manufacturer

Date	Regional anesthetic technique	Timing of catheter removal	Enoxaparin (anti-Xa units) (1000 U = 10 mg)	Timing of enoxaparin dose with needle placement	Onset of symptoms	Neurologic outcome	Comments
July 1992 (foreign report)	Unspecified		4000 U once daily	12 h preoperatively (2000-U dose)	4 days postoperatively	Paresis and cauda equina syndrome; subarachnoid hematoma (T9) decompressed without improvement	
October 1993	Continuous epidural	Catheter remained indwelling >24 h	3000 U twice daily	4 h after catheter placement	24 h postoperatively	Paralysis; epidural hematoma (above site of previous laminectomy) decompressed without improvement	
March 1994	Spinal		3000 U twice daily	Operative day	14 days postoperatively	Paralysis; subarachnoid hematoma (T11-12) evacuated without improvement	Symptoms occurred 11 days after discontinuation of LMWH; aspirin and ketorolac administered perioperatively
May 1994	Continuous epidural	48 h postoperatively	3000 U twice daily	24 h postoperatively	6 days postoperatively	Paralysis; epidural hematoma (T11-L2) decompressed, good recovery	
May 1994	Unspecified		3000 U twice daily	Unspecified	9 days postoperatively	Numbness, inability to void; laminectomy performed without improvement	
March 1995	Continuous epidural	Left indwelling, timing of removal unspecified	3000 U twice daily	8 h postoperatively	3 h after second LMWH dose	Paralysis; epidural hematoma on MRI, laminectomy performed with fair improvement	
June 1995	Continuous epidural	48 h postoperatively	3000 U twice daily	12 h postoperatively	Shortly after removal of catheter, 48 h postoperatively	Paralysis; epidural hematoma, intervention unknown, poor recovery	
October 1995	Continuous epidural	24 h postoperatively, and 1 h after LMWH and ketorolac administration	3000 U twice daily	6 h after catheter placement	48 h postoperatively	Paralysis; epidural hematoma evacuated, outcome unknown	Ketorolac also administered
November 1995	Continuous epidural	48 h postoperatively	3000 U twice daily	24 h postoperatively	48 h postoperatively	Paralysis and cauda equina syndrome; epidural hematoma T12-L3 on MRI, laminectomy performed with partial recovery	
January 1996	Continuous epidural	96 h postoperatively	3000 U twice daily	Postoperatively (on operative day)	7 days	Unilateral paresis; epidural hematoma L2-3 on MRI, laminectomy performed with fair recovery	
January 1996	Continuous epidural	72 h postoperatively, 5 h after LMWH dose	3000 U twice daily	9 h postoperatively	After catheter removal	Paralysis and cauda equina syndrome; epidural hematoma T12—sacrum on MRI, no surgical intervention, poor neurologic recovery	Patient also received ketorolac for 48 h postoperatively
January 1996	Continuous epidural	48 h postoperatively, <1 h before LMWH dose	3000 U twice daily	24 h postoperatively	30 min after catheter removed (paralysis), numbness and inability to void reported 8–10 h earlier	Paralysis and cauda equina syndrome; T8-L4 epidural hematoma on MRI, laminectomy with good recovery	Ketorolac administered concomitantly
August 1996	Continuous epidural—3 catheters placed in 3-wk period	48 h postoperatively	3000 U twice daily	Initiated after first procedure and continued for 3 wk	Before third surgical procedure/epidural	Back pain and fever; abnormality at L1-3 noted on MRI, laminectomy performed, no deficits	Infected epidural hematoma (pseudomonas cultured)
September 1996	Continuous epidural	36 h postoperatively, when patient complained of minor neurologic symptoms	3000 U twice daily	Immediately postoperatively	Complete paralysis developed on removal of catheter	Paralysis; epidural hematoma evacuated, poor recovery	
October 1996	Continuous epidural	48 h postoperatively	3000 U twice daily	Postoperatively (on operative day)	48 h postoperatively	Laminectomy performed to evacuate epidural hematoma, good neurologic recovery	
October 1996	Continuous epidural analgesia (chronic pain syndrome)	72 h after placement	Unspecified	LMWH initiated 5 days earlier, dose given 6 h before catheter placement	8 days after LMWH therapy initiated, 3 days after epidural catheter placed	Paralysis; laminectomy performed to evacuate epidural hematoma, fair recovery	

Information obtained from Rhône-Poulenc Pharmaceuticals, Inc., Collegeville, PA. Two additional cases have been reported (Table 4, references 76 and 77).
MRI = magnetic resonance imaging.

(Lovenox®; Rhône-Poulenc Rorer Pharmaceuticals, Inc.) recommends that the first dose be administered 12–24 h after surgery or when hemostasis is achieved, whichever is later. Postoperative initiation of thromboprophylaxis should actually improve the safety of regional anesthesia in patients receiving LMWH in the United States. Finally, the regional anesthetic technique may affect the risk of spinal hematoma. Of the 16 patients with spinal hematomas associated with LMWH thromboprophylaxis in the United States, 14 had indwelling epidural catheters for at least 24 h.

Identification of Risk Factors

Examination of the 24 spinal hematomas reported in Tables 4 and 5 demonstrates several possible risk factors. However, only a partial evaluation is possible; only patients with spinal hematomas are described, and nothing is reported on the patient, anesthetic, and surgical factors of the several million patients who uneventfully received the combination of LMWH and spinal or epidural anesthesia (35). Of the 22 cases of spinal hematoma in which the regional anesthetic technique was specified, 19 involved epidural anesthetics, 18 of which involved catheter placement. In addition, 7 of 18 patients with indwelling epidural catheters became paraplegic within a few hours of catheter removal, which again suggests that catheter removal is a traumatic event. Conversely, the number of spinal hematomas occurring in patients with epidural anesthesia and analgesia may simply reflect the patient population receiving LMWH thromboprophylaxis and regional anesthetic techniques—orthopedic surgical patients. Several other risk factors are apparent. In four cases, the patient received additional doses of LMWH or IV heparin and dextran perioperatively. Antiplatelet medications were administered in an additional five cases. Bleeding complications in patients receiving antiplatelet therapy in combination with LMWH is not unexpected. The potentiation of LMWH activity by antiplatelet medications has been reported *in vivo* (78). In 1995, in response to these cases, the manufacturer revised the product prescribing information (Lovenox®; Rhône-Poulenc Rorer Pharmaceuticals, Inc.) to urge caution in the use of enoxaparin in patients with indwelling intrathecal or epidural catheters or in patients treated concomitantly with platelet inhibitors.

Guidelines for the Management of Regional Anesthesia in Patients Receiving Perioperative Heparin

The decision to perform neuraxial blockade on a patient receiving perioperative SH or LMWH must be made on an individual basis, weighing the risk of spinal hematoma with the benefits of regional anesthesia for a specific patient. The following statements, based on the pharmacologic properties of SH and LMWH, as well as case reports and clinical studies involving patients undergoing spinal or epidural anesthesia while receiving these medications, will guide the clinician faced with this difficult decision.

IV Heparin

Spinal and epidural anesthesia may be safely performed in the patient undergoing subsequent therapeutic heparinization provided heparinization occurs a minimum of 60 min after needle placement, the heparin effect is monitored and maintained within acceptable levels (activated clotting time or activated partial thromboplastin time 1.5–2.0 times baseline), and indwelling catheters are removed at a time when heparin activity is low or completely reversed (4,31–33). Some authors also recommend cancellation of surgery should bleeding occur during needle or catheter placement (4,31).

SH

Recommendations for the performance of regional anesthesia in patients receiving subcutaneous SH include avoidance of needle placement or catheter removal within 4 h of administration, and monitoring of anticoagulant effect in patients with liver disease or long-term thromboprophylaxis (4,29). Extrapolation to patients receiving LMWH is tempting. However, the difference in pharmacokinetics must be considered.

LMWH

Preoperative LMWH. Patients receiving preoperative LMWHs can be assumed to have altered coagulation. LMWHs are potent antithrombotic agents with a 3- to 4-h half-life. Approximately 50% of peak anti-Xa activity is present 12 h after injection. Concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, SH, or dextran represents an additional risk of hemorrhagic complications perioperatively, including spinal hematoma. A single-dose spinal anesthetic may be the safest neuraxial technique in patients receiving preoperative LMWHs. Needle placement should occur at least 10–12 h after the last LMWH dose. Subsequent dosing should be delayed for at least 2 h after needle placement. The presence of blood during needle placement may warrant an additional delay in initiation of postoperative thromboprophylaxis.

Postoperative LMWH. Patients with postoperative initiation of LMWH thromboprophylaxis may safely undergo single-dose and continuous catheter techniques. If a continuous technique is selected, ideally the epidural catheter should be left indwelling overnight and removed the following day, with the first

dose of LMWH administered 2 h after catheter removal. The decision to implement LMWH thromboprophylaxis in the presence of an indwelling catheter must be made with care, and extreme vigilance of the patient's neurologic status is warranted. An opioid or dilute local anesthetic solution is recommended in these patients to allow continuous monitoring of neurologic function. For any LMWH prophylaxis regimen, the timing of catheter removal is of paramount importance. Catheter removal should be delayed for at least 10–12 h after a dose of LMWH. A true normalization of the patient's coagulation status could be achieved if the evening dose of LMWH is not given and the catheter is removed the following morning (24 h after the last dose). Again, subsequent dosing should not occur for 2 h after catheter removal.

Patients should be closely monitored in the perioperative period for early signs of cord compression, such as progression of numbness or weakness, and bowel and bladder dysfunction. Severe back pain was rare in our series of patients. If spinal hematoma is suspected, radiographic confirmation must be sought immediately, because delay may lead to irreversible cord ischemia. The treatment of choice is decompressive laminectomy. Recovery is unlikely if surgery is postponed more than 8 h (4).

In summary, regional anesthesia in association with perioperative heparin prophylaxis or systemic heparin anticoagulation is safe and effective with appropriate patient selection and anesthetic technique. A thorough knowledge of SH and LMWH biochemistry and pharmacology will allow optimal regional anesthesia management while minimizing the risk of intraspinal bleeding, as well as venous thromboembolism.

Addendum

Our series of patients with spinal hematoma associated with LMWH (Tables 4 and 5) is comprehensive through December 1996. However, in the first four months of 1997, there have been five additional cases reported to the manufacturer and one published report.

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