Venous Thromboembolism Prophylaxis in Meningioma Surgery: A Population-Based Comparative Effectiveness Study of Routine Mechanical Prophylaxis with or without Preoperative Low-Molecular-Weight Heparin

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OBJECTIVES: **Venous thromboembolism (VTE) is a serious complication after intracranial meningioma surgery. To what extent systemic prophylaxis with pharmacotherapy is beneficial with respect to VTE risk, or associated with increased risk of bleeding and postoperative hemorrhage, remains debated. The current study aimed to clarify the risk/benefit ratio of prophylactic pharmacotherapy initiated the evening before craniotomy for meningioma.**

METHODS: **In a Scandinavian population-based cohort, we conducted a retrospective review of 979 operations for intracranial meningioma between 2007 and 2013 at 3 neurosurgical centers with population-based referral. We compared 2 different treatment strategies analyzing frequencies of VTE and proportions of postoperative intracranial hematomas requiring surgery or intensified subsequent observation or care (intensive care unit or other intensified observation or treatment). One neurosurgical center favored preoperative prophylaxis with low-molecular-weight heparin (LMWH) (LMWH routine group) in addition to mechanical prophylaxis, and 2 centers favored mechanical prophylaxis with LMWH only given as needed in cases of delayed mobilization (LMWH as needed group).**

RESULTS: **In the LMWH routine group, VTE was diagnosed after 24/626 operations (3.9%), and VTE was diagnosed after 11/353 (3.1%) operations in the LMWH as needed group ($P = 0.56$). Clinically relevant postoperative hematomas occurred after 57/626 operations (9.1%) in the LMWH routine group compared with 23/353 (6.5%) in the LMWH as needed group ($P = 0.16$). Surgically evacuated postoperative hematomas occurred after 19/626 operations (3.0%) in the LMWH routine group compared with 8/353 operations (2.3%) in the LMWH as needed group ($P = 0.26$).**

CONCLUSIONS: **There is no benefit of routine preoperative LMWH starting before intracranial meningioma surgery. Neither could we for primary outcomes detect a significant increase in clinically relevant postoperative hematomas secondary to this regimen. We suggest that as needed perioperative administration of LMWH, reserved for patients with excess risk because of delayed mobilization, is effective and also appears to be the safest strategy.**

Key words
- Anticoagulants
- Low-molecular-weight heparin
- Meningioma
- Neurosurgery
- Postoperative hemorrhage
- Venous thromboembolism

Abbreviations and Acronyms
CT: Computed tomography
DVT: Deep vein thrombosis
LMWH: Low-molecular-weight heparin
MRI: Magnetic resonance imaging
PE: Pulmonary embolism
RCT: Randomized controlled trial
SCD: Sequential compression device
VTE: Venous thromboembolism

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INTRODUCTION

Intracranial meningioma is the second most common primary brain tumor[1,2] and surgical removal is the treatment of choice.[3] Because meningiomas are typically benign lesions,[4] expectations for patient safety are high and serious complications of treatment are less acceptable. Postoperative venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), after intracranial tumor surgery is reported as high as 26%[1,3,5-10] with 1.5%–5% risk of PE.[1,7,11] PE is a serious complication and reported mortality was 23% in a recent study of patients with meningioma.[4]

Early mobilization and mechanical prophylaxis (e.g., compression stockings and sequential compression devices [SCDs]) to reduce VTE may be used.[12-16] To further reduce the risk of VTE after intracranial tumor surgery, different schemes of pharmacologic prophylaxis have been implemented, most commonly subcutaneous injections of low-molecular-weight heparin (LMWH). The efficacy of perioperative pharmacologic prophylaxis with LMWH in patients with intracranial tumor has been assessed in 2 randomized controlled trials (RCTs).[1,17] One study including 307 patients[1] found a reduced incidence of VTE without increasing the risk of postoperative hemorrhage with LMWH administration the morning after surgery, but the study did not have enough power to detect potential differences in postoperative hematomas. Another study[17] that randomized 68 patients to placebo or LMWH at the beginning of surgery was stopped early because of increased risk of postoperative hematoma (11%). After these studies, a systematic review modeling patient outcomes favored mechanical prophylaxis alone over routine additional pharmacologic prophylaxis because of the increased risk of postoperative hematoma with potentially devastating consequences.[18] Because of the potentially negative consequences of systemic anticoagulation therapy on hemostasis during and after intracranial tumor surgery, there is still no consensus on the overall use and timing of pharmacologic prophylaxis.[6,13,19] To further elucidate on potential risks and benefits of routine LMWH prophylaxis in intracranial meningioma surgery, a large-scale study is needed. In this context, pragmatic comparative studies can complement RCTs, offering a real-life setting.[20,21]

The aim of this population-based retrospective comparative cohort study was to compare the proportions of VTE and postoperative hematoma at 3 neurosurgical centers with 2 different policies for thromboembolic prophylaxis in meningioma surgery. At 1 center, LMWH was started the evening before surgery and continued until adequate mobilization. In the 2 other centers, no preoperative pharmacologic prophylaxis for VTE was administrated routinely but rather given as needed if postoperative mobilization was delayed.

METHODS

The study was approved by the respective Stockholm regional ethical review board in Sweden (EPN 2013/634-31/7) and the Regional Committee for Medical and Health Research Ethics in Central Norway (2013/884). The study was registered in clinicaltrials.gov (NCT01941602) before data collection. The study is reported based on the STROBE statement.

Scandinavian Health Care System

The health care system in Norway and Sweden is divided into different geographic regions with compliant referral patterns for intracranial tumor surgery within these regions. A patient with an intracranial meningioma in the greater Stockholm region is referred to and cared for at the Neurosurgical Department at Karolinska University Hospital. Similarly, patients with meningioma in Northern Norway and Central Norway will be referred to the University Hospital of North Norway and St. Olavs University Hospital, respectively. Because no private health care alternative exists for patients with intracranial tumors and a strict regional referral is used, it is highly unusual that patients actively seek health care outside their region, in practice eliminating risk of referral bias.[22] Data from Statistics Norway (http://www.ssb.no) and Statistics Sweden (http://www.scb.se) were used to estimate the mean population of the respective hospital catchment areas during the study period.

Study Population

All patients undergoing resection of intracranial meningioma between 1 January 2007 and 30 June 2013 at the Departments of Neurosurgery at Karolinska University Hospital (Stockholm, Sweden), the University Hospital of North Norway (Tromsø, Norway), and St. Olavs University Hospital (Trondheim, Norway) were identified using the hospital patient administrative databases. In total, 979 craniotomies and meningioma resections were performed in patients aged 18 years or older. All cases were histopathologically verified.

Biopsies only, transsphenoidal surgery, and patients having undergone intracranial procedures or VTE within 3 months before meningioma surgery were excluded. Also, patients from abroad, actively seeking care and operated at the study centers, were excluded from the study.

We registered the perioperative course limited to the first 30 days after surgery through comprehensive review of the medical records and operating room logs.

Assessment of Population-Based Data

The University Hospital of Northern Norway served a population of 466,699 (14% of our total cohort), St. Olavs University Hospital served a population of 673,874 (21% of our total cohort), and Karolinska University Hospital served a population of 2,129,919 (65% of our total cohort). Crude incidence rates of craniotomy and meningioma resection were 4.1/100,000/year at University Hospital of North Norway, 5.3/100,000/year at St. Olavs University Hospital and 4.5/100,000/year at Karolinska University Hospital. The difference between expected proportion of caseload between centers compared with the actual caseload was not significant (χ^2, $P = 0.93$). This finding makes it unlikely that there are relevant differences in indications for surgical treatment of meningiomas between departments.

Treatment Regimens

At 1 center, patients with intracranial meningioma selected for craniotomy and tumor resection received subcutaneous LMWH (40 mg enoxaparin) approximately 12 hours before intracranial surgery, later referred to as the LMWH routine group. LMWH was

continued once a day until patients were sufficiently mobilized. Exceptions were patients with coagulopathy or those using other anticoagulant treatment. In addition to the above, patients routinely received mechanical VTE prophylaxis with compression stockings or SCD.

At the 2 other centers, patients with meningioma did not routinely receive preoperative pharmacologic VTE prophylaxis. Instead, patients with delayed postoperative mobilization were given LMWH (enoxaparin 40 mg or dalteparin 5000 IU daily) from the second postoperative day until sufficiently mobilized. Mechanical prophylaxis with compression stockings or SCD was routinely provided. We refer to this cohort as the LMWH as needed group.

End Points

All end points were preplanned before data collection unless otherwise clearly specified. The primary end point was a between-group comparison of radiologically confirmed VTE within 30 days after surgery. At all institutions, the first-line diagnosis of DVT and PE is lower extremity ultrasonography and contrast-enhanced spiral chest computed tomography CT, respectively. None of the centers performed VTE screening in asymptomatic patients. The coprimary end point was proportion of clinically relevant postoperative hematoma within 30 days of surgery. Clinically relevant postoperative hematoma was here defined as a radiologically detected hematoma (CT or magnetic resonance imaging [MRI]) having any possible association with postoperative course/events, including prolonged observation in intensive care unit, delayed mobilization, possibly related neurologic deficits (including transient deficits), or more severe related events like impaired consciousness and death.

Preplanned secondary end points were analysis of treatment regardless of treatment center for the primary end points, proportions of either DVT or PE, peroperative blood loss and proportions of patients reoperated as a result of postoperative intracranial hematoma. Explorative post hoc analyses were duration of surgery, postoperative hematomas when LMWH was provided within 24 hours postoperatively, and severe complications (Ibanez grade III–IV) within 30 days after surgery.[23]

Statistical Analysis and Power Estimate

All analyses were decided a priori (per protocol) unless otherwise specified. To avoid selection bias, primary end points were analyzed according to treatment policy and not according to treatment provided. Analyses of actual LMWH treatment, regardless of treatment center, are provided as secondary end points. Statistical significant level was set to $P < 0.05$, with no adjustments for multiple comparisons.

Comparisons of dichotomous data (including primary end point) were analyzed with Pearson χ^2 test. Distributions of continuous variables were analyzed with Q-Q plots. For continuous data, comparisons of groups were analyzed with independent sample t test if normally distributed or with Mann-Whitney U test if skewed.

We hypothesized that the proportion having VTE would be 10% in the LMWH as needed group, and 5% for the LMWH routine group.[10] Because of an expected 2:1 difference in cohort size, we found that to achieve 80% power using a 2-sided significance level of 0.05 we needed 1050 operations (350 and 700, respectively). We ended up with 979 operations in this study. Thus, our final inclusion ended below 80% power, but higher than 70% power (total 849 operations needed). We simply reversed the equation when calculating the risk of clinically significant postoperative intracranial hematoma.

Statistical analyses were performed using SPSS Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, Illinois, USA) and Figure 1 is created using GraphPad Prism 6 (GraphPad, La Jolla, California, USA).

RESULTS

Baseline and treatment characteristics for the 2 groups are presented and compared in Table 1. Other than for VTE prophylaxis, the 2 study groups were comparable except for World Health Organization grade, early postoperative CT/MRI, and previous radiation therapy.

In the LMWH as needed group, compression stockings alone were used in 251 cases (71.1%) whereas SCD was used in addition in 97 cases (27.6%). All patients in the LMWH routine group received mechanical prophylaxis, but SCD use was not reliably documented and consequently not reported. All mechanical prophylaxis in both groups was initiated immediately before surgery.

VTE

The primary end points are presented in Figure 1, and the differences in secondary outcomes between treatment strategies are summarized in Table 2.

For the entire study population, VTE was detected after 35/979 operations (3.6%). In the LMWH routine group, VTE was diagnosed after 24/626 operations (3.8%) compared with after 11/353 operations (3.1%) in the LMWH as needed group ($P = 0.56$).

When analyzed according to treatment and not according to policy, the risk of VTE when treated with preoperative LMWH was 3.4% (20/591). The corresponding risk in the group who did not receive LMWH before surgery was 3.9% (15/380, $P = 0.65$). Including patients treated with LMWH within 24 hours after surgery in the analysis did not alter the result ($P = 0.98$).

Postoperative Intracranial Hematoma

For the entire study population, clinically relevant postoperative hematomas were observed after 80/979 operations (8.2%). Postoperative hematomas were seen after 57/626 operations (9.1%) in the LMWH routine group and after 23/353 operations (6.5%) in the LMWH as needed group (Figure 1, $P = 0.16$). Postoperative hematomas in need of surgical evacuation were observed in 19/626 operations (3.0%) in the LMWH routine group compared with 8/353 operations (2.3%) in the LMWH as needed group ($P = 0.48$).

In the secondary analysis grouped according to LMWH treatment, a clinically significant postoperative hematoma occurred after 54/591 operations in patients who received preoperative LMWH prophylaxis (9.1%) compared with after 25/380 operations (6.6%) in the group who did not receive LMWH preoperatively ($P = 0.16$). When exploring cases in which LMWH was provided either preoperatively or within 24 hours after surgery, 59/636 operations (9.3%) were complicated with significant postoperative hematoma

Table 1. Demographic Data, Patient, and Tumor Characteristics*

	LMWH Routine Group (n = 626)	LMWH As Needed Group (n = 353)	*P* Value
LMWH given preoperatively	583 (93.6)	8 (2.3)	<0.001
LMWH given within 24 hours postoperatively†	603 (96.8)	33 (9.5)	<0.001
Any LMWH given as inpatient	608 (97.8)	107 (30.7)	<0.001
Previous thromboembolism	26 (4.2)	21 (5.9)	0.21
Preoperative therapeutic use of anticoagulants	24 (3.8)	16 (4.5)	0.60
Age, mean ± standard deviation, years	57.3 ± 12.1	56.8 ± 13.2	0.53
Female	443 (70.8)	232 (65.7)	0.10
Charlson Comorbidity Index >1	86 (13.7)	40 (11.3)	0.28
Preoperative Karnofsky Score ≥70*	550 (88.3)	307 (87.0)	0.55
Paretic limb	101 (16.1)	42 (11.9)	0.07
Location			0.49
Falx/parasagittal	158 (25.2)	93 (26.4)	
Sphenoid wing	109 (17.4)	58 (16.5)	
Convexity	154 (24.6)	102 (29.0)	
Olfactorius/planum/sella	106 (16.9)	52 (14.8)	
Other/infratentorial	99 (15.8)	47 (13.4)	
World Health Organization grade 1	561 (90.0)	273 (78.4)	<0.001
Perifocal edema on initial magnetic resonance imaging	306 (49.1)	150 (42.6)	0.05
Postoperative computed tomography/magnetic resonance imaging‡	429 (68.8)	275 (77.9)	<0.01
Previous intracranial meningioma surgery	89 (14.2)	62 (17.6)	0.16
Previous radiation therapy	2 (0.3)	15 (4.2)	<0.001
Previous stereotactic radiosurgery	27 (4.3)	5 (1.4)	0.01
Simpson grade I–III	422 (67.8)	253 (71.7)	0.21
Proximity to venous sinus	225 (36.0)	108 (30.6)	0.09

LMWH, low-molecular-weight heparin.
*Values are number (%) except where indicated.
†3 missing.
‡2 missing.

compared with 20/335 operations (6.0%) in the group not receiving LMWH within the first 24 hours postoperatively (P = 0.07).

Secondary Outcomes

As seen from Table 2, we observed no difference in serious complications defined as Ibanez grade III and IV between treatment strategies (P = 0.09). However, there were significant differences in median blood loss (450 vs. 300, P < 0.001) and duration of surgery (270 vs. 210 minutes, P < 0.001) between treatment strategies.

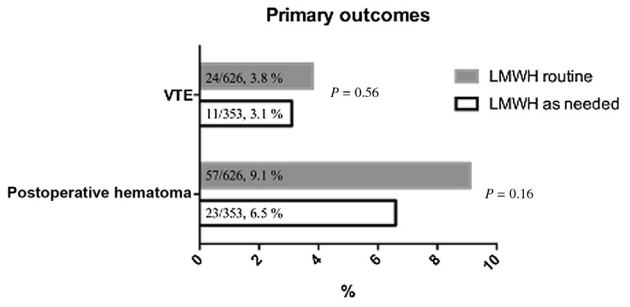
Table 2. Secondary End Points

	LMWH Routine Group	LMWH As Needed Group	*P* Value
As treated analysis for venous thromboembolism, n/N (%)	20/591 (3.4)	15/380 (3.9)	0.65
As treated analysis for postoperative hematoma, n/N (%)	54/591 (9.1)	25/380 (6.6)	0.16
Deep vein thrombosis, n/N (%)	11/626 (1.8)	1/353 (0.3)	0.04
Pulmonary embolism, n/N (%)	13/626 (2.1)	10/353 (2.8)	0.88
Reoperations for hematoma, n/N (%)	19/626 (3.0)	8/353 (2.3)	0.48
Intraoperative blood loss, mL, median (IQR)*	450 (200–800)	300 (150–600)	<0.001
Ibanez grade III–IV, n/N (%)[14]	50/626 (8.0)	18/353 (5.1)	0.09
Duration of surgery, minutes, median (IQR)†	270 (194–374)	210 (140–300)	<0.001

LMWH, low-molecular-weight heparin; IQR, interquartile range.
*28 (LMWH routine group) + 21 (LMWH as needed group) missing blood loss.
†3 missing.

Explanatory Post Hoc Analyses

Because LMWH effect in the LMWH routine group could be counteracted by longer duration of surgery observed in this group, we analyzed whether VTE was associated with duration of surgery in this cohort. No statistically significant association between duration of surgery and VTE (P = 0.145) was found.



Postoperative hematoma was defined as intracranial hematoma detected by computed tomography and/or magnetic resonance imaging that complicated the postoperative course.

VTE denotes postoperative deep-vein thrombosis and/or pulmonary embolism verified with diagnostic imaging.

Figure 1. Primary end points. LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

The timing of VTE and hematoma occurrence postoperatively was evaluated in a descriptive analysis, as seen in Table 3. The median time point of detection of postoperative hematomas for the LMWH routine group was postoperative day 1 (range 0–26), whereas the median time point in the LMWH as needed group was postoperative day 2 (range 0–10). VTE was detected after a median of 13 days in the LMWH routine group (range 2–30) compared with a median of 3 days in the LMWH as needed group (range 1–30).

DISCUSSION

This multicenter population-based study comparing routine mechanical prophylaxis with or without preoperative LMWH in patients undergoing intracranial meningioma surgery showed no benefit of preoperative LMWH in VTE prevention. There was no statistically significant increase in postoperative hematomas with preoperative LMWH administration. Including early postoperative (within 24 hours) LMWH administrations did not alter the results. Given the lack of effectiveness of routine perioperative LMWH in VTE prevention after intracranial meningioma surgery it seems reasonable to abandon this routine if mechanical prophylaxis is well established. Pharmacologic prophylaxis should be reserved for patients with delayed mobilization (e.g., second day after surgery), because prolonged bed rest is associated with increased VTE risk.[4]

Compared with the literature. both groups are in the lower range of clinically detected PE with 2.1% in the LMWH group and 2.8% in the mechanical group.[4,24] Our results are comparable with a study from 2005 concluding that VTE in a clinical setting using multimodal prophylaxis was uncommon, with PE detected in 2.2% of cases.[15] Further, the VTE detection rates reported here are also in line with large data sets from National (Nationwide) Inpatient Sample database reporting on results of benign brain tumor resection, making it likely that our results are valid in other clinical settings as well.[25] Because definitions of postoperative hematoma may vary between studies, it seems more relevant to compare reoperations caused by hematoma.[4,19] In our study, postoperative hematoma evacuation occurred in 3.0% in the LMWH routine group and 2.3% in the LMWH as needed group. These results are comparable with a recent, large single-center study reporting surgically evacuated hematomas in 2.9% of cases.[4] In regards to the timing of events, it is often seen that hematomas occur close to surgery, whereas VTE events are typically first detected a few days after surgery. This is presumably also why preoperative LMWH therapy is withheld in many neurosurgical departments.

Table 3. Timing of Postoperative Venous Thromboembolism and Hematoma

	LMWH routine		LMWH as needed	
Postoperative day	VTE (n, %)	Hematoma (n, %)	VTE (n, %)	Hematoma (n, %)
0	0 (0)	9 (16)	0 (0)	3 (13)
1–2	4 (17)	26 (46)	4 (36)	14 (61)
3–7	4 (17)	15 (26)	5 (45)	4 (17)
8–14	6 (25)	5 (9)	1 (9)	2 (9)
15–21	5 (21)	0 (0)	0 (0)	0 (0)
22–30	5 (21)	2 (4)	1 (9)	0 (0)
Total	24	57	11	23

LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

The lack of clinical benefit of LMWH presented here is not consistent with the findings in a landmark RCT from 1998 including 307 patients.[1] Agnelli et al. reported a significant reduction of VTE in the group receiving postoperative enoxaparin compared with placebo, but only 10 of 65 patients with diagnosed VTE were symptomatic and the others were detected by screening. The clinical relevance of asymptomatic DVT can be debated, so for clinical end points, their study was underpowered and consequently the clinical relevance of the result is less clear. In their study, the initiation of LMWH was postoperative. Timing of LMWH administration is presumably not the explanation why LMWH failed to reduce VTE in our study, because preoperative administration of LMWH should theoretically provide additional protection. Most VTE after intracranial surgery occur within 30 days, and 30 days is also by convention the period considered for postoperative complications and perioperative events.[22,23] In this time frame, we had 3 deaths (0.8%) in the LMWH as needed group and 3 in the LMWH routine group (0.5%). There was 1 death in which PE played a causative role, and this was in the LMWH routine group. Despite providing the highest level of evidence, the generalizability of results of RCTs may be questionable. For instance, patients with expected hospital stay less than 7 days were excluded in the study by Agnelli et al. Although we did not document length of hospitalization in this study, this expected length of stay is clearly longer than the average at our centers. Patients with preoperative Karnofsky Performance Score >70 undergoing uncomplicated intracranial meningioma surgery are typically discharged home or occasionally to a local hospital on the third or fourth postoperative day. Mobilization starts on the first postoperative day, and additional pharmacoprophylaxis for VTE is provided if mobilization is delayed in the LMWH as needed group, typically starting on the second postoperative day. In the study by Agnelli et al., there is apparently no crossover (before the diagnosis of VTE) and one may argue that the clinical setting appears artificial. The present study provides a real-life scenario and focus on clinical end points by comparing strategies and allowing for crossover when indicated. This strategy better reflects the dynamics of clinical decision making and improves the external validity of our results.

Concerning the risk profile (e.g., postoperative hematoma) of early preoperative LMWH administration, an RCT from Dickinson et al.[17] was terminated prematurely because of increased occurrence of hematomas. This increased risk could be explained by the timing of administration being direct preoperatively with enoxaparin 30 mg subcutaneously.[26] In our study, the administration was approximately 12 hours before surgery, and we did not observe a statistically significant increase in postoperative hematomas.[27] Still, an exploratory secondary analysis of LMWH treatment demonstrated an absolute difference of 3.3 %, albeit a statistically nonsignificant finding. Given the

possible lack of statistical power, there could still be a small increased risk of intracranial hematomas when LMWH is used preoperatively, even when used in prophylactic dosage.

To examine the possible effect on hemostasis, we analyzed the difference in estimated blood loss and found a significant difference in favor of the LMWH as needed group (450 mL vs. 300 mL, $P < 0.001$). Duration of surgery was also significantly longer in the LMWH routine group compared with the LMWH as needed group and this could be a confounding factor. The reasons behind longer duration of surgery are probably multifactorial, and possible explanations frequent enough to affect the median may be more problematic hemostasis or different traditions in surgical exposures and approaches.[28]

Our results are in line with the recommendations made in 2012 for thromboprophylaxis in neurosurgery.[29] The recommendations are that stand-alone mechanical prophylaxis is provided to patients undergoing craniotomy, but with add-on pharmacoprophylaxis to high-risk patients (e.g., malignant disease with a hypercoagulable state). In the light of this study and the recent literature, the add-on of pharmacoprophylaxis in meningioma surgery should be considered only after longer-lasting surgery in patients with increased risk factors,[14,18,28,30] and most importantly, with delayed mobilization.[4,29]

Strengths and Limitations

This study is to our knowledge the largest study to date assessing the risk/benefit ratio of routine prophylactic administration on LMWH in meningioma surgery. The multicenter, population-based approach with the parallel cohorts instead of historical controls provides a valid result for neurosurgical practice. As a supplement to RCTs, comparative effectiveness studies are known to offer a real-life setting and high generalizability. The Scandinavian model of population-based referral with no private health care alternative for intracranial tumor surgery practically eliminates the risk of referral bias. In retrospective studies, selection bias is frequently a major concern, but we have been careful in our design to eliminate this. In neurosurgical departments, the question of thromboprophylaxis is most often subject to a clear strategy because of perceived risk of systematic medical prophylaxis.[4,15,24,31] The high compliance to treatment policy in our study ensures representative findings and is the proof of no selection bias. Further, our strategy of analyzing according to department policy instead of treatment eliminates selection bias.

Having practically eliminated referral bias and selection bias by the setting and statistical workup, the main concern is the possibility for detection bias. The retrospective nature of this study is therefore the main limitation in this regard. Concerning the end point of VTE, there may be a difference between groups in the postoperative alertness and thresholds for effectuating radiologic examinations for suspected VTE. However, resources or difference in reimbursement are unlikely to influence our findings because VTE diagnostics are readily available at all study sites, and for this specific workup, costs are not an issue in socialized health care systems. Nevertheless we cannot fully exclude the possibility of detection bias, and this may be 1 reason for the observed difference in DVT because it is unlikely that LMWH add-on is associated with increased VTE risk.

Concerning postoperative hematomas, different traditions clearly existed between study centers with respect to routine postoperative radiologic assessment. At 1 of the centers in the LMWH as needed group, postoperative CT or MRI was routinely performed in all patients within 3 days after surgery. However, in this study, we assessed only clinically relevant postoperative hematomas, meaning that the hematoma had to have consequences in terms of surveillance (e.g., kept in intensive care unit/intermediate section longer than normally expected),[2,8] affecting clinical status or treatment. The center performing routine imaging had the lowest rate of clinically relevant hematomas; however, no statistically significant difference was observed (data not shown, $P = 0.375$). In our material, all patients with unexpected slow habilitation or postoperative events underwent postoperative CT or MRI scans. Gessler et al.[32] recently presented a study on clinical relevance of routine postoperative imaging after surgery for intracranial meningiomas in 206 patients, and reported it mandatory in clinically symptomatic patients but found it completely safe to withhold routine imaging in asymptomatic patients. We believe that this argues for a limited potential bias, and if affecting our results, the difference in routines for postoperative imaging is in favor of the LMWH routine group, which makes the small difference between groups concerning hematomas a conservative estimate.

Although the strategies of early mobilization were similar at the study sites, there may still be minor differences in how they are implemented that could influence outcome because prolonged bed rest is a known predictor of VTE.[4] In this retrospective study, it was impossible to reliably determine when adequate mobilization occurred. Additional factors that could be of importance that we could not control for in this study are the use of topical hemostatic agents previously found to be associated with VTE and various biological factors.[31,33] In particular, body mass index is a factor that could influence VTE risk. This variable was not possible to extract retrospectively from the patient charts. However, a population-based approach in the homogenous Scandinavian countries reduces the chances of major differences in proportion of predisposing factors.

CONCLUSIONS

This multicenter population-based study comparing routine mechanical prophylaxis with or without preoperative LMWH in meningioma surgery showed no benefit of LMWH in VTE prevention. There was not a significant increase in postoperative hematomas with preoperative LMWH administration. When planning intracranial meningioma surgery, we recommend implementing strict mechanical prophylaxis and early mobilization as routine, using pharmacologic prophylaxis only as needed.

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