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Clinical Article

Early antithrombotic prophylaxis with low molecular weight heparin in neurosurgery

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Summary

Background. Despite the high risk of venous thromboembolic events (VTE) in neuro-surgical patients, heparin prophylaxis has not been routinely established due to concern about bleeding complications. After initiating early low molecular weight heparin (LMWH) prophylaxis, we reviewed our patients in order to examine the viability of this practice.

Method. Over a 3 year period, the records of patients admitted for elective neuro-surgery (ES), head injury (HI) or spontaneous intracranial haemorrhage (ICH) were analysed. Prophylaxis was performed with certoparin (3000 U anti-factor Xa s.c.) on the evening before ES and within 24 hours after surgery or admission whenever a CT did not show a progressive haematoma. Contraindications for LMWH were prothrombin time <70%, partial thrombo-plastin time >40 s, platelet count <100.000/ml, and platelet aggregation test sum <60%. The incidence of bleeding complications, VTE, and resulting morbidity/mortality was assessed.

Findings. 294 patients were admitted for ES, 344 for HI, and 302 for ICH. 155 of these were excluded because of contraindications. Intracranial bleeding was recorded in 1.5% (ES 1.1%, HI 3.5%, ICH 0%) and operative revision was performed in 1.1% (ES 0.7%, HI 2.8%) of patients. One case of moderate disability and no mortality occurred. The incidence of VTE and pulmonary embolism was documented in 0.2% and 0.1% of patients, with no associated mortality. No heparin induced thrombocytopenia was observed.

Interpretation. In neurosurgical patients, antithrombotic prophylaxis with certoparin was determined to be safe and efficacious when contraindications are carefully considered and a 12-hour time interval before and after surgery was guaranteed. This retrospective analysis should encourage a prospective trial of early LMWH prophylaxis.

Keywords: Deep vein thrombosis; neurosurgery; heparin prophylaxis; bleeding complications; certoparin.

Introduction

In neurosurgical patients, a moderate to high risk for deep vein thrombosis (DVT) and venous thromboembolic events (VTE) exists. For instance, the mean frequency of DVT after elective surgery is 10%–30% and that of pulmonary embolism (PE) is 1.5%–5% with an associated mortality of 9%–50% [1]. In high risk patients with brain tumours or hemiparesis, the frequency of DVT increases to 40%–80% and of PE to 3%–10% [13, 26]. These complications contribute substantially to perioperative morbidity and mortality in neurosurgery.

Beside physical measures to prevent DVT, i.e. compression stockings and pneumatic devices, pharmacological options, including heparin prophylaxis, also exist. In several surgical fields, such as general surgery, orthopaedics, and urology, randomised controlled trials have confirmed a significant reduction of DVT by 50%–90% after heparin prophylaxis. Though pharmacological reduction of coagulation with heparins is associated with a slightly increased risk of postoperative bleeding complications [17], the reduction in morbidity and mortality by VTE surpasses the bleeding risk. Therefore, guidelines for preoperative thromboembolic prophylaxis have been established in these fields [12, 15, 19].

Thromboembolic prophylaxis has not been as strongly received in the neurosurgical field due to concerns of increased incidents of deleterious intracranial and spinal haematomas. Such is demonstrated in recently published surveys of the use of perioperative prophylaxis of VTE in neurosurgical patients which reveal a lack of consistent action in Germany [24] and in Great Britain [6].

Due to the threat of haemorrhage, the European Consensus Conference previously recommended only physical procedures for prophylaxis of venous thromboembolism in neurosurgery [12]. However, several studies have suggested that postoperative pharmacologic thromboembolic prophylaxis in neurosurgery is not associated with an increased rate of bleeding complications [1, 10, 25], while decreasing the incidence of VTE.

Furthermore, since evidence exists that many thrombi form during, not only after, surgery [18] preoperative initiation of thromboprophylaxis must also be seriously considered. One such investigation that administered LMWH to neurosurgical patients prior to the induction of anaesthesia was terminated because of the increased incidence of adverse bleeding events [7]. One can speculate that the failure of this trial is due to the short time interval between LMWH administration and surgery. For instance, in spinal anaesthesia the prophylactic application of LMWH is not recommended to occur within the intervals 12 hours before and 4 hours after the procedure [19]. Further studies are needed to clarify the risks and benefits of the heparin prophylaxis in neurosurgical patients.

Due to wavering support, the question of the type of heparin to be used for prophylactic purposes has not been considered. Low molecular weight heparin (LMWH, fractionated heparin) is a polymerised, chemically split heparin, stimulating antithrombin III for inhibition of factor Xa and only to a lesser degree for inhibition of thrombin. For pharmacodynamic reasons, this reduced interaction of LMWH with platelets compared with conventional heparin should reduce the risk of haemorrhage. This was confirmed by clinical investigations [11, 17], although this effect has been questioned by others [2]. In clinical trials, LMWH showed a comparable or improved effectiveness in the prevention of VTE when compared to standard low-dose heparin [9, 22]. Other advantages of LMWH in clinical application are the longer half-life, and the reduced antigenity resulting in a decreased risk of heparin-induced thrombocytopenia (HIT) type II compared to standard heparin.

Belonging to the six percent of neurosurgical departments in Germany which initiate LMWH antithrombotic prophylaxis preoperatively since 1997, we decided to analyse the records of our patients with regard to the incidence of VTE, haemorrhagic complications, required operative revisions, HIT, and resulting morbidity and mortality.

Patients and methods

Patients and pattern of antithrombotic prophylaxis

The records of patients 14 years of age or older undergoing elective neurosurgery (ES) or admitted by casualty because of head injuries (HI) or spontaneous intracranial haemorrhages (ICH) to the neurosurgical department were analysed retrospectively from the 1st of January 1999 to the 31st of June 2001. Patients received certoparin-sodium (Mono-Embolex ®NM, 3000 U anti-factor Xa; Novartis Pharma, Nürnberg, Germany) at a dose of 18 mg per day. Certoparin was given as a 0.3 ml subcutaneous injection once daily with preloaded syringes. In ES, administration was started on the evening before surgery. Contingent upon a routinely performed computed tomography (CT) scan, administration was continued the morning after surgery until discharge. Patients admitted for HI or ICH received certoparin whenever a control CT 24 hours after admission excluded any contraindication for heparin application like a progressive haematoma, and thereafter until discharge. Thigh-length compression stockings (thrombexin®climax, mediBayreuth, Germany) were placed on all patients on the morning of surgery or after admission by casualty and were worn until discharge. Excluded from heparin administration were patients with coagulation abnormalities (see below). Concomitant treatment with antiplatelet agents or other pharmacologic methods of antithrombotic prophylaxis or anticoagulation were not allowed.

Surveillance program

All patients were assessed on admission reviewing any history of oral anticoagulation, antiplatelet drugs or non-steroidal antiinflammatory drugs. Routinely, coagulation parameters such as thrombin time, partial thromboplastin time and a platelet count were investigated on admission. In cases of suspected drug interaction with platelet function, a platelet aggregation test was also performed. All coagulation abnormalities were treated in accordance with established guidelines depending on the level of emergency, and surgical intervention was delayed whenever possible until normalisation of coagulation. The following values were contraindications for LMWH application: prothrombin time below 70 percent of normal controls (corresponding INR above 1.2), partial thromboplastin time above 40 seconds, platelet count below 100.000 per ml, and platelet aggregation test sum below 60 percent of normal controls.

Patients were assessed daily during hospitalisation to review their clinical status, including signs and symptoms of VTE and bleeding side effects. In patients in whom DVT was clinically suspected, an additional laboratory examination of D-dimer and duplex sonography or venography of the deep veins was performed. DVT was defined as thrombosis after confirmation by real-time B-mode sonography (always performed by the same investigator) or constant intraluminal filling defect on 2 projections in venography. In patients with both clinical features suggestive of PE and elevated D-dimer levels, the diagnosis was confirmed by high probability ventilation-perfusion lung scan showing segmental perfusion defects or at autopsy. On the 5th postoperative day, a platelet count was performed routinely to rule out HIT. Within 24 hours after surgery or admission, a control CT scan was done to exclude bleeding complications or any event requiring operative revision. At discharge or in cases of neurological deterioration another control CT scan was performed.

Outcome measures

The principal outcome measures were symptomatic, objectively confirmed DVT or PE, HIT, and major bleeding. In HI and ICH patients not requiring surgical intervention, bleeding was considered relevant when the CT scan showed a progressive intracranial haematoma. In ES and all other patients requiring surgical intervention, bleeding was considered relevant when the postoperative haematoma comprised more than half of

the resection defect, caused more than local compression, or required operative revision. All deaths were classified as due to bleeding, VTE, or other causes.

Results

During the study period, 964 patients were admitted to the Neurosurgical Department. A total of 24 records were excluded for incompleteness. Of the 940 analysed records, 294 patients were admitted for ES, 344 for HI, and 302 for ICH. The mean age was 57.3 years (±15.3) and the duration of stay in our department was 13.3 days (±8.8). All patient characteristics are presented in Table 1.

Contraindications for LMWH prophylaxis

A total of 155 patients (16.5%) were excluded from the study protocol of early LMWH application because of coagulation abnormalities or relevant bleeding on the control CT 24 hours after admission. Forty-eight patients had received antiplatelet agents, 58 had an abnormal prothrombin time or prolonged thromboplastin time due to oral anticoagulation with cumarines or lysis, and 22 suffered of thrombocytopenia. In 27 HI and ICH patients, LMWH prophylaxis was withheld because of a progressive haematoma on the control CT. All coagulation abnormalities were treated in accordance with established guidelines and surgery was delayed depending on the level of emergency.

Venous thromboembolism

Altogether, a total of two patients (0.2%) suffered from VTE (ES 0%, HI 0%, ICH 0.8%). One ICH patient (0.1%) developed clinical signs of DVT which could be confirmed by real-time B-mode sonography. In another patient (0.1%) the lung scan confirmed PE after sudden onset of dyspnoea and additional work-up revealed a DVT without clinical symptoms. Upon findings of VTE, all patients received continuous intravenous heparin administration until prolongation of the partial thromboplastin time up to 50 seconds. These patients recovered well. The data are presented in Fig. 1a.

Bleeding complications

Three patients (1.1%) admitted for ES suffered from intracranial bleeding complications after preoperative LMWH prophylaxis with two of these requiring operative revisions. Of the three, one patient after operation on a meningeoma of the sphenoid wing showed a cerebellar haematoma on the postoperative CT scan. No operative revision was undertaken and the resultant problems with walking were minimal, resolving within weeks. Another patient, after resection of a metastasis of a bronchial carcinoma, showed a transient pronunciation of the preoperative existing hemiparesis due to a postoperative haematoma, thereby requiring operative revision. At discharge, the neurological deficits had been resolved. Unfortunately, one patient showed prolonged unconsciousness after surgical removal of a meningeoma of the posterior fossa. The CT scan revealed a postoperative haematoma causing compression of the brain stem. After immediate operative revision the patient recovered slowly. For therapy of ataxia, dysphagia and dysarthria the patient was admitted to a rehabilitation unit.

Table 1. *Characteristics of study patients including number, surgical intervention, age, duration of hospitalisation, diagnosis, excluded patients because of contraindication for LMWH application*

	Elective surgery	Head injury	Intracranial haemorrhage
Total (no.)	294	344	302
Surgery (no.)	294	153	170
Age (yr) ± SD	57.9 ± 12.7	53.5 ± 18.1	51.4 ± 15.8
Stay (d) ± SD	12.2 ± 5.5	10.0 ± 7.2	15.0 ± 12.5
Diagnosis (no.)	glioma (74) meningeoma (32) metastasis (37) pituitary adenoma (34) infratentorial tumors (22) skull tumors (9) shunt procedures (34) spinal tumors (8) other (13)	diffuse head injury (179) subdural haematoma (115) epidural haematoma (17) traumatic subarachnoid haemorrhage (23) polytrauma (6) other (6)	intracerebral haemorrhage (187) subarachnoid haemorrhage (88) arteriovenous malformation (21) cerebral infarction (4)
Excluded (no.)	27	64	64

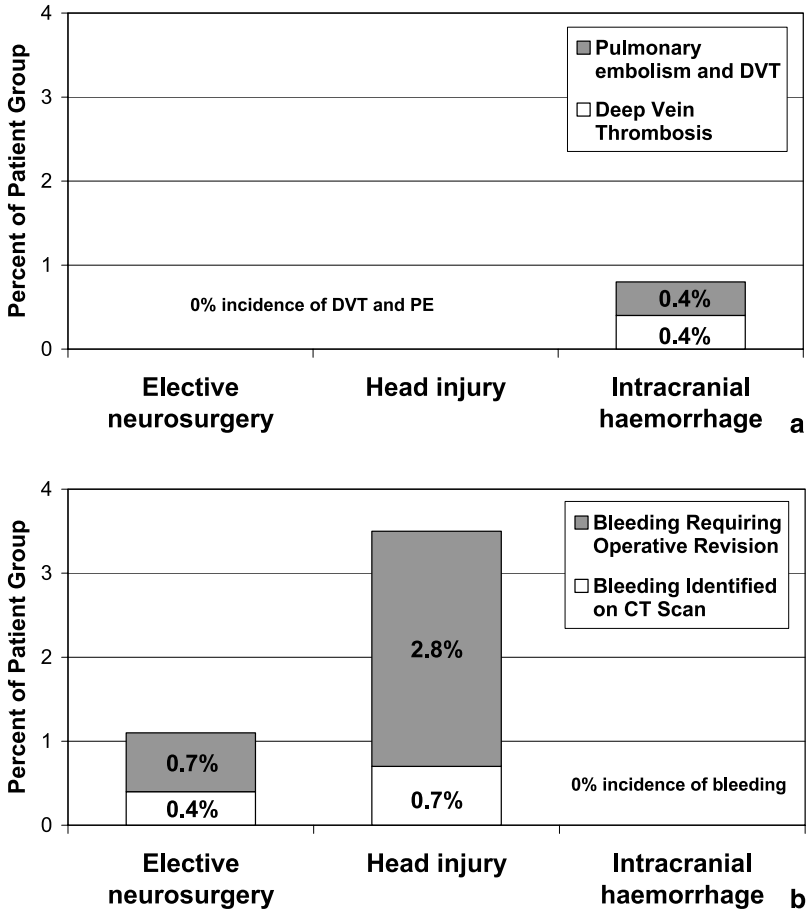

Fig. 1. Percentage of venous thromboembolic events (a) and bleeding complications (b) in study patients treated with early LMWH prophylaxis. In patients with elective neurosurgery, LMWH prophylaxis was started on the evening before and continued on the morning after surgery following a control CT. In patients with head injuries and intracranial haemorrhage, LMWH application was started after completion of a control CT 24 hours after admission

Table 2. *Initial diagnosis, therapy, symptoms, and day of diagnosis of complication, therapy of complication and outcome in patients with major bleeding complications*

No.	Age/sex	Diagnosis	Therapy	Diagnosis of bleeding	Intervention	Findings at discharge
Elective Surgery						
1	75/f	meningeoma	elective surgery	CT day 1	conservative	minimal deterioriation
2	78/f	meningeoma posterior fossa	elective surgery	unconscious CT after surgery	re-operation	moderate disability
3	43/f	metastasis	elective surgery	CT day 1	re-operation	complete remission
Head injury & Spontaneous Intracranial Haematoma						
4	46/f	subdural hematoma	surgery	CT day 1	conservative	no deficit
5	38/m	epidural hematoma	surgery	CT day 1	re-operation	no deficit
6	38/m	subdural hematoma	surgery	CT day 1	re-operation	no deficit
7	50/m	subdural hematoma	surgery	CT day 1	re-operation	no deficit
8	68/m	subdural hematoma	surgery	CT day 7	re-operation	no deficit
9	86/f	subdural hematoma	surgery	CT day 7	re-operation	no deficit
10	46/f	subdural hematoma, epidural hematoma contralateral	surgery subdural hematoma	MRI day 6	surgery epidural hematoma	no deficit
11	63/m	subdural hematoma	surgery	headache, CT day 6	re-operation	no deficit
12	49/m	subdural hematoma	surgery	headache, CT day 6	re-operation	no deficit

In 9 patients admitted for HI (3.2%; 7 subdural, 2 epidural), a control CT scan showed a progressive intracranial haematoma after early postoperative initiation of LMWH prophylaxis, resulting in 8 patients with operative revision (2.5%). In two patients, persistent headaches were the reason for a control CT, while all others were performed routinely. No neurological deterioration was observed and all patients recovered well. In ICH patients no major bleeding after LMWH application was recorded.

In 4 of the 9 HI patients, the bleeding complications were observed on the control CT scan routinely performed on the 1st postoperative day. According to our LMWH application protocol, administration of heparin on this day should have been delayed until the CT scan was complete. Unfortunately, these patients were treated with heparin for organisational reasons before the CT was performed. Altogether, no relevant extracranial bleeding complications, no HIT, and no bleeding-associated mortality occurred. The data of bleeding complications are presented in Fig. 1b, the details are summarized in Table 2.

Discussion

Incidence of thromboembolic events

The rationale for prophylaxis of DVT is based on the clinically silent nature of the disease. Both, DVT and PE manifest with few specific symptoms, and the clinical diagnosis is insensitive and unreliable. Most experts propose that a broad application of effective prophylaxis is more cost-effective than intensive surveillance [5]. Although underestimating the real incidence of DVT in our study because of the lack of a specific screening methodology, the use of clinical indicators of DVT as a study endpoint is a matter of clinical relevance [8, 10, 17]. Nevertheless, a highly sensitive screening method is valuable in a prospective randomized trial because it reduces the sample size required for significance.

Our results show that administration of LMWH certoparin – preoperative in ES and early postoperative in HI and ICH – used in combination with compression stockings was associated with a DVT and PE incidence of 0.2% and 0.1%. This frequency of clinically apparent VTE is substantially reduced compared to the 3%–17% risk of VTE in neurosurgical patients reported in the literature [1, 3, 4, 7, 21, 27]. Even compared to a fairly low 0.8% rate of VTE using low dose heparin early postoperatively [25], the preoperative initiation of LMWH prophylaxis in our study showed further improvement.

Incidence of bleeding complications

Weighing the risk of bleeding complications with the converse incidence of VTE has left many clinicians uncertain. Thus, the safety of preoperative heparins in neurosurgical patients has to be thoroughly addressed. Therefore, while starting LMWH application on the evening before elective surgery, we withheld the next dose until a postoperative control CT was completed in order to guarantee at least a 12 hour time interval before and after surgery. In HI and ICH patients who were subjected to a primarily conservative treatment, LMWH application was only started after confirmation of a stable haematoma size by a control CT 24 hours after admission. This policy was able to minimize bleeding complications within the conservative HI and ICH treatment group to 0%. We chose LMWH rather than low-dose standard heparin because it was found to have a similar rate of bleeding complications [9] and equal if not greater efficacy [28]. Furthermore, the lack of HIT in our study supports the known trend of a reduced incidence of HIT in LMWH as compared to standard heparin.

With regards to ES patients, the 1.1% incidence of bleeding complications is comparable to the incidence of 1.2% to 1.4% in placebo groups reported in the literature [16, 21]. Similar, the 0.7% rate of necessary surgical revisions is comparable to a 0.8% rate of a documented control group [14]. In ES patients subjected to preoperative initiation of LMWH prophylaxis, a 0.4% morbidity rate caused by bleeding complications is opposed to a 0% incidence of VTE and no mortality. In HI patients, the 3.5% incidence of relevant bleeding complications after postoperative initiation of LMWH prophylaxis is in accordance with the literature [20]. A recurrence of subdural and epidural haematomas, both known for their high incidence of necessary operative revisions, was collectively seen in 9 patients. Hence, in HI patients the early antithrombotic prophylaxis with LMWH was associated with no morbidity caused by bleeding complications and resulted in avoidance of any VTE. In ICH patients, no bleeding complications were seen after early initiation of LMWH prophylaxis while VTE was observed in only 0.8% of this patient group.

Implications on clinical practice

Therefore, in each of the neurosurgical patient groups – elective surgery as well as head injury and spontaneous intracerebral haemorrhage – the benefit of early thromboprophylaxis with LMWH seems to outweigh the possible negative side-effects. We are aware that this study

investigating clinical efficacy and side effects of early LMWH prophylaxis lacks a control group and does not allow any statistical analysis. Nevertheless, by inclusion of more than 900 patients this study of preoperative or early postoperative thromboembolic prophylaxis with certoparin (Mono-Embolex® NM) in neurosurgical patients demonstrates this practice to be both, safe and efficacious thereby supporting already existing data. Contraindications should be carefully regarded and a 12-hour time interval before and after surgery should be guaranteed. Furthermore, these findings give further impetus for a prospective multicentre trial of early LMWH-prophylaxis in neurosurgical patients in order to confirm the safety and establish guidelines of its perioperative use.

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Comment

The paper presented by Kleindienst *et al.* covers the important topic of pharmacological prophylaxis of thromboembolic events in neurosurgical patients. Although the efficacy of heparin or LMWH prophylaxis in preventing thromboembolic events is largely acknowledged, the fear of potential associated bleeding complications as a side effect of these compounds led only to a limited acceptance for this treatment in neurosurgery. Thus, there is still an ongoing debate, whether pharmacological prophylaxis is beneficial for neurosurgical patients and when prophylaxis should be started. Furthermore the pharmacological

compound, which seems to be the most appropriated for neurosurgical patients has not yet been defined.

Kleindienst *et al.* show in this retrospective analysis, that bleeding complications are not increased after a single administration of certoparin 12 hours before elective surgery and continued treatment the morning after surgery. Because it is thought, that formation of thrombi starts during surgery, the authors argue that a single dose about 12 h before elective surgery may be more effective in reducing DVT compared to prophylaxis started postoperatively. The pharmacological effect of certoparin in preventing DVT during surgery, when given as a single injection 12 hours before the operation, remains questionable. According to pharmacokinetic information provided by the company, certoparin exerts its maximum effect 2–4 hours after injection and is rapidly eliminated afterwards with a half life of 4.3 hours, which may result in an almost complete elimination of the compound at the beginning of surgery. A pharmacological prevention of DVT during surgery would imply to use the compound shortly before or at the beginning of surgery. But we have to keep in mind the study published by Dickinson *et al* [1], which was terminated because of the increased incidence of significant intracranial haemorrhage, when prophylaxis was initiated at the time of anaesthesia induction.

Controlled randomized studies, analysing the efficacy of DVT-prophylaxis when LMWH or unfractionated heparin was administered postoperatively, have shown a tremendous reduction of thromboembolic complications without increased bleeding [2]. We have shown a rate of 0.8% clinical symptomatic thromboembolic events [3] by postoperative pharmacological prophylaxis. It may be difficult to further decrease the rate of clinical symptomatic DVT, by starting prophylaxis preoperatively, without increasing the risk of bleeding. Whether a single injection of heparin or LMWH 12 hours prior to surgery is of advantage in preventing DVT, compared to postoperative prophylaxis has to be clarified by a prospective randomized trial. Until data of such a study are available it seems to be more appropriate to start pharmacological prophylaxis in neurosurgery postoperatively.

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V. Seifert

Author's Reply

In almost all trials investigating the efficacy and safety of any low molecular weight heparin (LMWH) including certoparin, prophylaxis was started 1 to 2 hours before surgery. However, the only trial examining this regime in neurosurgery was aborted because of an increased incidence of bleeding complications [1]. Therefore, we chose a substance proven to be efficacious when administered on the evening before surgery and only once daily [2]. The prolonged biological antithrombotic effect of certoparin is believed to be a result of stimulation of the endothelial release of TFPI (tissue factor pathway inhibitor) rather than of an antithrombin-mediated inhibition of factor Xa. Without any doubt, our regime of administration was in accordance with the companies recommendations confirmed by clinical trials. We agree completely that a prospective controlled multicentre trial is needed to establish guidelines for the perioperative use of LMWH in neurosurgery.

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