Prevention of Venous Thromboembolism in Neurosurgery*

A Metaanalysis

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Background: **Venous thromboembolism (VTE) is an important complication of neurosurgery. Current guidelines recommend pharmacologic prophylaxis in this setting with either unfractionated heparin or low-molecular-weight heparin (LMWH). We conducted a systematic review asking, "Among patients undergoing neurosurgical procedures, how safe and effective is the prophylactic use of heparin and mechanical devices?"**

Methods: **We searched the medical literature to identify prospective trials reporting on VTE prevention (either mechanical or pharmacologic). The rates of VTE and bleeding were our primary end points and were pooled using a random-effects model.**

Results: **We identified 30 studies reporting on 7,779 patients. There were 18 randomized controlled trials and 12 cohort studies. The results of pooled relative risks (RRs) showed LMWH and intermittent compression devices (ICDs) to be effective in reducing the rate of deep vein thrombosis (LMWH: RR, 0.60; 95% confidence interval [CI], 0.44 to 0.81; ICD: RR, 0.41; 95% CI, 0.21 to 0.78). Similar results were seen when pooled rates from all 30 trials were analyzed. In head-to-head trials, there was no statistical difference in the rate of intracranial hemorrhage (ICH) between therapy with LMWH and nonpharmacologic methods (RR, 1.97; 95% CI, 0.64 to 6.09). The pooled rates of ICH and minor bleeding were generally higher with heparin therapy than with non–heparin-based prophylactic modalities.**

Conclusions: **In a mixed neurosurgical population, LMWH and ICDs are both effective in the prevention of VTE. Sensitivity analyses have suggested that isolated high-risk groups, such as those with patients undergoing craniotomy for neoplasm, may benefit from a combination of prophylactic methods, suggesting the need for a more individualized approach to these patients.**

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Key words: hemorrhage; intracranial hemorrhages; neurosurgery; thromboembolism; thrombosis

Abbreviations: CI = confidence interval; CS = compression stocking; DVT = deep venous thrombosis; ICD = intermittent compression device; ICH = intracranial hemorrhage; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RCT = randomized controlled trial; RR = relative risk; UFH = unfractionated heparin; VTE = venous thromboembolism

Neurosurgery patients are at high risk of venous thromboembolic events postoperatively, particularly patients undergoing intracranial surgery for malignancy, the elderly, and those undergoing prolonged surgery. In patients undergoing elective posterior lumbar spinal surgery, the known risk factors include prolonged immobilization/bed rest, lengthy operative procedures, prone positioning on frames with flexion of the hips/knees, and distraction of the spine (which may compress lower extremity venous return).[1,2] The current recommendations for thromboembolism prophylaxis include the use of intermittent compression devices (ICDs) postoperatively, with or without compression stockings (CSs), low-dose unfractionated heparin (UFH) perioperatively, or low-molecular-weight heparin (LMWH) postoperatively.[3–7] However, neurosurgeons are concerned about bleeding complications, and to date there has been no systematic assessment of the data on pharmacologic prophylaxis efficacy and safety in neurosurgery and spinal surgery patients. Our purpose was to conduct a systematic review to answer the question, "Among patients undergoing neurosurgical procedures, what is the relative efficacy of LMWH,

UFH, and mechanical devices in preventing thromboembolism, and what are the relative bleeding complications?"

Materials and Methods

Literature Search

While our goal was to analyze only randomized controlled trials (RCTs) that were head-to-head comparisons of different methods of prophylaxis, in order to systematically retrieve the literature from around the world, we also searched for prospective cohort trials of venous thromboembolism (VTE) prophylaxis. Two investigators, with the assistance of a medical librarian, independently searched the published literature (from 1960 through August 2007) to identify published RCTs and prospective clinical trials of VTE prophylaxis in neurosurgical patients, using either pharmacologic or mechanical methods. The search was not limited to studies published in the English language. The following databases were searched: MEDLINE; PubMed; Cochrane RCT; Embase; Biosis; PASCAL; Sci Search; IPA; and Computer Retrieval of Information on Scientific Projects. The search terms included "neurosurgery," "neurosurgical procedures," "thromboembolism," "thromboprophylaxis," "heparin," "Lovenox," and "enoxaparin." Full-text articles of all potentially appropriate studies were reviewed, and a hand search of the bibliographies of each retrieved article was conducted.

Study Selection Criteria

The inclusion criteria included the following: (1) a randomized trial or prospective cohort study evaluating pharmacologic VTE prophylaxis (with UFH or LMWH); or (2) a randomized trial or prospective cohort study evaluating mechanical VTE prophylaxis (with ICDs or CSs); (3) an objective assessment of deep venous thrombosis (DVT) [*ie*, with Doppler compression sonography, impedence plethysmography, radiofibrinogen uptake scanning, autopsy, or venography] and pulmonary embolism (PE) [*ie*, with CT angiography, ventilation perfusion scanning, or pulmonary angiogram, or by autopsy] with the reporting of incidences; and (4) a neurosurgical population. Studies were excluded if they were not primarily related to neurosurgery patients, were not prospective studies, were not specifically about VTE prophylaxis, or if they were articles primarily about patients with penetrating or closed head injuries, spinal cord injuries, or stroke.

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Study Quality Assessment

RCTs were rated for eight elements of quality using the methods of Jadad et al.[8] In addition, we created a quality assessment tool that was adapted from the criteria of McMaster[9] for evaluating the validity of studies about prognosis, which we also used for the evaluation of RCTs in addition to the prospective cohort trials. Studies were assessed for the presence of the following eight features: a description of the characteristics of the patient sample; a description of the inclusion and exclusion criteria; potential selection bias; the completeness of the follow-up; a description of the reasons for incomplete follow-up; the definition of outcomes stated at the start of the study; and the objectivity of outcomes. Two raters independently assessed quality (Jadad et al criteria: κ, 0.56; McMaster criteria: κ, 0.37; $p = 0.005$). Disagreements were resolved by consensus.

Data Extraction

We extracted the following data from each study: study design (*ie*, efficacy, safety, and prospective, randomized, or double-blind); exclusion criteria; patient demographics (*ie*, number of patients, sex, age, and type of neurosurgical intervention); DVT prophylaxis modality (*ie*, mechanical [ICDs or CSs]; or pharmacologic [LMWH or UFH]); the method of DVT diagnosis (*ie*, fibrinogen scanning, venography, or ultrasound); the method of PE diagnosis (*ie*, CT scan, pulmonary angiogram, or ventilation perfusion scan); the length of follow-up; and the number of patients lost to follow-up and the reasons for being lost to follow-up. The outcomes assessed were DVT, PE, minor bleeding events, major bleeding events, intracranial hemorrhage (ICH), reoperation for bleeding and deaths, and whether deaths were study related.

Statistical Analysis

Our primary goal was to pool the relative risks (RRs) from RCTs that included head-to-head comparisons of different modalities of prophylaxis. These RRs were pooled using the DerSimonian and Laird[10] random-effects method. Because there were relatively few such trials, and in order to exhaustively synthesize the literature, we also calculated the overall rates as well as the annualized rates from the data provided in each article for all trials, including both prospective cohort trials and RCTs. The variance for each outcome was calculated using exact binomial methods[11] and were pooled using a random-effects model.[10] For both RRs and rates, pooled heterogeneity was assessed visually with Galbraith plots,[12] Q statistics (χ^2 test),[13] and the I^2 statistic. Studies with an I^2 statistic of 25 to 50% are considered to have low heterogeneity, those with an I^2 statistic of 50 to 75% to have moderate heterogeneity, and those with an I^2 statistic of $> 75\%$ to have a high degree of heterogeneity.[14] Publication bias was assessed visually using funnel plots as well as statistically using the methods of Begg and Berlin,[15] Egger et al,[16] and Duvall and Tweedie.[17] In addition, we performed a sensitivity analysis, assessing the effects of study quality and various other study characteristics using stratified analysis and metaregression. A random-effects metaregression was used to adjust for the potential differences between studies. All analyses were performed using a statistical software package (Stata, version 9.2; StataCorp; College Station, TX).

Results

We identified 2,520 potential studies in our literature search. We excluded 2,490 studies, leaving 30