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ORIGINAL ARTICLE

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Postoperative nadroparin administration for prophylaxis of thromboembolic events is not associated with an increased risk of hemorrhage after spinal surgery

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Abstract Aim: To determine the risk of postoperative hemorrhage during a 3-year period of early postoperative administration of nadroparin (Fraxiparin) plus compression stockings in a large cohort of patients who underwent spinal surgery. Methods: A total of 1,954 spinal procedures at different levels (503 cervical, 152 thoracic and 1,299 lumbar), performed between June 1999 and 2002 at the Department of Neurosurgery, Johann-Wolfgang-Goethe University Frankfurt, were included in this study. To prevent venous thromboembolic events (VTE), all patients were routinely treated subcutaneously with 0.3 ml of early (less than 24 h) postoperative nadroparin calcium (Fraxiparin) (2850 IU anti-Xa, Sanofi Winthrop Industrie, France) plus intra- and postoperative compression stockings until discharge. The occurrence of a postoperative hematoma (defined as a hematoma requiring surgical evacuation because of space occupation and/or neurological deterioration) and a deep venous thrombosis (DVT) were recorded in a database and analyzed retrospectively. Results: 13 (0.7%) of the 1,954 spinal operations were complicated by major postoperative hemorrhages. In 5 of the 13 patients (38.5%) the hemorrhage occurred on the day of surgery before the administration of nadroparin. Thus, the hemorrhage rate of patients receiving nadroparin was 0.4% (8/1,949). Ten (77%) of the 13 patients with major postoperative hematoma showed a progressive neurological deficit, which resolved in 6 patients and resulted in a hematoma-related morbidity of 31% (4/13). Only 1 patient (0.05%) in this series developed a clinically evident DVT, and none of the patients suffered from pulmonary embolus during the hospital stay. Conclusion: Although retrospective, this is to date the largest study providing information about the hemorrhage rate associated with early postoperative anticoagulation following spinal surgery. The results confirm that early postoperative pharmacological thromboembolic prophylaxis using nadroparin in patients with spinal surgery is not associated with an increased risk of postoperative hemorrhage.

Keywords Spinal surgery · Hemorrhage · Thrombosis · Thromboembolism · Heparin

Introduction

Patients with spinal disorders that have to be treated surgically are at considerable risk of developing a postoperative deep venous thrombosis (DVT) [18] or venous thromboembolic events (VTE) like pulmonary embolism (PE) [1] - especially those patients with spinal cord injury and/or impaired motor function. Numerous prospective, randomized, double-blind trials have shown a significant de-

crease in VTE when using mechanical and/or pharmacological DVT prophylaxis in patients undergoing general, urological or orthopedic surgery [5, 7, 11, 13, 16].

The incidence of DVT after various spinal procedures ranges from 0.9 to 15.5% [9, 10, 18, 20]. Mechanical devices, such as intermittent pneumatic compression, significantly reduced the incidence of acute postoperative DVT compared to compression stockings [10]. However, pharmacological prevention of VTE is rarely used in contemporary spinal surgery because of concern about postoperative hemorrhage. Moreover, given the potential complications of pharmacological anticoagulation, some authors recommend only mechanical prophylaxis after spinal surgery [9]. Up to date, only a few studies have addressed the risk of postoperative hemorrhage after spinal surgery using pharmacological thromboembolic prophylaxis [4].

Nadroparin (Fraxiparin) is a low-molecular-weight heparin (LMWH) with a mean weight of 4,500 Da. Several studies have demonstrated its safety and effectiveness in postoperative DVT prophylaxis when injected subcutaneously in a daily single standard dose of 0.3 ml in surgical patients without an increase in postoperative hemorrhage [14, 15].

The objective of our study was, therefore, to analyze the rate of postoperative hemorrhage during a 3-year period of routine early postoperative administration of nadroparin plus compression stockings in a large cohort of consecutive patients who underwent spinal surgery.

Patients and methods

A total of 1,954 consecutive spinal procedures were included in this study. Patients were operated on between June 1999 and 2002 at the Department of Neurosurgery, Johann-Wolfgang-Goethe University Frankfurt at different levels of the spine, including 503 cervical, 152 thoracic and 1,299 lumbar procedures (Tables 1, 2, 3). All procedures were performed under general anesthesia. Mobilization of the patients usually started the next morning after surgery.

Major postoperative hemorrhage was defined as a hemorrhage associated with a mass effect on postoperative spinal MRI and/or neurological deterioration, as well as a large-wound hematoma with intractable pain. All patients with postoperative hematoma, who required surgical treatment, were retrieved from the operative database and analyzed retrospectively.

At our institution, we did not perform routine postoperative MRI in neurologically intact patients. Thus, the time of postoperative hematoma formation could only be exactly determined if they presented with progressive neurological deterioration or intractable pain.

Surveillance of VTE was done clinically. When patients presented with clinical criteria of a DVT or pulmonary embolism (PE; i.e,. pain and swelling of the leg, sudden onset of respiratory difficulties without a previous history of dyspnea), a venography was performed to confirm clinical diagnosis. However, no routine venography or duplex ultrasound was performed for DVT exclusion.

Table 1 Summary of procedures performed at the cervical spine to treat different pathologies. All operations were performed at the Department of Neurosurgery, University of Frankfurt between June 1999 and 2002

Procedure	No.	(%)
Cervical disc herniation and/or spinal stenosis (ventral fusion)	390	77.5
Miscellaneous tumor surgery	37	7.3
Cervical abscess and empyema	21	4.2
C1/2 posterior stabilization	23	4.6
Stabilization of cervical spine fractures	23	4.6
Anterior screw fixation of dens fractures	7	1.4
Spontaneous intraspinal hematoma	2	0.4
Total	503	100

Table 2 Summary of procedures performed at the thoracic spine

Procedure	No.	‰
Decompression of spinal cord (metastasis)	48	31.6
Miscellaneous tumor surgery	37	24.3
Meningioma	16	10.5
Thoracic disc herniation	13	8.6
Spontaneous intraspinal hematoma	12	7.9
Abscess and empyema	11	7.2
Decompression of syrinx	5	3.3
Traumatic fractures	5	3.3
Occlusion of arterio-venous fistulae	5	3.3
Total	152	100

Table 3 Summary of procedures performed at the lumbar spine

Procedure	No.	(%)
Lumbar disc herniation and/or spinal stenosis	1,215	93.5
Miscellaneous tumor surgery	44	3.5
Posterior and/or anterior stabilization procedures	20	1.5
Abscess and empyema	20	1.5
Total	1,299	100

Routine coagulation testing

Perioperative platelets (PLTS), partial thromboplastin time (PTT), prothrombin time (PT), fibrinogen (Fib) and antithrombin III (AT) were routinely monitored. Postoperative tests were performed either the same day (dorsal transpedicular stabilization, anterior stabilization procedures) or the day following surgery, depending on the type of surgery and the amount of blood loss. If major deficiencies were detected, fresh frozen plasma, prothrombin complex concentrate, Fib or AT-concentrate was administered to maintain PT >60%, PTT <40 s, PLTS >100,000, Fib >1.5 g/l and AT >80%.

Anticoagulation protocol

Our protocol for prophylaxis of VTE included early postoperative daily subcutaneous administration of 0.3 ml of nadroparin calcium (Fraxiparin) (2850 IU anti-Xa, Sanofi Winthrop Industrie, France) in a preloaded syringe until hospital discharge plus intra- and postoperative compression stockings. Early postoperative anticoagula-

tion was defined as nadroparin administration less than 24 h after surgery, usually starting at 8 a.m. the day after surgery.

Patients with a history of cardiac valve surgery or known hypercoagulopathy were treated with 2×0.3–0.6 ml of nadroparin daily, depending on the individual risk assessment. In all patients with preoperative oral anticoagulation, this medication was replaced by 2× 0.6 ml nadroparin subcutaneously until 12 h before surgery, and continued 12 h after surgery. Aspirin was found to be a significant risk factor for postoperative hemorrhage [19]. Therefore, patients who were treated with aspirin stopped this medication at least 7 days before surgery, if planned for an elective procedure.

Results

Postoperative hemorrhage

Major postoperative hematoma occurred in 13 (0.7%) of the 1,954 spinal procedures (Table 4). Except for three patients with progressive paraplegia (patients 2, 3 and 4 in table 4), all patients with postoperative hematoma underwent elective surgical procedures. Hematoma were surgically evacuated immediately after diagnosis. In five patients, the hemorrhage occurred on the day of surgery before the first administration of nadroparin. Therefore, the hemorrhage rate of patients receiving nadroparin was 0.4% (8/1,949).

One of the patients with postoperative hematoma displayed signs of a complex hemorrhagic disorder (combined factor deficiency and thrombocytopenia) due to the hemato-oncological disease. Ten (77%) of the 13 patients with hematoma developed a progressive neurological deficit, which resolved in 6 patients until discharge and resulted in a hemorrhage-related morbidity in 4 of all 1,954 patients (0.2%), or 4 of the 13 patients (31%) with postoperative hematoma. The persistent neurological deficit was found in four patients who suffered from postoperative hemorrhage at cervical (one patient), thoracic (two patients) and lumbar level (one patient). Therefore, neurological consequences were more likely after hemorrhage occurring over the solid spinal cord than the cauda equina.

The location of the hematoma was epidural in all patients. Hematoma was diagnosed on the day of surgery in five patients (38.5%), on day 1 in three patients (23.1%), on day 2 in two patients (15.3%) and on day 3 in three patients (23.1%). Of the five patients with a postoperative hematoma on the day of surgery before pharmacological prophylaxis, four patients showed a progressive neurological deterioration, which was permanent in only one patient. Of the six patients who developed the hematoma after nadroparin administration, three patients improved and were discharged without a neurological deficit. However, three patients were discharged with residual neurological impairment.

Postoperative thromboembolic events

Clinically overt VTE confirmed by venography occurred in only one of the 1,954 patients (0.05%) during the hospital stay. This patient underwent occlusion of a spinal arteriovenous fistulae and developed a right-sided distal

Table 4 Characteristics of the patients who presented with a postoperative hemorrhage after spinal surgery requiring surgical evacuation (*EDH* epidural hematoma)

No.	Age/sex	Diagnosis	Postoperative day of diagnosis of hemorrhage	Location	Level of postoperative hemorrhage	Progressive neurological deficit	Preexisting coagulation abnormality
1	71/M	Dural AV fistula	2	EDH	T 12	+	–
2	67/M	Plasmocytoma metastases	3	EDH	T 6–8	+	+
3	45/M	Epidural malignant lymphoma	1	EDH	T 7–9	– (Preoperative paraplegia)	–
4	61/M	Renal cell carcinoma metastases	Same day	EDH	T 11	+	–
5	49/F	Lumbar disc herniation	Same day	EDH	L 3/4	+	–
6	75/M	Lumbar disc herniation	3	EDH	L 2/3	+	–
7	77/F	Lumbar disc herniation combined with spinal stenosis	Same day	EDH	L 3/4	+	–
8	78/F	Lumbar disc herniation	Same day	EDH	L 2/3	+	–
9	62/M	Lumbar disc herniation combined with spinal stenosis	Same day	EDH	L 2	–	–
10	49/F	Lumbar disc herniation	1	EDH	L 4/5	+	–
11	38/M	Neurinoma	2	EDH	T 11	–	–
12	37/F	Ependymoma	1	EDH	C 1–3	+	–
13	60/M	Syringomyelia	3	EDH	T 8	+	–

DVT (fibular vein extending towards the popliteal vein) on the first postoperative day. None of the patients developed a PE in this series.

Discussion

The benefit-to-risk ratio of pharmacological thromboembolic prophylaxis, the ideal regimen and the optimal starting point for the different spinal procedures remain unclear. Although recent data support the benefit of pharmacological thromboembolic prophylaxis in general, urological or orthopedic surgery [5, 7, 11, 13, 16], many authors do not currently recommend anticoagulation in spinal surgery [9, 17, 20]. Because neurological impairment caused by postoperative hemorrhage could easily offset the reduction of DVT-caused morbidity, we need data about the safety of postoperative pharmacological prophylaxis after spinal surgery.

The LMWH nadroparin was more effective in preventing DVT than standard heparin in general surgery without significant differences in postoperative bleeding [15]. Compared with unfractionated heparin, nadroparin has a greater ratio of anti-factor Xa to anti-factor IIa activity, greater bioavailability and a longer duration of action, allowing it to be administered by subcutaneous injection once daily for prophylaxis, or twice daily for treatment of thromboembolic disorders [2, 8]. Doses recommended for prophylaxis of VTE (which is 0.3 ml for nadroparin) produced only a minimal effect on a PTT [6].

Interpretation of study results and limitations of the study

This study does not primarily address the issue of efficacy in preventing DVT and VTE. The primary endpoint of this study was to analyze the occurrence of a major postoperative hemorrhage (requiring surgical evacuation) in patients with different spinal procedures and pharmacological DVT prophylaxis. The rate of postoperative hemorrhage was 0.7% (13/1,954) (Table 4). The hemorrhage rate of patients treated with nadroparin was 0.4% (8/1,959).

Among the patients with postoperative hematoma, one patient had a severe hemorrhagic disorder (combined factor deficiency and thrombocytopenia) due to the hematooncological disease, which may be the cause of postoperative hemorrhage independent of the postoperative anticoagulation. The hemorrhage-associated morbidity was 0.2% (4/1,954). Therefore, our results are consistent with other studies, which determined a rate of postoperative hemorrhage between 0.2 and 1% [3].

We did not perform routine postoperative MRI in this study. Therefore, only patients with a symptomatic hemorrhage showing either postoperative neurological deterioration or intractable pain were assessed by MRI. However, it is unlikely that clinically silent minor hemorrhages without any neurological impairment will change the management or outcome of these patients.

A review of the literature on patients who underwent spinal surgery and were at risk of developing VTE showed that the clinical manifestations ranged from minimal or no symptoms to sudden death. Clinical symptoms of DVT were almost always silent [18], but generally carried the risk of PE, especially from more proximal thrombi. However, there is data in the literature showing no differences in the risk of PE from more proximal thrombi as compared to distal thrombi [12]. The incidence of DVT after spinal surgery varied in different studies from 0.9% (3 of 317 patients) [20] to 15.5% (17 of 110 patients) [18].

Based on their own prospective data, some authors think that routine screening for the detection of asymptomatic thrombosis in patients who have had a procedure on the spine is unwarranted [20]. It is very likely that our figures for DVT are too low because we did not perform routine duplex ultrasound or venography. Therefore, our data can not be compared with data from prospective trials in which all patients received duplex ultrasound, radioactive-labeled Fib or venography to diagnose DVT.

However, only 1 of the 1,954 patients (0.05%) developed a DVT during the hospital stay, which demonstrates the effectiveness of the pharmacological prophylaxis with nadroparin. As we retrospectively analyzed the rate of postoperative hemorrhage and DVT in this study, we unfortunately cannot yet provide more reliable data on DVT prevention by nadroparin treatment. However, our data show that the rate of postoperative hemorrhage is not increased after nadroparin administration and the rate of DVT is very low.

Conclusion

Early pharmacological anticoagulation after spinal surgery using nadroparin is safe and not associated with an increased risk of postoperative hemorrhage. We are well aware that our data are retrospective and that the study lacked a control group. Nevertheless, the data about the hemorrhage risks represent, to our knowledge, one of the largest cohorts on early postoperative pharmacological prophylaxis after spinal surgery. Our data support the concept of early postoperative pharmacological venous thromboembolic prophylaxis in patients after spinal surgery.

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