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Review Article

A direct comparison of prophylactic low-molecular-weight heparin versus unfractionated heparin in neurosurgery: A meta-analysis

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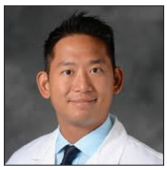

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ABSTRACT

Background: Several studies have confirmed the role of prophylactic low-molecular-weight heparin (LMWH) for venous thromboembolism (VTE) in neurosurgery; however, a paucity of literature has assessed its safety and efficacy versus prophylactic unfractionated heparin (UFH). The objective is to present a meta-analysis directly comparing prophylactic LMWH to UFH for the prevention of VTE in neurosurgery.

Materials and Methods: Relevant studies that directly compared LMWH to UFH for prophylaxis of VTE in neurosurgery and/or spine surgery were identified by MEDLINE and EMBASE searches plus a scrutiny of references from the original articles and reviews. Three randomized trials were included in the meta-analysis. Efficacy and safety were ascertained per three primary outcome measures: VTE, minor complications (decline in hemoglobin/hematocrit), and major complications. Forest plot analysis provided odds ratio (OR), 95% confidence intervals (CIs), and *P*-values.

Results: Of the 429 patients in the pooled analysis, the postoperative VTE rate of 5.6% (12/213) after LMWH chemoprophylaxis was equivalent to 3.7% (8/216) after UFH chemoprophylaxis (OR = 1.42, 95% CI 0.62–3.75, *P* = 0.308). Minor complications of 4.7% versus 4.6%, respectively, were nearly equal (OR = 1.01, 95% CI 0.41–2.50, *P* = 0.929). All four major complications included intracranial hemorrhages: three after LMWH (1.4%) and one after UFH (0.5%) (OR = 2.32, 95% CI 0.34–16.01, *P* = 0.831). Tests for heterogeneity were nonsignificant in all three outcome measures.

Conclusion: Rates of VTE, minor complications, and major complications were equivalent between prophylactic LMWH and UFH in neurosurgery. Further, randomized clinical trials comparing the two heparin products are required to elucidate superior safety and efficacy in neurosurgical patients.

Keywords: Chemoprophylaxis, Heparin, Low-molecular-weight heparin, Meta-analysis, Neurosurgery, Prophylaxis, Unfractionated heparin

INTRODUCTION

In 1983, the pharmaceutical company (now known as) Sanofi™ created a low-molecular-weight heparin (LMWH) drug – an abbreviated formulation from the traditional unfractionated heparin (UFH). The short-chain polysaccharide, called enoxaparin (Lovenox, enoxaparin sodium; Sanofi-Aventis, Bridgewater, New Jersey, USA), promised less frequent subcutaneous dosing

without the need to monitor activated partial thromboplastin time. Beginning, in 1993, the Food and Drug Administration approved LMWH for prophylaxis of deep vein thrombosis (DVT) and prophylaxis for ischemic complications of unstable angina/non-Q wave myocardial infarction. Nevertheless, neurosurgeons remained perturbed by the new chemoprophylactic agent in a postoperative regimen. This manuscript presents the first meta-analyses of studies that directly compare prophylactic LMWH to prophylactic UFH in neurosurgery with the primary outcome measures: venous thromboembolism (VTE) and complications.

MATERIALS AND METHODS

This study was registered *à priori* in our institution's Library Protocol for Systematic Reviews. Per this protocol, all citations were collected by a trained reference analyst with a Master of Library and Information Science and a designation by the Academy of Health Information Professionals. The analyst must follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in the Enhancing the QUAlity and Transparency Of health Research resources, in which a systematic review identified relevant studies through a computer-aided search of American articles (MEDLINE from 1946 to July 17, 2017) and European articles (EMBASE 1947–July 17, 2017) [Figure 1].

The following key words provided sensitivity inclusive of all types of neurosurgical procedures with postoperative chemoprophylaxis: "neurosurgery" and any of its possible endings, "spine" and any of its possible endings, "brain neoplasm" in addition to "prophylaxis" and any of its possible endings, as well as heparin, dalteparin, enoxaparin, Lovenox, and nadroparin. This technique also ensured that citations in the spine subspecialty were not overlooked in orthopedic literature. The references within literature reviews and systematic reviews generated by the computer-aided search were also scrutinized for relevant studies. Only publications

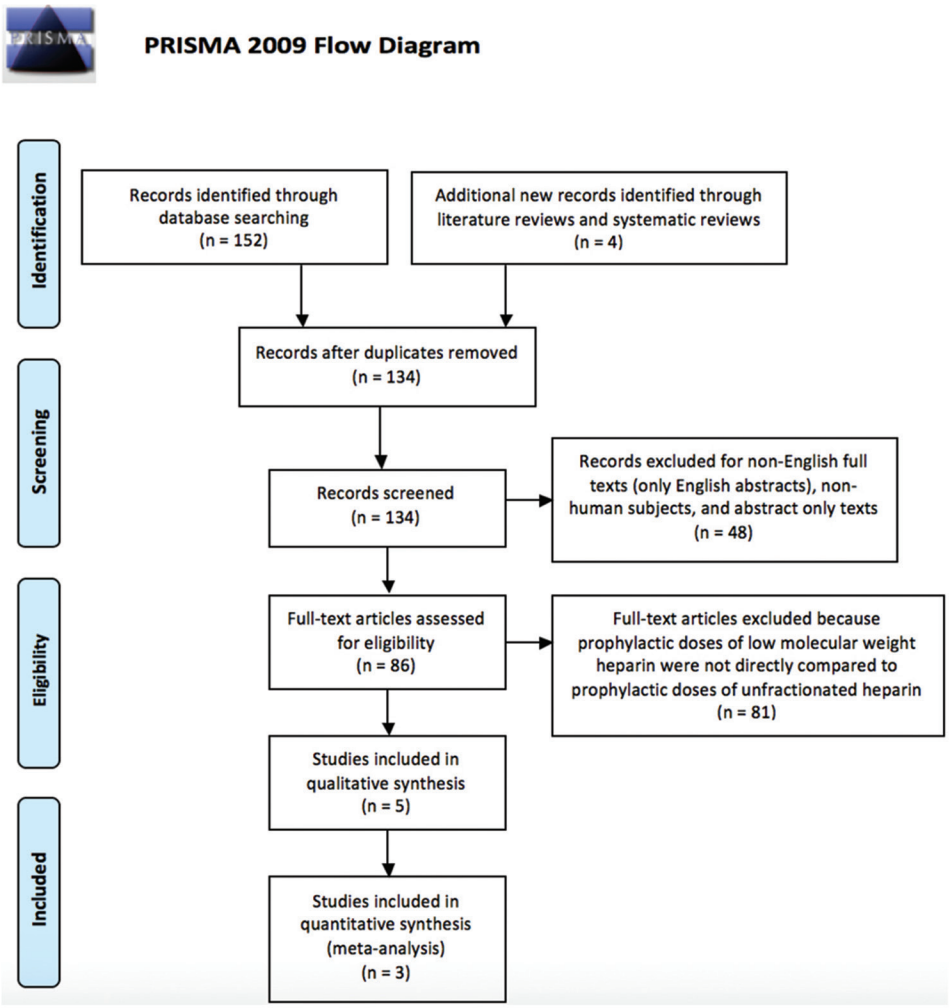

Figure 1: Flow diagram for the selection of articles in the current meta-analysis.

that directly compared the efficacy of prophylactic doses of LMWH versus UFH were included in the study. Due to the abundance of literature comparing prophylactic heparin to placebo, studies that did not complete a head-to-head comparison of the two heparin derivatives were excluded from this review. Resources on therapeutic doses of heparin products address topics outside the scope of this analysis and were, thus, excluded from the study. Manuscripts on nonhuman subjects and in languages other than English were similarly excluded from the study. The primary outcomes measure includes incidence of VTE on prophylactic doses of LMWH versus UFH. Secondary outcome measures explored suspected adverse events secondary to chemoprophylaxis. Minor complications were limited to active, noncranial bleeding diathesis, as evidenced by an unexpected decline in hemoglobin/hematocrit. Major complications were defined as other hemorrhagic complications. Data were extracted from the articles by two independent reviewers.

Three articles met the inclusion and exclusion criteria [Table 1]. Postoperative VTE chemoprophylaxis with LMWH compared to UFH was compared with summary statistics, reporting means ± standard deviations or frequencies/percentages. Binary outcomes were compared using a Chi-square test. Continuous outcomes were compared with *t*-test.[9] As detailed in the materials and methods section of a meta-analysis on prophylactic heparin in neurosurgery by Iorio and Agnelli, each group treated with prophylactic LMWH was compared with prophylactic UFH.[7] The primary outcome measures (observed minus expected number of events, O-E) and its variance (V[O-E]) were calculated for each trial. The data from the individual studies were then pooled following the fixed effects model using the Mantel and Haenszel method. Briefly, the overall odds of the outcome measure and its variance follow:

$$\text{Variance}\left(V\left[O-E\right]\right)=\frac{\left(\frac{nd}{N}\right)\left(1-\frac{n}{N}\right)(N-d)}{N-1}$$

Where, n equals the number of patients treated, d equals the number of patients with the event, and N equals the total number of patients in the trial. Two-tailed *P* values were calculated from the 95% confidence intervals (CIs) from the individual studies and the overall odds ratio (OR). The data from the three studies were illustrated on a forest plot. To emphasize larger studies, the size of the squares is proportional to variance (V[O-E]).

Since the evaluation of VTE was determined heterogeneously (i.e., 100 μCi of ^{125}I-labeled fibrinogen, phlebography, and/or duplex venous ultrasonography) in each of the three publications, the efficacy of prophylactic LMWH was ascertained from the per-protocol analysis. Safety, on the other hand, was assessed by the intention-to-treat analysis. The heterogeneity (I^2) of the studies was tested with the χ^2 statistic.

RESULTS

Of a search through 156 articles, three studies met the aforementioned inclusion and exclusion criteria for the current meta-analysis [Figure 1]. Chemoprophylaxis of UFH versus LMWH following a spine operation was found in only one study[11] and the following cranial operations in two studies[5,8] [Table 1]. A total of 429 patients were pooled to calculate the incidence of VTE and suspected chemoprophylaxis-related complications.

VTE

Within each individual study, the Chi-square comparisons of the incidences of VTE between LMWH and UFH chemoprophylaxis cohorts did not reach statistical significance [Table 1]. In total, the pooled incidence of postoperative VTE culminated in 5.6% (12/213) after LMWH chemoprophylaxis versus 3.7% (8/216) after UFH chemoprophylaxis ($P = 0.343$). According to the forest plot in Figure 2, the overall odds of VTE did not statistically significantly differ following postoperative LMWH compared to UFH chemoprophylaxis (OR = 1.42, 95% CI 0.62–3.75, $P = 0.308$). No significant heterogeneity with respect to VTE events was observed among the three articles ($I^2 = 15.1\%$, $P = 0.308$). Notably, Voth *et al*. only measured the incidence of deep VTE, not pulmonary embolism.[11] Goldhaber *et al*. noted that only one patient with a deep VTE developed a pulmonary embolism in UFH group.[5] No pulmonary emboli were observed in the study by Macdonald *et al*.[8]

Suspected chemoprophylaxis-related complications

In all three publications in the present meta-analysis, minor complications were uniformly defined as drops in postoperative hemoglobin/hematocrit requiring blood transfusions.[5,8,11] One notable exception: Macdonald *et al*. prematurely withdrew two craniotomy patients from LMWH arm of the randomized trial due to thrombocytopenia.[8] The low platelet count dropped to 98,000 in a patient with a symptomatic proximal and distal DVT; the heparin-induced antiplatelet antibodies were negative. The other patients saw a platelet nadir of 86,000 without VTE events; no antibody testing was completed because the platelet count recovered on discontinuing the study drug. The other two randomized trials in this meta-analysis did not mention heparin-induced thrombocytopenia.

Within each study, the Chi-square comparisons of the incidences of minor complications between LMWH and UFH chemoprophylaxis cohorts did not reach statistical significance [Table 1]. In total, the pooled incidence of postoperative minor complications was 4.7% (10/213) after LMWH chemoprophylaxis versus 4.6% (10/216) after UFH chemoprophylaxis ($P = 0.974$). According to the forest plot in Figure 3, the overall odds of minor complications did

Table 1: Three articles that directly compared prophylactic doses of LMWH to UFH for the prevention of VTE following neurosurgical procedures.*

Article	Study population	Primary outcome measure (per-protocol analysis)	Suspected chemoprophylaxis-related complications (intention-to-treat analysis)
**Voth *et al*., 1992[11]	Surgical operation due to a prolapsed lumbar intervertebral disc	Immediately after operation, each patient received ^{125}I-labeled fibrinogen for the daily screening of deep vein thrombosis ---if (+) ---> confirmation with phlebography, which was positive in: • 1/87 (1.1%) patients with 32 mg LMWH+0.5 mg dihydroergotamine once daily • 3/92 (3.3%) patients with 5000 u UFH+0.5 mg dihydroergotamine twice daily (*P*=0.339)	Minor complication–Postoperative blood transfusion • LMWH: 4/87 (4.6%) • UFH: 5/92 (5.4%) }*P*=0.797 Major complication–None
Goldhaber *et al*., 2002[5]	Craniotomy for suspected primary or metastatic brain neoplasm	All patients underwent one predischarge duplex venous ultrasonography examination from bilateral femoral veins to bilateral calf veins • 9/75 (12.0%) patients with 40 mg enoxaparin every morning • 5/75 (6.7%) patients with 5000 UFH twice daily (one patient developed pulmonary emboli) (*P*=0.401)	Minor complication-Postoperative blood transfusion • LMWH: 1/75 (1.3%) • UFH: 1/75 (1.3%) }*P*=1.000 Major complication-Hemorrhagic stroke • LMWH: 1/75 (1.3%) • UFH: 0/75 }*P*=0.559
Macdonald *et al*., 2003[8]	Craniotomy for brain neoplasm (including transsphenoidal surgery), intracranial aneurysm, vascular malformation, infection, spontaneous intracranial hematoma, closed head injury, or cortical resection for epilepsy.	All patients underwent lower extremity duplex ultrasound scanning of both lower limbs (entire lower limb) 7 days postoperatively • 2/51 (4.0%) patients with dalteparin 2500 μ factor Xa activity once daily • 0/49 patients with 5000 μ UFH twice daily (*P*=0.317) No pulmonary emboli were noted.	Minor complication – Postoperative blood transfusion • LMWH: 5/51 (9.8%) • UFH: 4/49 (8.2%) }*P*=0.774 Major complication–Intracranial hemorrhage • LMWH: 2/51 (3.9%), not requiring surgery }*P*=0.581 • UFH: 1/49 (2.0%), required surgery

*None of the comparisons were statistically significant. **Pulmonary embolism was not studied. LMWH: Low-molecular-weight heparin, UFH: Unfractionated heparin, VTE: Venous thromboembolism

not statistically significantly differ following postoperative LMWH compared to UFH chemoprophylaxis (OR = 1.01, 95% CI 0.41–2.50, *P* = 0.929). No significant heterogeneity with respect to minor complications was observed among the three articles (I^2 = 0.0%, *P* = 0.929).

Major complications encompassed all other salient adverse events. All four major adverse events included intracranial hemorrhages: three after prophylactic LMWH (1.4%) and one after prophylactic UFH (0.5%) (*P* = 0.992). Goldhaber *et al*. reported a 66-year-old female in LMWH cohort with intraventricular hemorrhage 7 days after a craniotomy for metastatic brain neoplasm (*n* = 1/75, 1.3%).[5] The patient was managed with an external ventricular drain (EVD) followed by a ventriculoperitoneal catheter. Although no major complications were ascertained in UFH cohort in the study by Goldhaber *et al*., no statistically significant differences were

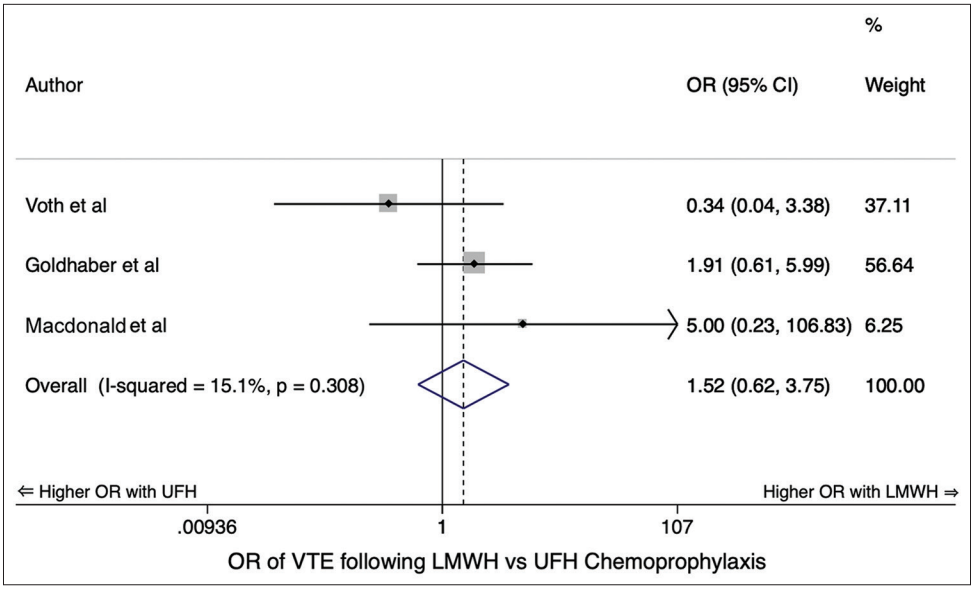

Figure 2: Forest plot of the odds of venous thromboembolism in prophylactic low-molecular-weight heparin over unfractionated heparin in neurosurgery.

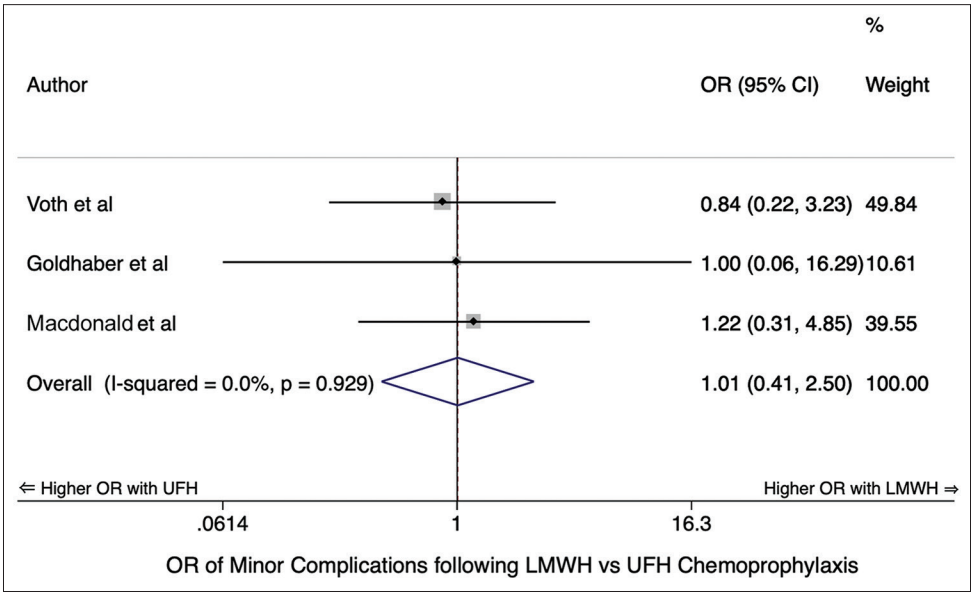

Figure 3: Forest plot of the odds of minor complications in prophylactic low-molecular-weight heparin over unfractionated heparin in neurosurgery.

calculated between UFH and LMWH prophylaxis cohorts ($P = 0.559$). In the randomized clinical trial by Macdonald *et al*., intracranial hemorrhages were observed in 2/51 patients (3.9%) in LMWH cohort versus 1/49 patients (2.0%) in UFH cohort ($P = 0.581$).[8] In the former cohort, a 74-year-old female developed nonconfluent patchy hemorrhages in the cortical tissue adjacent to the meningioma resection cavity. A 36-year-old male hemorrhaged into the tumor bed with subsequent obstructive hydrocephalus 1 day after a craniotomy for a pituitary adenoma. A ventricular drain was placed for depressed consciousness. Neither patient in LMWH required further surgery and both patients improved to moderate disability in the follow-up clinic. A 55-year-old female in the prophylactic UFH cohort by Macdonald *et al*. developed tract hemorrhage along EVD catheter after clipping of an anterior communicating artery aneurysm.[8] EVD was removed on placement of a ventriculoperitoneal shunt on postoperative day 2. The patient was severely disabled at 1-month follow-up. Voth *et al*. did not observe any major complications and were, thus, excluded in the forest plot

in Figure 4.[11] The overall odds of major complications did not statistically significantly differ following postoperative LMWH compared to UFH chemoprophylaxis (OR = 2.32, 95% CI 0.34–16.01, $P = 0.831$). No significant heterogeneity with respect to major complications was observed among the three articles ($I^2 = 0.0\%$, $P = 0.831$).[5,8,11]

DISCUSSION

In a meta-analyses that focus on studies that directly compare the two heparin injections in neurosurgery, we identified three articles, whose pooled results did not yield a statistically significant difference in the rates of VTE ($P = 0.343$), minor complications ($P = 0.974$), or major complications ($P = 0.559$) [Table 1]. Forest plot analyses similarly failed to illustrate a difference in the odds of VTE, minor complications, or major complications [Figures 2-4]. These findings corroborate a similar meta-analysis on "LMWH and UFH for the prevention of VTE in neurosurgery" by Iorio and Agnelli who explored four articles that compared either prophylactic UFH to mechanical prophylaxis only or prophylactic LMWH to mechanical prophylaxis only.[7] Unfortunately, none of the meta-analyses in the four neurosurgical studies directly compared prophylactic UFH to LMWH. Although any type of heparin prophylaxis resulted in 45% relative risk reduction of VTE events, the conclusions stated that "LMWH and UFH have been shown to be effective for prophylaxis of VTE in elective neurosurgery without excessive bleeding risk."[7] Forest plot analyses did not demonstrate a difference in bleeding complications compared to mechanical prophylaxis only. The authors did not elaborate on direct comparisons of prophylactic UFH versus LMWH for VTE events or bleeding complications.

While the efficacy of prophylactic LMWH has been well validated in literature;[1] historically speaking, concern for hemorrhagic-related complications has discouraged neurosurgeons from using prophylactic LMWH in surgical patients. Dating back to 1998, Dickinson *et al*. randomized patients undergoing craniotomy for tumor to preoperative prophylactic LMWH + sequential compression devices (SCDs) to SCDs alone.[3] The study was terminated prematurely because 5 of 46 patients in the former group sustained postoperative intracranial hemorrhages. However, these alarming outcomes have been questioned because (A) chemoprophylaxis was initiated before surgery, and (B) no direct comparisons of prophylactic LMWH to UFH were included in the study. In a systematic review and meta-analysis on VTE prophylaxis in neurosurgical patients, Hamilton *et al*. wrote "intracerebral hemorrhage was more common in those receiving heparin (prophylactic UFH or LMWH), but not statistically significantly."[6] In a prospective study of 1319 major intracranial procedures and 1504 minor intracranial procedures (e.g., shunts and biopsies) by Gerlach *et al*., prophylactic LMWH was started within 24 h of surgery.[4] The postoperative hemorrhage rate for major intracranial procedures and minor intracranial procedures was 3.2% and 0.07%, respectively, leading the author to "support the concept of postoperative pharmacological thromboembolic prophylaxis in patients undergoing intracranial surgery." To that end, the Journal of Neurooncology published a systematic review of perioperative thromboprophylaxis in patients with craniotomy for brain tumors titled, "The addition of enoxaparin starting the day after surgery, significantly reduces clinically manifest VTE, despite an increase in major

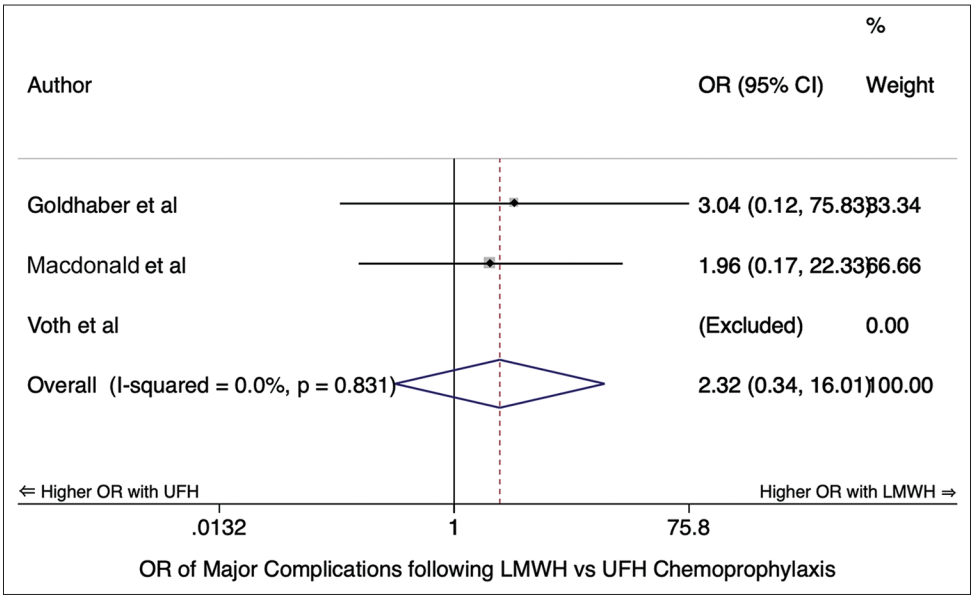

Figure 4: Forest plot of the odds of major complications in prophylactic low-molecular-weight heparin over unfractionated heparin in neurosurgery.

bleeding events."[10] With respect to prophylactic UFH in neurosurgery, Cerrato *et al*. randomly assigned 100 patients undergoing elective neurosurgery to half with UFH and half to control.[2] No statistically significant differences were elucidated in postoperative blood transfusion, decline in hemoglobin, and hematomas. These recommendations help to illustrate the efficacy of prophylactic LMWH or UFH, with an acceptable safety profile in neurosurgery.

Limitations

Although the tests for heterogeneity (I^2) in the set meta-analysis did not reach statistical significance for all three outcome measures – VTE episodes (I^2 = 15.1%, P = 0.308), minor complications (I^2 = 0.0%, P = 0.929), and major complications (I^2 = 0.0%, P = 0.831) – all three studies utilized different doses of prophylactic LMWH. However, the frequency of injections was limited to once daily, whereas the dose and frequency of prophylactic UFH remained constant across all three studies.

This meta-analysis is also subject to a selection bias because the tight inclusion and exclusion criteria led to a review of only three studies. As such, a relatively small number of 429 patients were entered into the pooled analysis, which may limit our ability to detect a statistically significant difference between LMWH and UFH. Further, randomized clinical trials comparing prophylactic LMWH versus UFH are required to elucidate superior safety and efficacy in neurosurgical patients.

CONCLUSION

This is a meta-analysis of studies that directly compare prophylactic LMWH to UFH in neurosurgery. Prophylactic doses of both LMWH and UFH equally prevented VTE after neurosurgical operations. LMWH, compared to UFH, did not statistically significantly increase the odds of minor or major complications. While these results preliminarily suggest similar profiles of both chemoprophylactic heparin injections, further, randomized clinical trials comparing prophylactic LMWH versus UFH are required to elucidate superior safety and efficacy in neurosurgical patients.

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Conflicts of interest

There are no conflicts of interest.

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