Low-Molecular-Weight and Unfractionated Heparin for Prevention of Venous Thromboembolism in Neurosurgery

A Meta-analysis

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Background: Venous thromboembolism is a common, life-threatening complication in neurosurgery, but prophylaxis with anticoagulant agents has not gained wide acceptance because of concern about intracranial bleeding. We performed a meta-analysis of controlled randomized trials on the efficacy and safety of heparin in the prophylaxis of venous thromboembolism in neurosurgery.

Objective: To review the clinical benefit of prophylaxis of venous thromboembolism with heparin in the controversial setting of neurosurgery.

Methods: Relevant trials evaluating heparin for prophylaxis of venous thromboembolism in neurosurgery were identified by a MEDLINE search, scan of meeting abstracts, and scrutiny of the references of original articles and reviews. Four controlled randomized studies, 3 of which involved low-molecular-weight heparin, were included in the analysis, and 4 uncontrolled studies are commented on in the article. The outcome measure (observed minus expected number of events) and its variance were calculated for each single trial and then summed. Two-tailed P values and 95% confidence intervals (CIs) were calculated. Efficacy was assessed per protocol and safety by intention-to-treat analysis. The homogeneity of the studies was tested with the χ² statistic. The results were also expressed as number needed for 1 extra event.

Results: A total of 187 thromboembolic events were recorded in 827 patients (22.6%). Heparin prophylaxis resulted in a 45% relative risk reduction of venous thromboembolic events (odds ratio [OR], 0.48; 95% CI, 0.35-0.66; P<.001). Nineteen major bleedings were recorded in 1022 patients. None were fatal. Heparin treatment resulted in a 71% relative risk increase of major bleeding (OR, 1.72; 95% CI, 0.69-4.27; P=.24). The number needed to treat was 7.7 for venous thromboembolism and 16 for proximal deep vein thrombosis. The number needed to harm was 102 (115 for low-molecular-weight heparin).

Conclusions: Low-molecular-weight and unfractionated heparin have been shown to be effective for prophylaxis of venous thromboembolism in elective neurosurgery without excessive bleeding risk.

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Venous thromboembolism (VTE) is a life-threatening complication of neurosurgery. The risk of pulmonary embolism in neurological patients has been reported to be as high as 5%, with a mortality rate ranging from 9% to 50%.

Analysis of the major trials indicates that pulmonary embolism is a major cause of death in neurological patients. The incidence of clinically overt deep vein thrombosis (DVT) has been reported to range from 1.6% to 4%.

The incidence of objectively proven DVT has been estimated to range from 19% to 43% in case series using fibrinogen labeled with iodine 125 (¹²⁵I) to screen for DVT and from 24% to 33% in clinical trials using venography to screen for DVT.

Neurosurgery appears from these figures as a high-risk clinical setting for development of VTE, definitely requiring an effective prophylaxis. Heparin is widely used in the prophylaxis of VTE in moderate- and high-risk clinical settings. However, it is scarcely used in neurological patients because of the potential consequences of bleeding in the brain or spine. The results of a recent survey of current practice showed that only 32% of neurological units use subcutaneous heparin for the prophylaxis of VTE. This rate is reduced to 6% in units performing emergency neurosurgery.

Data on the incidence of perioperative hemorrhagic complications in neurosurgery are scanty. In the absence of anticoagulant prophylaxis, a computed tomographic scan surveillance program at...
MATERIALS AND METHODS

Relevant randomized trials were identified by computer-aided (MEDLINE) search (up to 1999), scan of meeting abstracts, scrutiny of the reference list of original articles and review articles, and informal search with colleagues.

The data from the individual studies13-16 were pooled following the method of meta-analysis described by Yusuf et al.17 As discussed in detail elsewhere,18 the method presents a single requirement that all the data from all randomized trials are available without any material bias due to nonavailability of unproven results or patient withdrawal. There is no assumption regarding the comparability of patients among studies, since all the statistics are based on comparison "intra" each single trial, ie, each treated group is compared with its own control group in the original study. The outcome measure (observed minus expected number of events, O-E) and its variance (V[O-E]) were calculated for each single trial and then summed to give the total and its variance. The formula used to calculate V(O-E) was (nd/N) (1-n/N)(N-d)/(N-1), where n indicates the number of patients treated, d indicates the number of patients with the event, and N indicates the total number of patients in the trial. For evenly balanced trials, O-E is equal in size to half the number of patients protected. Two-tailed P values were used in the analysis, and 95% confidence intervals (CIs) were calculated for the individual studies and overview results. The homogeneity of the studies was tested with an approximate χ² statistic, calculating Σ[(Oi-Ei)/Ei] - Σ(Vi/1) N/1, with df of 1 less than the number of nonvariances. The results of each single trial and the pooled data were also expressed as number needed for 1 extra event (NNE), ie, number needed to treat (NNT) for efficacy and number needed to harm (NNH) for safety analysis.

Since the evaluation of efficacy was performed by objective methods (venography or 125I-fibrinogen scanning), efficacy was analyzed per protocol. Safety was assessed by intention-to-treat analysis by allocated treatment. The classification of bleeding events as major and minor was performed following the adjudication done in each single trial. However, bleeding was consistently considered to be major across the trials when it was clinically overt and associated with a decrease in hemoglobin level of at least 20 g/L or with transfusion of 2 or more units of packed red blood cells. Intracranial and retroperitoneal bleeding and bleeding that required surgical intervention were also considered major. All other bleeding events were considered minor.

To give a greater emphasis to larger studies, the areas of the squares used to plot the results were made proportional to V(O-E), because this is a measure of the statistical information content of each trial.

day 7 showed a 26.7% rate of bleeding complications, of which 10.8% were intracerebral and 15.9% extradural hematoma.36 The need for reintervention because of bleeding complications has been estimated to vary between 1% and 8%.7,8 The use of perioperative and postoperative low-dose unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) has been claimed to be safe in several uncontrolled series of neurosurgical patients. Five hundred seven patients were enrolled in 4 uncontrolled cohort studies.9-12 Among them, 277 were treated with UFH, 5000 U subcutaneously twice a day starting preoperatively; 138 with UFH, 5000 U subcutaneously twice a day starting postoperatively; and 97 with the LMWH nadroparine calcium, 7500 antifactor Xa Institute Choay units subcutaneously once a day postoperatively. The prospective observation of these patients showed a cumulative incidence of major hemorrhagic complications of 3.7% (19% evidence of hemorrhage with a computed tomographic scan surveillance in the LWMH study) and a rate of reintervention of 0.4%.

The aim of this study was to perform a meta-analysis of randomized controlled trials on the efficacy and safety of heparin in the prophylaxis of VTE in neurosurgery.

RESULTS

The main characteristics of the studies included in the analysis are shown in Table 1. Four randomized controlled studies were performed to assess the efficacy and safety of heparin prophylaxis in elective neurosurgery.13-16 Three of these studies evaluated LMWH and were placebo-controlled, double-blind clinical trials that used venography to assess the end point.13-15 Study population and design were similar for the 3 LMWH studies. The study by Cerrato et al16 was different, since it evaluated UFH, it was not double-blind, and it used 125I-fibrinogen scanning for the outcome assessment. As the result of the inclusion of this last study in the analysis, the χ² statistic used to test the heterogeneity of treatment effect increased from 1.26 to 5.79, thus supporting the homogeneity assumption only marginally (P=.12). For these reasons, the results of the meta-analysis are presented with and without this study.

The overview included 1022 patients for safety and 827 for efficacy analysis. The comparison studies between LMWH and placebo included 922 patients for safety and 727 for efficacy analysis. The study population was homogeneous for both safety and efficacy analysis.

THROMBOEMBOLIC EVENTS

The results concerning efficacy are shown in Table 2 and Figure 1. One hundred eighty-seven thromboembolic events were recorded in 827 patients, for a mean incidence of 22.6%. Heparin (UFH or LMWH) prophylaxis resulted in a 45% relative risk reduction of VTE (odds ratio [OR], 0.48; 95% CI, 0.35-0.66; P<.001). The NNT, shown in Table 2 as NNE, was 7.7 (95% CI, 5.4-13.7), ie, 1 extra VTE would occur in about every 8 patients who are denied treatment. The data on the incidence and prevention of proximal DVT are shown in Table 2, bottom. A total of 58 events were recorded in 616 patients, for a mean incidence of 9.4%. The NNT for proximal DVT was 16 (95% CI, 9.2-59.5).
Treatment with LMWH resulted in a 38% relative risk reduction of VTE (OR, 0.54; 95% CI, 0.38-0.77; \( P = .001 \)). The NNT for LMWH was 9.2 (95% CI, 5.9-20.9). Treatment with LMWH resulted in a 50% relative risk reduction for proximal DVT (OR, 0.48; 95% CI, 0.28-0.83; \( P = .001 \)) (Table 2, bottom).

Overall, 195 patients (19.1%) were excluded from the efficacy analysis because venography was not performed or available: 101 treated patients (19.8%) and 94 controls (18.4%). All patients excluded from the efficacy analysis were followed up for the occurrence of clinically overt thromboembolic events for at least 2 months. At follow-up, 3 patients in the treated group and 7 in the placebo group had a clinically overt thromboembolic event, confirmed by objective testing. After cumulating venography assessment and clinically overt events at follow-up, the results of the meta-analysis for proximal DVT were as follows: NNE, 16.7; \( P = .003 \); OR, 0.47; 95% CI, 0.28-0.77.

**BLEEDING**

The results concerning bleeding are shown in Table 3 and Figure 2. Four deaths were related to bleeding but not to the study treatment. Forty-five bleeding events were observed in 1022 patients, for a mean incidence of 4.4%. Heparin (both UFH and LMWH) treatment resulted in a 100% relative risk increase of bleeding events (OR, 2.06; 95% CI, 1.12-3.77; \( P = .02 \)). The NNH, shown in Table 3 as NNE, was 34.1 (95% CI, 18.4-234.7). The figures for LMWH were similar: NNH was 32.9 (95% CI, 17.5-284.0). When only major bleeding events were con-
considered, 19 nonfatal events were recorded, for a mean incidence of 1.8%; 12 (2.3%) occurred in the heparin group and 7 (1.4%) in the control group. Heparin (both UFH and LMWH) treatment resulted in a 71% relative risk increase of major bleeding events (OR, 1.71; 95% CI, 0.69-4.27; P = .24). The NNH for UFH and LMWH or LMWH alone was 102.2 (low 95% confidence limit, 18.4) and 115.3 (low 95% confidence limit, 39.2), respectively. None of the 19 major bleeding events was considered from the blinded adjudication committees of the trials to be related to the study treatments. Of the 12 major bleeding events that occurred in treated patients, 11 were intracranial bleeding and 1 was gastrointestinal bleeding. Of the 7 major bleeding events that occurred in control patients, 6 were intracranial bleeding and 1 was gastrointestinal bleeding.

DEATHS

The results concerning deaths are shown in Table 4. Forty-three patients (4.2%) died and 61 (6.0%) experienced an adverse outcome event (death, clinically overt pulmonary embolism, and major bleeding). An NNE of 46.5 for death alone and an NNE of 39.3 for the combined adverse outcome event were observed. None of the deaths was considered by the blinded adjudication committees of the studies to be related with the study treatments. The most common causes of death were intracranial nonhemorrhagic postsurgery complications (12 patients, 9 in the treated group and 3 controls).
bleeding (4 patients, 2 treated and 2 controls), and pulmonary embolism (3 patients, 1 treated and 2 controls). Of the 4 deaths related to bleeding, in the treatment group one patient started to bleed during surgery and died on the first postoperative day, inadvertently receiving the first LMWH administration 24 hours after surgery, and one other patient died on day 12 from bleeding associated with full-dose anticoagulant treatment instituted for documented VTE. In the control group, one patient died from hemorrhage during a course of oral anticoagulant treatment for venous thrombosis, and another patient had spontaneous intracranial bleeding on day 22. One other patient in the treated group died of cardiorespiratory failure, and one in the control group died of tumor progression; in 2 cases the cause of death remained unknown, and in the remaining 20 cases death was generically referred to as events not related to bleeding or pulmonary embolism.

The analysis showed the efficacy of heparin (LMWH and UFH) in the prophylaxis of VTE in neurosurgery. All the individual trials showed a protective effect of treatment (ORs ranging from 0.18 to 0.65; NNTs ranging from 3.6 to 13.2). In the trial of Agnelli et al., the difference in efficacy between treatment and control was statistically significant. The analysis of pooled data from the studies defined a reliable CI around the OR estimation (0.35-0.66) or the NNT (5.4-13.7).

Heparin treatment resulted in a 45% relative risk reduction of VTE, ie, 53 events were prevented by treatment of 410 patients (1 event prevented for every 7.7 patients treated). Considering only the trials using LMWH, treatment resulted in a 38% relative risk reduction of VTE, ie, 39 events were prevented by treatment of 360 patients (1 event prevented for every 9.2 patients treated). Considering only proximal DVT, LMWH saved 19 events in 304 treated patients (1 event prevented for every 16 treated patients), for a 50% relative risk reduction.

The conclusions on the efficacy of heparin prophylaxis do not imply the validation of the 3 different compounds and 4 different dosages that have been used in the considered trials. Indeed, taking into account the heterogeneity of LMWH and the dose dependence of their effect, each agent and regimen have to be validated in a randomized controlled clinical trial. Enoxaparin sodium can be addressed as an example: the use of 40 mg/d in the study by Agnelli et al. was associated with a 49% relative risk reduction of VTE; this was 33% for the 20-mg/d dose used in the study by Melon et al.

Furthermore, it should be taken into account that most patients (88%) included in the analysis received LMWH; thus, the issue of the efficacy of UFH remains to be solved.

The safety analysis requires 2 considerations with respect to bleeding and 2 with respect to death. Concerning bleeding, the meta-analysis mainly relies on LMWH trials; thus, safety of UFH administration in neurosurgery patients remains to be assessed. However, it should be taken into account that the prospective uncontrolled observation of 400 neurosurgery patients who received UFH showed a low incidence of hemorrhagic complications. Furthermore, in the 3 studies with LMWH, the treatment was started postoperatively, and the study protocols excluded patients with a high surgery-related bleeding risk. The multicenter design of all 3 studies demonstrated that this approach, although it implies some subjectivity, is standardizable and applicable. None of the bleeding events was fatal or required reinsertion. An increase in bleeding events was recorded for treated patients. Heparin prophylaxis resulted in a statistically significant 100% relative risk reduction.

### Table 4. Safety Analysis

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Events/No. of Patients (%)</th>
<th>Statistical Calculations†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated to Treatment</td>
<td>Allocated to Control</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agnelli et al. 1998</td>
<td>5/153 (3.3)</td>
<td>6/154 (3.9)</td>
</tr>
<tr>
<td>Nurmohamed et al. 1996</td>
<td>22/241 (9.1)</td>
<td>10/244 (4.1)</td>
</tr>
<tr>
<td>Melon et al. 1987</td>
<td>0/67 (0...)</td>
<td>0/63 (0...)</td>
</tr>
<tr>
<td>All LMWH</td>
<td>27/461 (5.9)</td>
<td>16/461 (3.5)</td>
</tr>
<tr>
<td>Cerrato et al. 1978</td>
<td>0/50 (0...)</td>
<td>0/50 (0...)</td>
</tr>
<tr>
<td>All studies</td>
<td>27/511 (5.3)</td>
<td>16/511 (3.1)</td>
</tr>
<tr>
<td>Deaths, Pulmonary Embolism, and Major Bleeding Events</td>
<td></td>
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<tr>
<td>Agnelli et al. 1998</td>
<td>9/153 (5.88)</td>
<td>11/154 (7.14)</td>
</tr>
<tr>
<td>Nurmohamed et al. 1996</td>
<td>26/241 (10.79)</td>
<td>12/244 (4.92)</td>
</tr>
<tr>
<td>Melon et al. 1987</td>
<td>0/67 (0...)</td>
<td>0/63 (0...)</td>
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<tr>
<td>All LMWH</td>
<td>32/461 (7.99)</td>
<td>22/461 (4.99)</td>
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<tr>
<td>Cerrato et al. 1978</td>
<td>2/50 (4.0)</td>
<td>1/50 (2.0)</td>
</tr>
<tr>
<td>All studies</td>
<td>37/511 (7.24)</td>
<td>24/511 (4.7)</td>
</tr>
</tbody>
</table>

*Test for heterogeneity between the studies for deaths: all low-molecular-weight heparin (LMWH), \( \chi^2 = 1.95, P = .38 \); all studies, \( \chi^2 = 1.95, P = .38 \). Test for heterogeneity between the studies, all LMWH, \( \chi^2 = 3.164, P = .21 \); all studies, \( \chi^2 = 3.199, P = .21 \).

†O−E indicates observed minus expected number of events; V(O−E), variance of O−E; OR, odds ratio; CI, confidence interval; RR, risk ratio; and NNE, number needed for 1 extra event.
increase of bleeding events and in a statistically nonsignificant 71% relative risk increase of major bleeding events. In other words, 15 bleeding events in excess were recorded by treating 511 patients for 10 days: 5 were major (1 major bleeding event for every 102 treated patients; 1 for every 115 patients treated with LMWH). Concerning death, we should first consider that the overall mortality rate of 4.2% is not different from that reported in the literature for neurosurgery and second that the negative trend showed for the treated group was for more than half due to non–treatment-related causes of death (55.7% overall, 59.4% in treated patients, and 50% in controls).

A better estimate of the efficacy-safety ratio for heparin prophylaxis of DVT in neurosurgery would be observed from the combination of the data relative to efficacy and safety: one may expect to have 1 major nonfatal bleeding event in excess of every 11 (LMWH) or 13 (overall) thrombotic events prevented or 1 major nonfatal bleeding event for every 7 proximal DVTs prevented. In conclusion, LMWH can offer the clinician an effective and relatively safe prophylaxis for VTE in patients undergoing elective neurosurgery. The role of UFH is still unclear.

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REFERENCES