

# Thromboembolic Prophylaxis in Neurosurgical Practice: A Review

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## Abstract

**Purpose:** Literature is ambiguous on the incidence of deep venous thrombosis and pulmonary embolism by neurosurgical patients. The objective of this systematic review is to assess the incidence of thromboembolic complications associated with neurosurgical interventions, evaluate current prophylaxis methods and propose a prophylaxis strategy.

**Methods:** PubMed, Embase and Cochrane Central were searched systematically and studies involving neurosurgical procedures describing postoperative complications DVT and PE. The risk of bias was assessed using (adjusted) Cowley criteria.

**Results:** Twenty studies (14 case series, 3 comparative studies, 3 RCT's) were included, describing 8905 neurosurgical patients. Without prophylaxis the incidence of DVT was reported in 28% of neurosurgical cases (range 21-34%). Studies that provided any kind of prophylaxis, in which clinical evaluation was used to diagnose DVT, reported a 2.5% incidence of DVT (range 0 to 5%), however, when systematically assessed with ultrasound the occurrence was 6.4% (range 0-17%). Pulmonary embolism was presented in 0 to 4% of all cases. Venous thromboembolic events were more frequent in intracranial procedures compared to spinal procedures. Patients, receiving a combination of low molecular weight heparins and compression stockings, showed a 50% lower incidence of DVT than patients receiving mechanical or chemical prophylaxis alone.

**Conclusion:** Optimal antithrombotic prophylaxis regime in neurosurgical interventions lowers the incidence of DVT's from 28% to about 3 to 6%. We recommend a combination of LMWH and compression stockings for intracranial procedures. For spinal procedures this same prophylactic regimen is indicated, however it is defendable to choose single treatment with LMWH or compression stockings alone.

**Keywords:** Thromboembolic events; Neurosurgery; Complications

## Introduction

Post-operative venous thromboembolism is a serious surgical complication and most often it results in morbidity and mortality [1]. Venous thromboembolism (VTE) includes deep venous thrombosis and pulmonary embolism. Deep venous thrombosis (DVT) occurs mostly in the deep veins of the calf, thigh and pelvis. Pulmonary embolism (PE) is the most severe complication of DVT, caused by dislodgement of an embolism to the lungs. The clinical relevant symptoms associated with DVT are an erythematous, swollen and painful limb, and changes in skin color. Clinical examination in combination with Doppler ultrasound or venography is used to confirm a DVT [2].

Etiology of VTE is classically explained by Virchow's triad: stasis, endothelial injury and hypercoagulability. During and after surgery, the patient is at higher risk to develop DVT, due to immobilisation causing stasis of blood which frequently leads to local hypoxia and consequently endothelial injury [3].

In neurosurgical patients, the risk to develop a VTE is high [1,4] due to the relatively long duration of surgical interventions, long immobilization times after surgery, and possible neurological deficits which can influence mobility negative. Also neoplasms and subarachnoidal bleeding induce a state of hypercoagulability [5], further increasing the risk of a thromboembolic event. Postoperative VTE is the second most common surgical complication, the second most common cause of lengthening of hospital stay, and the third most common cause of morbidity and mortality in the USA [6].

To prevent DVT and PE, postoperative low-molecular-weight heparin (LMWH) or peri- or postoperative intermittent compression devices (ICDs) are recommended in the Chest Guidelines [1]. The Chest Guidelines are based on clinical DVT numbers only and do not take into account all performed studies. The risk of treating patients with anti-coagulation medication prior to or following neurosurgical interventions is the increased risk of bleeding. Especially

in neurosurgical procedures, the consequences of bleeding may be deleterious. In neurosurgical clinical practice there is lack of consensus on the choice of prophylaxis for VTE. An evaluation of the use of VTE prophylaxis in all seven University Neurosurgical clinics in The Netherlands shows a wide diversity in choice (intermittent compression devices, compression stockings, heparin, LMWH) and timing (pre-operative, post-operative) of prophylactic measures.

We systematically reviewed the literature of the incidence of thromboembolic events by patients undergoing spinal or intracranial neurosurgical procedures. Secondly, we have evaluated the correlation of perioperative mechanical and chemical prophylaxis with the reported incidence of DVT. Of these results we aim to distillate the best medical practice recommendations to prevent VTE in neurosurgery.

## Methods

### Types of studies

A comprehensive and systematic literature search was conducted in the databases PubMed, Cochrane Central Register of Controlled Trials and Embase up to October 3, 2012. The electronic search strategy is shown in Table 1.

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The titles and abstracts resulting of the search were reviewed by two independent reviewers (JL and JG). Eligible abstracts were selected for full text review. Both prospective and retrospective (non) randomised controlled trials and case series were included when they met with the inclusion criteria as defined in Table 2. Consensus about the selection was reached in open discussion. Citation tracking and reference screening were done with additional studies.

### Quality assessment

The quality of the included studies was assessed by two independent reviewers (JG and CVL) using an adjusted version of the Cowley criteria [7] for uncontrolled case series, comparative studies and randomized controlled studies. The score was composed on four domains: selection bias, patient selection, attrition bias and detecting bias (Table 3). After assessment consensus was sought between the reviewers. A score of seven points or more, (out of maximal 15) calculated as the sum of the score on the four domains, was defined as a low risk of bias.

### Analysis

The following data were extracted from the included studies: study design, demographic data, exclusion criteria, type of neurosurgical intervention, type of antithrombotic prophylaxis, method of DVT diagnosis and method of PE diagnosis. The primary outcome assessed was DVT and/or PE. In order to calculate the average incidence of VTE in neurosurgical patients data were pooled.

## Results

### Search and selection results

The search yielded 1537 unique references. Citation track and reference track did not result in further references. After screening titles and abstracts 75 articles were subjected to full text review (Figure 1). A total of 55 studies were excluded after full text review due to the absence of specific information about the diagnostic method for DVT (38 studies) and only reporting bleeding complications (17 studies). 20 articles were subjected to quality assessment. Due to insufficient data pooling of the data was not deemed meaningful, and only a descriptive analysis was performed.

### Study characteristics

Of the 20 included studies, three were randomised controlled trials, three were comparative studies and fourteen were case series (Table 4). Together the studies describe 8905 neurosurgical patients. The mean number of cases per study was 430 (range 16-2779) and the mean age of patients included in all studies was 52,8 years (range 45.0 – 62.4). Eight studies investigated clinical relevant DVT [8-15], twelve studies rendered subclinical DVT by pre- and post-operative Doppler ultrasound scan [16], duplex ultrasound scan [17-23], I-labelled fibrogen up taking test [24,25] or by elevated D-dimer levels [26]. Eleven studies reported patients undergoing intracranial surgery [9-11, 13,14,16,17,20-24,27], three studies reported patients subjected to spinal surgery [12,18,26] and four studies reported a mix of aforementioned patients [8,15,19,25],but one of those four did not specify results for spinal and intracranial patients [8]. Seventeen studies reported the incidence of pulmonary embolisms [8-22,25,26]. In all those studies PE was diagnosed by the follow up of clinical symptoms and confirmed by spiral CT, CT angiography or V/Q scan. Low-molecular-weight heparin (LMWH), unfractionated heparin, intermittent compression devices (ICDs) and compression stockings (CS) peri- and/or postoperatively were described as prophylaxis methods (Table 4).

### Assessment of risk of bias

Nine of fourteen case series were rated to have low risk of bias (Table 4), having a score of seven points or more out of 15 points on the risk of bias scale. All RCTs were assessed to have a low risk of bias. All three comparative studies had a high risk of selection bias.

### Overall DVT rate in neurosurgical patients

The incidence of DVT in neurosurgical patients ranged from 0% [10,18,21] to 34% [24]. If no prophylaxis for VTE was provided, DVT was reported to occur in 28% of cases (range 21 to 34%) [11,24,25,27]. Studies that provided prophylaxis of any kind in which clinical evaluation was used to diagnose DVT, reported a 2.5% incidence of DVT (range 0 to 5%).

However, if all patients that received VTE prophylaxis were systematically evaluated for DVT, regardless of the presence of clinical symptoms, a higher incidence of 6.4% (range 0 to 17.4%) was reported. In one study that did provide prophylaxis, still a DVT rate of 24% was reported [16]. We hypothesized that this incongruent value was due to the inclusion of patients suffering from subarachnoid haemorrhage (SAH). SAH is known to induce DVT/PE. Data on a retrospective analysis of 2613 patients admitted with a diagnosis of stroke, SAH, ICH or TIA were evaluated for DVT/PE [5]. Usually patients in this ward received prophylaxis, but unfortunately no prophylactic measurement was given per patient or diagnosis. The diagnosis of DVT/PE was made on clinical grounds, and not with routine screening. Even then, the relative risk of developing DVT/PE appeared to be 2.69, this being diagnosed in a population that is known to have an increased risk of DVT/PE [28,29]. Hypercoagulability was demonstrated before in rats suffering from SAH [30,31]. Therefore, this value was regarded as an outlier (Table 5).

### Pulmonary Embolism in neurosurgical patients

Seventeen of twenty studies [8-23,26] reported the incidence of PE in neurosurgical patients. A total of 117 cases of PE are reported in 8689 patients. The reported PE rate ranged from 0% [9,10,17,18,20,21,23] to 4% [11]. The reported incidence of PE after spinal surgery varied from 0% [8,18] to 3.6% [8]. After intracranial surgery a PE incidence of 0% [8,10,17,20,21,23] to 4% [8] was reported. After neurosurgical procedures without antithrombotic prophylaxes the reported incidence of PE was 4% [11]. With the usage of compression stockings only the incidence of PE was 0% in intracranial surgical patients [20] and 0.7% in patients that had undergone spinal surgery [12]. In patients receiving LMWH the reported PE rate ranged from 0% [10,17] to 4% [8].

### Spinal surgery and incidence of DVT

Seven studies reported specified DVT rates after spinal surgery, reporting a total of 1454 patients (Table 5). Length of the spinal surgical procedures was not reported. In four studies other procedures besides spinal surgery were described but only DVT rates for spinal surgery were analysed [19,15,26]. The reported DVT rate in spinal surgery ranged from 0 [18] to 21% [25]. In patients who did not receive antithrombotic prophylaxis the reported DVT rate was 21% [25]. If this study was disregarded, the clinical DVT rate was 2.7% (range 2.6 [8,15] to 2.8% [12]). The reported incidence of subclinical DVT was 4.1% (range 0 [18] to 5.7% [31]).

### Intracranial surgery and incidence of DVT

Seventeen studies reported DVT rates after intracranial surgery (Table 5). A total of 7451 patients were included. The length of the neurosurgical procedures was not reported in the studies. The reported

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|--|
| <b>General Search String</b>   |
| (Neurosurgical intervention OR Neurosurgical Procedures OR Neurological surgery) AND (Bleeding OR Thrombo-embolism OR Complication OR Clotting OR problem OR hemorrhage) AND indication OR type of patient OR sample OR Medication OR treatment  |
| <b>Pubmed Search String</b>  |
| ("Neurosurgical intervention"[All Fields] OR "Neurosurgical procedures"[MESH] OR "Neurological surgery"[All Fields] OR neurosurgical[tiab]) AND ("hemorrhage"[MeSH Terms] OR bleeding[tiab] OR thrombo-embolism OR thrombo-embolism[MESH] OR "blood coagulation"[MeSH Terms] OR Complication OR "Venous Thrombosis"[MESH]) AND (prevalence[tiab] OR incidence[tiab]) |
| <b>Embase Search String</b>  |
| Neurosurgery AND "(bleeding OR thromboembolism OR blood clotting).kw. OR neurological Complication OR Vein Thrombosis" AND "prevalence OR incidence"   |
| <b>Cochrane Search String</b>  |
| (Neurosurgical intervention OR Neurosurgical procedures OR Neurological surgery OR neurosurgical) AND (hemorrhage OR bleeding OR thrombo-embolism OR thrombo-embolism OR blood coagulation OR Complication OR Venous Thrombosis) AND (prevalence OR incidence)   |

**Table 1:** Search strategy.

|   |
|---|
| Studies included patients diagnosed with DVT or PE due to neurosurgical operations  |
| Type of interventions were clearly indicated (intracranial, spinal or peripheral)   |
| Outcome measures should be specified for DVT or PE  |
| A VTE outcome (DVT or PE) was evaluated objectively (as a result of a screening protocol or after clinical suspicion)   |
| The study was a case study (with a minimum of ten patients), cohort study or (randomized) controlled trial. Systematic reviews or meta-analysis were not included |
| Pre-operative and postoperative anti-thrombotic prophylaxis usage was clearly described as none, mechanical or chemical prophylaxes                               |

**Table 2:** Inclusion criteria.

|                                   | Case series  | Comparative study  | RCT   |
|-----------------------------------|--|--|---|
| <b>selection bias</b>             | Method of selection given properly.  | Method of assignment of patients described patients groups were matched or effect of any differences evaluated in valid statistical analysis.  | Appropriate method of randomization and patients groups matched or effect of any differences evaluated in valid statistical analysis.<br>Absence of detecting bias could be awarded with three points.<br>A point was awarded when: The amount of positively scored items was summated per study. |
| <b>well defined patient group</b> | The follow up period was given<br>The type of treatment was specified<br>The criteria for measuring outcomes were clearly defined<br>age mean and range and were given<br>male-female characteristics were described<br>preoperative diagnoses with percentages were given | The follow up period was given<br>the type of treatment was specified<br>clearly defined criteria for measuring outcomes   | The follow up period was given<br>the type of treatment was specified<br>clearly defined criteria for measuring outcomes  |
| <b>attrition bias</b>             | Valid statistical analysis<br>results relevant for subgroups were reported<br>quantification of outcomes,<br>number of patients deceased or lost to follow-up reported<br>follow-up data was compared with preoperative data   | Valid statistical analysis<br>results relevant for subgroup were reported<br>quantification of outcomes<br>number of patients deceased or lost to follow-up were reported<br>follow-up data was compared with preoperative data. | Valid statistical analysis<br>quantification of outcome<br>number of patients deceased or lost to follow-up were reported<br>follow-up data was compared with preoperative data.  |
| <b>detecting bias</b>             | Independence of investigators<br>independent radiological evaluation<br>clinical evaluation independent of surgeon.  | Independence of investigators, if retrospective,<br>patients selected without knowledge of outcomes and if prospective follow-up assessments blind to neurosurgical procedure  | Independence of investigators<br>patients blinded to neurosurgical procedure<br>assessments of clinical outcome were blind to neurosurgical procedure.  |

**Table 3:** Cowley criteria for quality assessment for case series, comparative studies and RCTs.

DVT rate in intracranial surgery ranged from 0 to 34%. In patients not receiving any antithrombotic prophylaxis the reported DVT rate ranged from 5 [11] to 34% [24]. If those studies were disregarded, studies in which clinical evaluation was used the reported DVT rate was 2.1% (range 0 [8,10] to 4.8% [10] ). The reported subclinical DVT incidence is 7.4% (range 0 to 17.4% [17]).

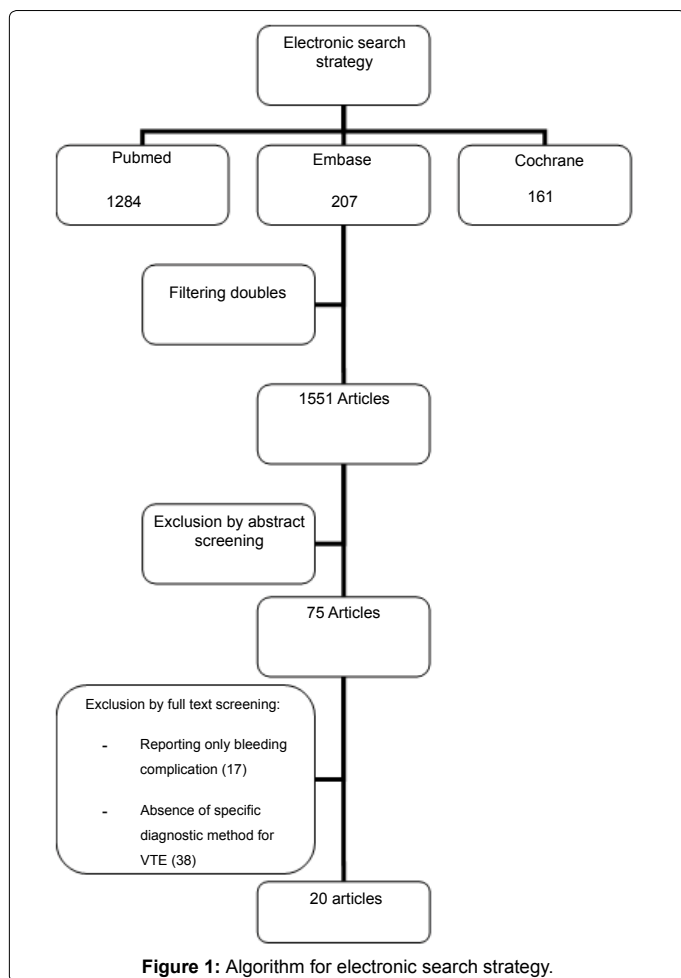
### DVT incidence related to prophylaxis strategy

With the usage of compression stockings alone the overall incidence of DVT was 4.2% (range 2.8 to 5.0%; Table 5) [12,18,20]; In patients who received intermittent compression devices (ICD) only the incidence was 13, 6% [17]. When perioperative compression stockings were combined with post-operative ICD, the incidence of DVT was reported to be 5.1% (range 0 to 13.5%) [9,10,18,19,22,23,26]. In patients receiving LMWH as prophylaxis a 4,8% DVT rate (range 4.3 to 5.4) was described [10,17].

By patients in whom the administration of post-operative LMWH was combined with compression stockings, the DVT rate was 1.5% (range 0.1 to 3%) [13-15]; in patients receiving the combination of LMWH and ICD the incidence of DVT was 10.7% (range 4 to 17.4%) [17,21]. In patients receiving a combined prophylaxis protocol of LMWH, compression stockings and intermittent compression devices were provided, a clinical DVT rate of 0% was reported [8,10]. This same DVT rate was described in patients who received heparin and ICD [21]. In patients receiving unfractionated heparin prophylaxis only the reported DVT rate was 6% [24] (Table 5)

### Best evidence synthesis

Additionally, our analysis depicted twelve studies with a low risk of bias (Table 4 and Table 5, printed in bold). Here, the reported incidence of clinical DVT was 34% in patients not receiving antithrombotic



prophylaxis [24]. In a regime with LMWH and CS, a clinical DVT rate of 1.9% (range 0.1-3%) was reported [13,15]. The reported incidence of subclinical DVT was 5.4% in patients receiving LMWH only [8] in patients with LMWH+CS a clinical DVT rate of 1.9% (range 0.1-3) was reported [13,15]. The subclinical DVT incidence was reported to be 13.6% [17] with the usage of intermittent compression devices only, 10.7% (range 4-17.4%) in patients receiving a combination of LMWH and intermittent compression devices [17,21].

Overall, the reported rate of DVT is an approximate two fold lower in studies reporting clinical DVT compared to studies using systematic screening methods like duplex ultrasonography. In patients receiving CS prophylaxis, the incidence of clinical DVT was documented to be 2.8% [12] compared to a DVT rate of 4.7% after screening with duplex ultrasonography [20]. In patients receiving ICD and CS, a clinical DVT rate of 2.2 % was present [9] compared to 5.1% (range 4-5.7%) after diagnostic DVT screening [19,23,26].

### Randomised controlled trials

Three studies were randomised controlled trials. Cerrato et al. included 100 patients who had elective intracranial surgery. 50 patients were randomised to a control group and 50 to the 5000 unit-dose of heparin group. DVTs were diagnosed by <sup>125</sup>I-labeled fibrinogen test. The incidence of DVT was statistically significant reduced from 34% in the control group to 6% in the unfractionated heparin group [24]. Dickinson and colleagues randomized 68 patients with neoplasms, had craniotomy or stereotactic biopsy and received prophylaxis with ICD,

enoxoparin or ICD+enoxoparin. Patients were screened for DVT by duplex US during the first month after surgery. The reported incidence of DVT was 13.6% in the ICD group, 4.3% in enoxoparin treated patients and 17.4% in the combined group. The differences were not statistical significant. This study was prematurely terminated because of the elevated risk of intracranial haemorrhage in the enoxoparin group [17]. MacDonald et al. compared ICD and deltaparin (2500 units od for 7 days) with ICD and heparin (5000U bid for 7 days) in 100 patients undergoing elective craniotomy. DVTs were diagnosed by screening with duplex one month after surgery. Comparable outcome was found: by the deltaparin group 2 patients developed DVT compared to none in the heparin group [21].

### Discussion

The perioperative prophylaxis strategy to prevent VTE in neurosurgery is variable between centres and much debated. We here provide a concise overview of the available evidence prophylaxis and formulate recommendations. Available studies were assessed on their risk of selection bias, attrition bias and detecting bias. A subclinical DVT rate, ranging from 25% to 34% after neurosurgery without providing antithrombotic prophylaxis, was found. This value is comparable to the value described by the CHEST guidelines and the study of Hamilton [4] suggesting a subclinical DVT rate of 15-40% [1]. Optimal antithrombotic prophylaxis decreases the DVT rate from 28 to 1.5-6%.

On average, studies, in which all patients were systematically evaluated for DVT a twofold higher rate of VTE was reported (6.4%) were compared to studies in which patients were clinically evaluated (2.5%), suggesting underreporting of VTE events in those studies. There is conflicting data about the clinical role of subclinical DVT on the long term and the appropriate treatment of those patients [32-36]. Nevertheless, we considered the percentages obtained for subclinical DVT relevant, because subclinical DVT is associated with the formation of PE [37]. Therefore, prevention and detection of subclinical DVT is essential to prevent the serious complication of PE [37]. On average, the DVT rate is higher after intracranial procedures (7.4%) compared to 4.1% after spinal procedures. A prophylaxis strategy employing a combination of LMWH and compression stockings resulted in a 1.5% DVT rate, which is lower than other prophylaxis strategies, both in spinal and intracranial surgical patients. (Table 5) Only the combination of CS, ICD and OAC resulted in an even lower DVT rate (0%) in one small study [10]. The overall risk on DVT in spinal procedures is lower than in intracranial procedures. Therefore, we recommend LMWH combined with CS for intracranial procedures and LMWH or CS for spinal procedures.

In the three performed small RCTs, DVT rates were systematically evaluated [24,17,21]. Here, LWMH combined with ICD resulted in a low DVT rate. However, Dickinson and colleagues reported a high postoperative bleeding risk in the enoxoparin+ICD group [17]. Other studies using LMWH for antithrombotic prophylaxis did not report an increased bleeding risk. A bleeding risk is of major concern in neurosurgical procedures, and possibly results in suboptimal VTE protection.

The Chest Guidelines are less stringent than the measures we would propose: only for patients with a high thrombosis risk a combination of mechanical and pharmacological prophylaxis is recommended. Patients who have had spinal surgery, early mobilization are recommended, combined with mechanical prophylaxis for patients at high risk for DVT [1]. However these proposals are mostly based on studies focusing on clinical DVT. Therefore, the DVT risks are



| A. Risk of bias assessment of case series         |                 |                             |                            |                           |                           |                           |
|---|-----------------|-----------------------------|----------------------------|---------------------------|---------------------------|---------------------------|
| Study   | Number of cases | Score on risk of bias scale | Well-defined patient group | Absence of selection bias | Absence of attrition bias | absence of detecting bias |
| Yoshiiwa [38]                                     | 88              | 11/15                       | ■■■■■□                     | ■                         | ■■■■■                     | □□                        |
| Flinn [12]  | 2643            | 10/15                       | ■■■■□□                     | ■                         | ■■■■■                     | ■□                        |
| Ting [34]   | 100             | 10/15                       | ■■■■□□                     | □                         | ■■■■□                     | ■■                        |
| Auguste [2]                                       | 180             | 9/15                        | ■■■■□□                     | ■                         | ■■■■□                     | □□                        |
| Epstein [10]                                      | 139             | 9/15                        | ■■■■□□                     | □                         | ■■■■□                     | □□                        |
| Kleindienst [18]                                  | 809             | 9/15                        | ■■■■□□                     | ■                         | ■■■■□                     | □□                        |
| Ray [27]  | 125             | 9/15                        | ■■■■□□                     | ■                         | ■■■□□                     | ■□                        |
| Kumar [20]  | 106             | 8/15                        | ■■■■□□                     | ■                         | ■■■□□                     | ■□                        |
| Smith [30]  | 2779            | 7/15                        | ■■■■□□                     | ■                         | ■■■□□                     | □□                        |
| Tauro [33]  | 16              | 6/15                        | ■■■■□□                     | □                         | ■■■□□                     | □□                        |
| Valladares [35]                                   | 100             | 6/15                        | ■■■■□□                     | □                         | ■■■□□                     | □□                        |
| Constantini [6]                                   | 633             | 5/15                        | ■■□□□□                     | □                         | ■■■□□                     | □□                        |
| Kleindienst [19]                                  | 390             | 5/15                        | ■■□□□□                     | ■                         | ■■■□□                     | □□                        |
| Taniguchi [32]                                    | 37              | 5/15                        | ■■■□□□                     | □                         | ■■■□□                     | □□                        |
| A. Risk of bias assessment of comparative studies |                 |                             |                            |                           |                           |                           |
| Study   | Number of cases | Score on risk of bias scale | Well-defined patient group | Absence of selection bias | Absence of attrition bias | absence of detecting bias |
| Ferree [11]                                       | 185             | 5/12                        | ■□□                        | □□                        | ■■■□□                     | ■■                        |
| Aloweidi [1]                                      | 223             | 4/12                        | ■□□                        | □□                        | ■■■□□                     | □□                        |
| Cage [4]  | 86              | 4/12                        | □□□                        | □□                        | ■■■□□                     | ■■                        |
| A. Risk of bias assessment of RCTs                |                 |                             |                            |                           |                           |                           |
| Study   | Number of cases | Score on risk of bias scale | Well-defined patient group | Absence of selection bias | Absence of attrition bias | absence of detecting bias |
| MacDonald [24]                                    | 100             | 11/12                       | ■■■                        | ■■                        | ■■■■                      | ■■□                       |
| Cerrato [5]                                       | 100             | 8/12                        | ■■■                        | ■□                        | ■■■□                      | ■□□                       |
| Dickinson [8]                                     | 66              | 7/12                        | ■■■                        | □□                        | ■■■□                      | ■□□                       |

Table 4: Risk of bias assessment of (A) case series, (B) comparative studies and (C) RCTs. The filled boxes represent the number of items of the Cowley criteria which were fulfilled in mentioned study.

considered lower in comparison to the subclinical DVT risks we consider relevant.

### Risk factors for developing deep venous thrombosis

In intracranial surgery patients the risk to develop DVT is more increased compared to patients whom had spinal surgery. This is probably due to a significant higher DVT rate reported by patients with an intracranial neoplasm (glioma and meningioma) [11]. Also, in four studies a positive correlation was found between DVT rate and paralysis [24, 11, 20, 22]. In literature, both meningioma and paralysis were described as known risk factors for developing DVT [4]. Also length of surgery could increase DVT risk, however slightly higher incidence of DVT were reported in a small group with longer operation times, this did not reach statistical significance in one prospective study [8]. So there are numerous confounding variables that could explain the lower DVT risk by patients undergoing spinal surgery.

### Limitations and external validity

Limitations of this review are the heterogeneity with respect to diagnostic methods for VTE events and variable antithrombotic prophylaxes. Some studies (n=9) excluded patients with coagulation abnormalities [9,10,13,14,17, 21,23,24, 27]. This makes it inadmissible to compare the results between the studies because of potential selection bias. Therefore, if questions about the value of antithrombotic therapy in neurosurgical patients are to be asked again, the answers will not come from analyses of data from already completed studies with different clinical populations and different treatment protocols because these data are not applicable to the current clinic.

### Clinical implementation

A randomized controlled trial investigating different antithrombotic

prophylaxis strategies is feasible at this point. Not only patient-bound risk factors, but also factors related to the applied surgical intervention and perioperative care should be taken into account. Of particular interest are the duration of surgical interventions, immobilization times after surgery (with or without neurological deficits), and the presence of neoplasm or subarachnoid bleeding. From this we could personalise the perioperative prophylaxis regime in neurosurgical care. Occurrence of intracranial bleeds after using LMWH as prophylaxis is an issue that needs further studies. In 2000 Iorio et al. reviewed literature and found that the rates of intracranial bleeding were 2.1% in the patients receiving postoperative LMWH and 1.1% in those whom had mechanical or no prophylaxis [37]. Also, timing of the preventive measurements is an issue, as the long immobilisation and hypercoagulability during surgery suggests that preventive measures (eg. ICS) should be started peri-operative rather than post-operative.

### Conclusion

Intracranial surgical patients are more at risk to develop a DVT compared to spinal surgery patients, but there are numerous confounding variables that would prevent us from drawing the conclusion that spinal surgery is truly associated with a lower VTE incidence. The use of antithrombotic prophylaxis in neurosurgical interventions lowers the DVT incidence from 30 % to about 1.5 to 6%. We found a twofold higher DVT rate in patients systematically screened for DVT. Subclinical DVT is associated with the formation of a pulmonary embolism. Therefore, a systematic evaluation of DVT in all post-operative patients is recommended.

A prospective trial with appropriate sample size and detailed information on both patient-bound factors (malignancy, subarachnoid

| Study [Ref]            | Antithrombotic prophylaxes    | Type of surgery     | N           | Study design       | Risk of bias score | Method of assessment DVT | Outcome DVT   |
|------------------------|-------------------------------|---------------------|-------------|--------------------|--------------------|--------------------------|---------------|
| <b>Cerrato[5]</b>      | <b>No prophylaxes</b>         | <b>intracranial</b> | <b>50</b>   | <b>comparative</b> | <b>8/12</b>        | <b>FUT</b>               | <b>34%</b>    |
| Valladares[35]         | no prophylaxes                | spine               | 50          | case series        | 6/15               | FUT                      | 20.7%         |
| Valladares[35]         | No prophylaxes                | intracranial        | 50          | case series        | 6/15               | FUT                      | 32.3%         |
| Tauro[33]              | No prophylaxes                | intracranial        | 16          | case series        | 6/15               | DUS                      | 25%           |
| Constantini[6]         | No prophylaxes                | intracranial        | 633         | case series        | 5/15               | Clinical                 | 5%            |
| <b>Epstein[10]</b>     | <b>CS</b>                     | <b>spine</b>        | <b>139</b>  | <b>case series</b> | <b>9/15</b>        | <b>Clinical</b>          | <b>2.8%</b>   |
| <b>Kumar[20]</b>       | <b>CS</b>                     | <b>intracranial</b> | <b>106</b>  | <b>case series</b> | <b>8/15</b>        | <b>DUS</b>               | <b>4.7%</b>   |
| Ferree[11]             | CS                            | spine               | 74          | comparative        | 5/12               | DUS                      | 5%            |
| <b>Dickinson[8]</b>    | <b>ICD</b>                    | <b>intracranial</b> | <b>22</b>   | <b>RCT</b>         | <b>7/12</b>        | <b>DUS</b>               | <b>13.60%</b> |
| <b>Yoshiiwa[38]</b>    | <b>ICD + CS</b>               | <b>spine</b>        | <b>88</b>   | <b>case series</b> | <b>11/15</b>       | <b>D-dimer+ CTv</b>      | <b>5.7%</b>   |
| <b>Flinn[12]</b>       | <b>ICD + CS</b>               | <b>spine</b>        | <b>454</b>  | <b>case series</b> | <b>10/15</b>       | <b>DUS</b>               | <b>1.50%</b>  |
| <b>Flinn[12]</b>       | <b>ICD + CS</b>               | <b>intracranial</b> | <b>1439</b> | <b>case series</b> | <b>10/15</b>       | <b>DUS</b>               | <b>7.70%</b>  |
| <b>Ting[34]</b>        | <b>ICD + CS</b>               | <b>intracranial</b> | <b>100</b>  | <b>case series</b> | <b>10/15</b>       | <b>DUS</b>               | <b>4%</b>     |
| <b>Auguste[2]</b>      | <b>ICD + CS</b>               | <b>intracranial</b> | <b>180</b>  | <b>case series</b> | <b>9/15</b>        | <b>Clinical</b>          | <b>2.2%</b>   |
| Taniguchi[32]          | ICD + CS                      | intracranial        | 37          | case series        | 5/15               | DUS                      | 13.5%         |
| Ferree[11]             | ICD + CS                      | spine               | 111         | comparative        | 5/12               | DUS                      | 0%            |
| Cage[4]                | ICD + CS                      | intracranial        | 86          | comparative        | 4/12               | Clinical                 | 4.8%          |
| <b>Cerrato[5]</b>      | <b>Unfractionated heparin</b> | <b>intracranial</b> | <b>50</b>   | <b>comparative</b> | <b>8/12</b>        | <b>FUT</b>               | <b>6%</b>     |
| <b>Dickinson[8]</b>    | <b>LMWH</b>                   | <b>intracranial</b> | <b>23</b>   | <b>RCT</b>         | <b>7/12</b>        | <b>DUS</b>               | <b>4.3%</b>   |
| Aloweidi[1]            | LMWH                          | spinal              | 110         | comparative        | 4/12               | Clinical                 | 5.4%          |
| <b>Kleindienst[18]</b> | <b>LMWH + CS</b>              | <b>intracranial</b> | <b>809</b>  | <b>case series</b> | <b>9/15</b>        | <b>Clinical</b>          | <b>0.1%</b>   |
| <b>Smith[30]</b>       | <b>LMWH + CS</b>              | <b>intracranial</b> | <b>2409</b> | <b>case series</b> | <b>7/15</b>        | <b>Clinical</b>          | <b>3%</b>     |
| <b>Smith[30]</b>       | <b>LMWH + CS</b>              | <b>spinal</b>       | <b>423</b>  | <b>case series</b> | <b>7/15</b>        | <b>Clinical</b>          | <b>2.6%</b>   |
| Kleindienst[19]        | LMWH + CS                     | intracranial        | 390         | case series        | 5/15               | Clinical                 | 0.4%          |
| <b>MacDonald[24]</b>   | <b>LMWH + ICD</b>             | <b>intracranial</b> | <b>49</b>   | <b>RCT</b>         | <b>11/12</b>       | <b>DUS</b>               | <b>4%</b>     |
| <b>Dickinson[8]</b>    | <b>LMWH + ICD</b>             | <b>intracranial</b> | <b>23</b>   | <b>RCT</b>         | <b>7/12</b>        | <b>DUS</b>               | <b>17.4%</b>  |
| <b>Ray[27]</b>         | <b>LMWH + ICD + CS</b>        | <b>intracranial</b> | <b>125</b>  | <b>case series</b> | <b>9/15</b>        | <b>DUS</b>               | <b>24%</b>    |
| Cage[4]                | LMWH + ICD + CS               | intracranial        | 24          | comparative        | 4/12               | Clinical                 | 0%            |
| Aloweidi[1]            | (LMWH* +) ICD + CS            | intracranial        | 113         | comparative        | 4/12               | Clinical                 | 2.9%          |
| <b>MacDonald[24]</b>   | <b>Heparin + ICD</b>          | <b>intracranial</b> | <b>51</b>   | <b>RCT</b>         | <b>11/12</b>       | <b>DUS</b>               | <b>0%</b>     |

**Table 5: Prophylaxes for DVT categorized by method of antithrombotic prophylaxis method.** In bold typesetting the studies with highest quality, based on risk of bias. \*single dose at induction anaesthesia. N= Number of cases; RCT=Randomized controlled trial; CS=compression stockings; ICD=intermittent compression device; LMWH=Low Molecular weight heparin; FUT=125I-labelled fibrinogen up taking test; DUS=Duplex ultrasonography; CTv=CT venography

haemorrhage, pre-existing coagulopathies) and treatment-associated risk factors (type of surgery, length of surgery, post-operative immobilisation) is needed to assess optimal antithrombotic prophylaxis for neurosurgical patients. During this trial various agents and prophylaxis methods should be assessed to derive valid treatment recommendations. Special attention for bleeding complications is warranted in these studies. Awaiting such a trial, we recommend a VTE preventive strategy with LMWH combined with CS for intracranial procedures and LMWH or compression stockings for spinal procedures. For long surgical procedures and high-risk patients perioperative CS should be used.

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