J Neurooncol (2009) 93:151–156
DOI 10.1007/s11060-009-9886-4

CLINICAL STUDY - PATIENT STUDIES

Adjuvant enoxaparin therapy may decrease the incidence of postoperative thrombotic events though does not increase the incidence of postoperative intracranial hemorrhage in patients with meningiomas

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Received: 4 February 2009 / Accepted: 30 March 2009

Abstract Patients with brain tumors including intracranial meningiomas are at increased risk for developing deep vein thrombosis (DVTs) and suffering thromboembolic events (VTEs). Many surgeons are concerned that early use of low dose enoxaparin may increase the risk of intracranial hemorrhage which outweighs the benefit of DVT/VTE reduction. We aimed to address concerns around the use of enoxaparin after meningioma resection in the development of postoperative intracranial hemorrhages and DVT/VTEs. This is a retrospective review of 86 patients with intracranial meningiomas who underwent craniectomy and surgical resection of the mass, treated by one attending surgeon at UCSF Medical Center between 2000 and 2005. Within 48 h after surgery patients treated 2003–2005 routinely received enoxaparin therapy unless there was documented intracranial hemorrhage, lumbar subarachnoid drain, enoxaparin hypersensitivity, or thrombocytopenia ($n = 24$). These were compared to a cohort treated 2000–2002 who did not receive the drug ($n = 62$). Exclusion criteria were prior VTEs or coagulopathies. The groups were similar in tumor and surgical characteristics. Enoxaparin therapy did not increase the incidence of intracranial hemorrhage following surgical meningioma resection and the incidence of DVTs/VTEs was 0% ($n = 0$) versus 4.8% ($n = 3$) in the non-enoxaparin group. Results did not reach statistical significance. In this retrospective study, postoperative administration of enoxaparin following meningioma resection does not increase the risk of intracranial hematoma though enoxaparin administration may slightly decrease the incidence of post-surgical thromboembolic events. Due to study design and power, we were not able to demonstrate DVT/VTE reduction with statistical significance.

Keywords Meningioma · Enoxaparin · Thromboembolic event · Anticoagulation

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Introduction

Meningiomas are benign intracranial tumors treated by craniotomy and surgical resection. Postoperative complications of surgical tumor resection include spontaneous intracranial hemorrhage [1–3]. However, postoperative brain tumor patients are also at increased risk of developing thromboembolic events (VTEs) [4, 5]. It is thought that thromboembolic events that occur postoperatively following resection may be due to the tumor-induced hemostatic changes resulting in a hypercoagulable state and may be exacerbated by the post-surgical recovery period when patients are initially non-ambulatory. Because of this, patients with brain tumors, including meningiomas are at increased risk of developing deep vein thrombosis (DVT) and experiencing venous thromboembolic events (VTE) [6–9]. DVT and VTEs significantly increase tumor patient morbidity and mortality and therefore are important aspects of tumor treatment to address. Prior studies have shown

that prophylactic treatment with low molecular weight heparin leads to fewer vascular complications such DVT and VTEs [10–15]. However, the risk of postoperative hematoma has been shown to increase with early anticoagulation [16]. Some studies have evaluated the use of heparin or enoxaparin with different regimens and different doses and there is no good consensus for preferred post-operative anticoagulation regimen. Neurosurgeons are frequently concerned about the use of anti-coagulation in the post-craniotomy setting. Meningoma surgery tends to require extensive bone and soft tissue dissection which may increase the risk of anti-coagulation treatment-related post-operative hemorrhagic complications.

Because of the duality of positive and negative effects of anticoagulation therapy in the post meningioma resection setting, the use of enoxaparin remains controversial. At our institution, there is no standard of practice amongst meningioma surgeons about the use of anti-coagulation with meningioma resection, although there is Class 1 evidence to support its use in glioma and meningioma patients post-operatively. One surgeon uses it routinely while the others do not. We decided to evaluate the use of enoxaparin by a single surgeon and the associated incidence of post-operative hematomas and DVT/VTEs in a control cohort group. Our aim is to address concerns around the use of enoxaparin after meningioma resection in the development of postoperative hematomas and thromboembolic events.

Materials and methods

Patient population

Only one surgeon at our institution began using enoxaparin routinely in 2002 beginning within two days after surgery. 86 patients surgically treated at the University of California San Francisco Neurosurgery Department between 2000 and 2005 by this surgeon for histologically confirmed meningiomas were retrospectively identified from the database. Patients who underwent surgical resection of intracranial meningiomas between 2003 and 2005 (after enoxaparin was routinely administered) were eligible for treatment with enoxaparin starting within 48 h after surgery. Patients did not receive enoxaparin therapy if they had a documented intracranial hemorrhage, presence of a lumbar subarachnoid drain, hypersensitivity to heparin or enoxaparin, or thrombocytopenia. The patients who were treated between 2003 and 2005 and who received enoxaparin ($n = 24$) are compared to those who underwent surgical resection for meningioma between 2000 and 2002, before enoxaparin was routinely administered, and therefore did not receive enoxaparin in the post-operative period ($n = 62$). Patients were excluded from the study if they had a prior DVT/VTE, other thromboembolic event, or coagulopathy.

The average age of patients at initial diagnosis was 56 years for patients who received enoxaparin and those who did not (range: 30–73 years and 31–80 years respectively). Records were analyzed for symptoms present at diagnosis, prior chemotherapy or radiotherapy, and pre-operative embolization to treat the tumor. In addition, we analyzed tumor characteristics (primary or recurrent tumor, tumor location and volume) and pathologic diagnosis (WHO classification of tissue).

Surgical treatment

Between 2000 and 2005, patients underwent craniotomy and surgical resection of the tumor. Gross total resection (Simpson Grade I) or near gross total resection (Simpson Grade II) was performed in most cases studied.

Features of the surgical procedure were noted including length of procedure and estimated blood loss.

Enoxaparin therapy

Between 2003 and 2005, with start times ranging from within 24 h up to 48 h after surgery, patients were treated with enoxaparin delivered as a subcutaneous injection for between one and seven days. The most common dose of enoxaparin treatment is 40 mg daily, one patient received a dose of 30 mg. Of the 24 patients in the treatment group, 8 patients began treatment within 24 h after the operation and 16 initiated treatment between 24 and 48 h after surgery.

The use of post-operative anti-embolic prophylaxis including TED hose and pneumatic sequential compression devices (SCD) was also noted.

Statistical analysis

Data were collected through a retrospective review of charts and were summarized. Records were reviewed for radiographic evidence of post-operative hematoma and other complications occurring within the first 30 days of surgery. Also, records were reviewed for clinical or radiographic evidence of deep vein thrombosis (DVT) or venous thromboembolic events (VTEs) following surgical treatement for meningioma and adjuvant therapy with enoxaparin. Only one subject from the treatment group died prior to 30 days following surgery, all other subjects had follow-up data for 30 days.

We identified complications as clinical symptoms and deficits following hemorrhage, radiographic evidence of DVT, VTE, or hematoma, complications leading to further surgical or medical treatment, and death. Postoperative hemorrhages were identified clinically then confirmed and

classified by CT scan. DVT was diagnosed clinically and confirmed with doppler ultrasound. Data were analyzed using GraphPad Software.

Results

Patient characteristics

The two populations of patients, those who received enoxaparin and those who did not, had similar tumor and treatment characteristics with the exception of tumor-associated edema. The tumor qualities and treatment approach are represented in Table 1. The majority of meningiomas were WHO grade 1, and the dominant location of these tumors is in the middle fossa. More patients who received enoxaparin are known to have had edema-associated tumors (41.7%) than those who did not receive enoxaparin therapy (21.0%) ($P = 0.45$). The majority of meningiomas in this patient population are medium to large size and in many cases, treatment included preoperative embolization followed by resection.

Prior DVT was an exclusion criterion for this study and therefore 100 percent of patients in the enoxaparin and non-enoxaparin groups had no history of DVT. All patients received pneumatic calf compression devices as DVT prophylaxis until ambulatory.

Table 1 Tumor and resection characteristics of enoxaparin group and non-enoxaparin group

Tumor characteristics	Enoxaparin group; *n* (%)	No Enoxaparin group; *n* (%)
WHO grade		
1	20 (83.3)	54 (87.1)
2	3 (12.5)	6 (9.7)
3	1 (4.2)	2 (3.2)
Tumor site		
Anterior fossa	4 (16.7)	9 (14.5)
Middle fossa	12 (50)	29 (45.2)
Posterior fossa	8 (33.3)	23 (37.1)
Intraventricular	0	1 (1.6)
Associated edema		
Yes	10 (41.7)	13 (21.0)
No	8 (33.3)	24 (38.7)
Unknown	6 (25)	25 (40.3)
Preoperative embolization		
Yes	9 (37.5)	25 (40.3)
No	15 (62.5)	37 (59.7)
Simpson grade resection		
0	0	2 (3.2)
1	6 (25)	16 (25.8)
2	10 (41.7)	20 (32.3)
3	3 (12.5)	12 (19.4)
4	0	2 (3.2)
5	0	1 (1.6)
Unknown	5 (20.8)	9 (14.5)
Primary versus reoperation		
Primary	19 (79.2)	55 (88.7)
Reoperation	5 (20.8)	7 (11.3)

Postoperative hemorrhages

12.5 percent ($n = 3$) in the enoxaparin group and 12.9% ($n = 8$) in the non-enoxaparin group suffered postoperative intracranial hemorrhages. Of these, one patient in the treatment group and 5 patients in the non-treatment group suffered clinically symptomatic deficits as a result of the hemorrhage (Table 2).

Of the intracranial hematomas in the group that received enoxaparin, one was classified as intraparenchymal and two others as subarachnoid. Of the group that did not received enoxaparin, postoperative hemorrhages were classified as intraparenchymal, mixed, and not classified hematomas (Table 2).

Postoperative DVT/VTEs

There was a slight apparent decrease in the incidence and percentage of patients with postoperative thromboembolic events in the enoxaparin group (one and 62.5% respectively) compared to those who did not receive treatment (five and 67.8% respectively) though these differences did not achieve statistical significance ($P > 0.5$). No patients receiving enoxaparin experienced clinically diagnosed VTEs/DVTs. A total of three patients from the non-treatment group experienced DVT/VTE. Two had both pulmonary embolism and extensive DVTs, involving bilateral iliac veins and the inferior vena cava in one and the distal lower extremity in the other. And one patient who did not

Table 2 Postoperative hemorrhage characteristics in the enoxaparin group and the non-enoxaparin group

Hemorrhage characteristics	Enoxaparin group; *n* (%)	No Enoxaparin group; *n* (%)
Postoperative hemorrhage	3 (12.5)	8 (12.9)
Symptomatic hemorrhage	1 (4.2)	5 (8.1)
Hemorrhage classification		
Intraparenchymal	1 (4.2)	2 (3.2)
Subdural	0	0
Subarachnoid	2 (8.3)	0
Mixed	0	3 (4.8)
Not classified	0	3 (4.8)

Table 3 Reported complications following surgical resection of meningioma

Reported complications	Enoxaparin			No enoxaparin		
	Number of pts with comps	Percentage of all pts who received enox	Number of events	Number of pts with comps	Percentage of all pts who did not receive enox	Number of events
Hemorrhage-related	1	4.2	2	5	8.1	8
Progressive somnolence	1	4.2	1	0	0	0
Altered mental status	0	0	0	1	1.6	1
Language impairment	0	0	0	0	0	0
Seizure	0	0	0	2	3.2	2
Headache	0	0	0	1	1.6	1
Hematoma evacuation	1	4.2	1	2	3.2	2
Craniectomy	0	0	0	2	3.2	2
Venous thrombotic events	0	0	0	3	4.8	5
DVT	0	0	0	3	4.8	3
Pulmonary embolism	0	0	0	2	3.2	2
Intracranial embolic infarct	1	4.2	1	2	3.2	2
Surgery-related	3	12.5	3	12	19.4	19
CSF leak	1	4.2	1	0	0	0
Scalp/wound infection	2	8.3	2	2	3.2	2
Pseudomeningocele	0	0	0	3	4.8	3
Pneumocephalus	0	0	0	1	1.6	1
Hydrocephalus	0	0	0	8	12.9	8
VP shunt placement	0	0	0	5	8.1	5
Constitutional	0	0	0	1	1.6	1
Neurologic	13	54.2	20	29	46.8	41
Pulmonary	1	4.2	1	5	8.1	5
GU	2	8.3	2	0	0	0
Hematologic	1	4.2	1	0	0	0
Cardiac	0	0	0	1	1.6	1
Death	1	4.2	1	0	0	0
Other	0	0	0	4	6.5	4
Total	15	62.5	31	42	67.8	86

Pts patients, *comps* complications, *enox* enoxaparin

receive enoxaparin had an extensive right lower extremity DVT alone.

In addition, three patients total suffered intracranial arterial embolic strokes, one in the enoxaparin group and two in the non-enoxaparin group. Table 3 represents all reported postoperative hemorrhage-related, thrombotic, and other complications. Reported complications were greater in the non-treatment group except neurologic, genitourinary (UTI and acute renal failure), hematologic (anemia), and the one death (due to renal failure) $P > 0.5$.

Discussion

No consensus about postoperative administration of enoxaparin as thromboembolic prophylaxis following meningioma resection has been reached thus far. The biggest confounding complication is undoubtedly published evidence of increased risk of postoperative intracranial hemorrhage with the administration of a low molecular weight heparin [17]. Other contributing factors may include surgeon preference as well as conflicting studies some of which support anticoagulation in decreasing the risk of DVT and PE and others which show no difference in their occurrences [18, 19]. Individual patient characteristics such as age, preexisting compromise of vascular integrity, use of lumbar drains or coagulopathies make each meningioma resection unique and therefore may prolong controversy in the field around adjuvant enoxaparin administration post meningioma resection [1, 20, 21]. Perhaps a large multi-center, randomized control trial is necessary to conclusively establish practice guidelines.

In agreement with many and in direct opposition to other studies, we have found that postoperative administration of enoxaparin following resection of meningiomas is consistent with a lower rate of clinically significant thromboembolic events such as DVT or VTEs however we were not able to demonstrate this definitively. Though this retrospective study was not designed or powered to evaluate the reduction in thromboembolic risk (retrospective, cohort design), we have demonstrated that the incidence of DVTs/VTEs with enoxaparin therapy does not increase over non-treatment. Prior studies showing a reduction in thromboembolic events in neurosurgical patients include those of Frim et al. 1992 (low-dose heparin plus pneumatic compression boots) and Agnelli et al. 1998 while those of Barnett et al. 1977, Goldhaber et al. 2002 and Boström et al. 1986 do not. Of the studies that did show a difference all were prospective randomized controlled trials with $P = 0.020$ and $P = 0.04$, respectively. Similarly, the negative studies all were prospective randomized trials. This lack of agreement with seemingly properly designed and conducted trials, has raised questions for surgeons about the external validity and applicability of the conclusions from one study alone. Our control (non-enoxaparin) and study (enoxaparin) populations were similar in terms of WHO grade, tumor location, associated edema, preoperative embolization, Simpson grade resection and newly diagnosed or recurrent tumor.

In addition, our investigation suggests that for the population studied, postoperative enoxaparin administration does not cause an increase in the number of postoperative intracranial hemorrhages nor does it increase the percentage of symptomatic intracranial bleeds. In fact, the percentage of hemorrhage and symptomatic hemorrhage was greater in the non-enoxaparin control group though was not statistically significant. This is critical information when considering the initiation of enoxaparin therapy post meningioma resection. For patients who may benefit from the anticoagulation properties of enoxaparin, it is critical to understand that they may not be at increased risk of developing intracranial hemorrhages if therapy is begun. At our institution for the senior authors cases enoxaparin is begun the morning of the second day following surgery if no contraindications to its use exist. Frequently postoperative scanning is done within 48 h or earlier if there is a clinical problem and radiographic evidence of hemorrhage may influence the decision on whether or not to start prophylactic therapy.

Conclusions

Our study suggests that there is no significant increased risk of postoperative hemorrhage in patients who receive enoxaparin compared to those who do not. The overall incidence of a symptomatic hemorrhage requiring treatment is thankfully low in both treated and non-treated groups. We were not, however, able to conclusively demonstrate statistically significant improvement in DVT/VTEs with enoxaparin therapy due to limitations such as small sample size, retrospective design, and unknown patient characteristics that cannot be screened for. Another limitation of this retrospective study is that time to first ambulation is not documented and therefore was not available for all patients. Although antiembolic prophylaxis such as SCD and TED were routinely used in all patients until ambulatory, early ambulation is known to decrease the incidence of DVT/VTE in postoperative paitents. These limitations contribute to the dispute regarding enoxaparin use in postoperative meningioma resection patients. Our results suggest an agreement with prior studies reporting that the frequency of thromboembolic events is lower in meningioma patients who receive enoxaparin therapy within the first 48 h after surgical resection and offer some support for the routine administration of enoxaparin following meningioma resection to decrease the incidence of postoperative thromboembolic events.

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