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European guidelines on perioperative venous thromboembolism prophylaxis

Neurosurgery

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Although there are numerous publications addressing venous thromboembolism and its prevention in neurosurgery, there are relatively few high-quality studies to guide decisions regarding thromboprophylaxis. In patients undergoing craniotomy, we recommend that if intermittent pneumatic compression (IPC) is used, it should be applied before the surgical procedure or on admission (Grade 1C). In craniotomy patients at particularly high risk for venous thromboembolism, we suggest considering the initiation of mechanical thromboprophylaxis with IPC preoperatively with addition of low molecular weight heparin (LMWH) postoperatively when the risk of bleeding is presumed to be decreased (Grade 2C). In patients with non-traumatic intracranial haemorrhage, we suggest thromboprophylaxis with IPC (Grade 2C). For patients who have had non-traumatic intracranial haemorrhage, we suggest giving consideration to commencement of LMWH or low-dose unfractionated heparin when the risk of bleeding is presumed to be low (Grade 2C). We suggest continuing thromboprophylaxis until full mobilisation of the patient (Grade 2C). For patients undergoing spinal surgery with no additional risk factors, we suggest no active thromboprophylaxis intervention apart from early mobilisation (Grade 2C). For patients undergoing spinal surgery with additional risk factors, we recommend starting mechanical thromboprophylaxis with IPC (Grade 1C), and we suggest the addition of LMWH postoperatively when the risk of bleeding is presumed to be decreased (Grade 2C).

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Introduction

Among neurosurgical patients, the risk of venous thromboembolism (VTE) varies widely depending on patient mix, the procedure, method of diagnosis and use of various methods of thromboprophylaxis. Although there are numerous publications addressing VTE and its prevention in neurosurgery, there are relatively few high-quality studies to guide decisions regarding thromboprophylaxis. With this limitation, we discuss the incidence, risk factors and prevention of VTE in patients undergoing craniotomy and those who have had non-traumatic intracranial haemorrhage or spinal surgery. We provide recommendations for the prevention of VTE in these patient groups. These recommendations are drawn from and expand upon other recent thromboprophylaxis guidelines such as those produced by the American

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College of Chest Physicians (ACCP) and by the National Institute for Health and Care Excellence.[1]

Craniotomy

Patients who undergo craniotomy are at increased risk of VTE for a number of reasons, including the presence of malignancy in many patients, long duration of procedures, reduced mobility or paresis and direct release of pro-coagulants such as tissue factor from brain tissue.[2,3] VTE was found in 1.7% of neurosurgery patients from the 2006 to 2011 American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP).[4] Another study that included 10 477 craniotomy patients in the 2011 to 2012 ACS-NSQIP diagnosed VTE in 3.2%.[5] A retrospective study, in which a heterogeneous group of 2593 neurosurgery patients underwent twice weekly Doppler ultrasound screening for asymptomatic deep venous thrombosis (DVT), found DVT in 9.7% and proximal DVT in 7.4% despite routine thromboprophylaxis with intermittent pneumatic compression (IPC) and low-dose heparin (LDH).[6] In a retrospective analysis of the ACS-NSQIP database from 2006 to 2010, the rate of VTE in a neurosurgical cohort was 3.5%, including 1.4% pulmonary embolism and 2.6% DVT.[7] The authors highlighted the following preoperative, intraoperative and postoperative risk factors: transfer from acute care hospital [odds ratio (OR) 3.31], preoperative sepsis (OR 3.06), emergency case (OR 2.99), dependent functional status (OR 2.87), age at least 60 years (OR 1.56), neoplasm (OR 1.49), surgery for tumour (OR 1.42), surgery duration at least 4 h (OR 1.67) and postoperative complications [pneumonia (OR 6.38), postoperative mechanical ventilation ≥48 h (OR 6.04), urinary tract infection (OR 3.82) and reoperation (OR 2.68)].

Risk factors for VTE in craniotomy patients include surgery for brain tumour, leg weakness, duration of surgery and absence of thromboprophylaxis (Table 1).[7–10] Several recent studies demonstrate that patients undergoing surgery for brain tumour have a particularly high risk of VTE.[9–13] For example, in a single-centre review of 1148 adult patients who underwent surgical resection of brain tumour, the incidence of DVT was 14 and 3% had a pulmonary embolism.[10] Only approximately 10% of patients received delayed anti-coagulant thromboprophylaxis. No multi-component risk assessment model in patients receiving no thromboprophylaxis has been validated to guide the use of thromboprophylaxis in neurosurgery patients.

Table 1 Risks of venous thromboembolism and risk factors for postoperative venous thromboembolism in neurosurgery

Positive risk factors	Inconsistent or uncertain risk factors
Neoplasm – primary or metastatic	Previous VTE
Perioperative immobility/motor weakness	Obesity
Age	Steroid use
Duration of surgery	Mobility
Lack of thromboprophylaxis	Infection

VTE, venous thromboembolism.

Prevention of venous thromboembolism in craniotomy

Several meta-analyses and the 2012 American College of Chest Physicians clinical practice guidelines have assessed randomised trials of various methods of thromboprophylaxis in patients undergoing neurosurgical procedures.[14–16] Many of the included trials are small, unblinded, more than 15 years old, with omitted use of routine mechanical thromboprophylaxis and with a general focus on surrogate outcomes for clinically important VTE (e.g. asymptomatic DVT).[15] In fact, our literature search identified only a single randomised trial of thromboprophylaxis in neurosurgery over the past 10 years.

In a recent retrospective analysis involving 207 neurosurgical patients, the additional use of intraoperative and postoperative IPC, graduated compression stockings (GCS) and low molecular weight heparin (LMWH) given 24 to 48 h postoperatively decreased the incidence of DVT from 9.9 to 3.5%.[17] The use of IPC also reduced the incidence of pulmonary embolism from 2.5 to 1.2%. A single randomised trial in neurosurgical patients showed that a portable calf compression device reduced asymptomatic calf DVT to a greater extent than usual thromboprophylaxis, but only 30% of patients used it for at least 50% of the time, and 23% of patients discontinued the device pre-maturely.[18] The compliance with appropriate use of mechanical methods of thromboprophylaxis has repeatedly been shown to be low and patients often poorly tolerate the devices.[19]

Anti-coagulant thromboprophylaxis, with LMWH or LDH, has repeatedly been shown to be effective in neurosurgery patients, and the addition of LMWH to mechanical thromboprophylaxis has been shown to be more efficacious than mechanical methods alone.[14–16] In a recent meta-analysis comparing LMWH or LDH with a no-heparin control group (with or without mechanical thromboprophylaxis), the risk reduction for VTE was 0.42 (95% CI, 0.24 to 0.75) favouring LMWH/LDH when no mechanical thromboprophylaxis was used and 0.64 (95% CI, 0.48 to 0.85) when mechanical thromboprophylaxis was used.[15] In summary, systematic reviews show that mechanical or anti-coagulant thromboprophylaxis (with LMWH or LDH) reduced VTE compared with no thromboprophylaxis.[14–16]

Intracranial bleeding occurs in approximately 1 to 1.5% of craniotomy patients who do not receive anti-coagulant thromboprophylaxis.[15,20] The use of anti-coagulant thromboprophylaxis may be associated with a small increase in the risk of intracranial haemorrhage (ICH) in craniotomy patients compared with mechanical thromboprophylaxis.[14,15] However, a prospective study of 746

craniotomy patients who were given routine postoperative LMWH thromboprophylaxis starting on the first postoperative day reported intracranial bleeding in only 1%.[21] Among 213 patients who were cared for in a neurosurgical ICU and received LDH, there were no intracranial bleeding episodes and no difference in any type of bleeding compared with 309 patients who only received VTE prophylaxis in the form of IPC.[20] A meta-analysis of randomised trials directly comparing LMWH and mechanical thromboprophylaxis found no statistically significant difference in the rate of ICH.[14] Among the six randomised trials that compared LDH or LMWH with no thromboprophylaxis or with mechanical thromboprophylaxis in neurosurgical patients, the rates of ICH were low in both groups, and with randomised trials of anti-coagulant thromboprophylaxis demonstrating no increased risk of intracranial bleeding.[22,23] The timing of initiation of anti-coagulant thromboprophylaxis appears to influence postoperative bleeding rates.[24] If anti-coagulant thromboprophylaxis is started prior to or soon after the craniotomy, bleeding rates appear to be higher than with delayed postoperative initiation, although we are unaware of any trials that have directly compared different starting times. Based on the existing literature, we assess the incidence of clinically important bleeding, including intracranial bleeding, to be very low and unlikely to be increased when anti-coagulant thromboprophylaxis is started in craniotomy patients beyond the first postoperative day and with evidence of sufficient haemostasis. Therefore, for patients who have undergone craniotomy, a decision about thromboprophylaxis should be made on admission or preoperatively based on the patient's bleeding and thrombosis risks. It is recommended to use mechanical thromboprophylaxis with IPC and/or GCS started before surgery in elective cases or soon after admission in emergency cases. For patients with a moderately increased risk of VTE (e.g. craniotomy for malignancy, a prolonged procedure or reduced mobility) and in whom there is evidence that primary intracranial haemostasis has taken place (usually based on postoperative head computed tomography scan), we recommend that anti-coagulant thromboprophylaxis with LMWH or LDH should be added to the mechanical method of prophylaxis.

Non-traumatic intracranial haemorrhage

It is clear that patients who have had intracranial bleeding are at high enough risk of VTE to warrant thromboprophylaxis.[25,26] Among 695 patients with subarachnoid haemorrhage (SAH) or spontaneous intracranial haemorrhage, symptomatic VTE was detected during admission in 6.7 and 2.9%, respectively.[27] Among almost 16 000 SAH patients who were managed with either clipping or endovascular coiling, 4.4% were found to have VTE (DVT 3.5%, pulmonary embolism 1.2%).[26] Two studies using routine Doppler ultrasound screening approximately every 5 days found asymptomatic DVT in 21% of 198 patients and 24% of 125 patients with SAH despite routine thromboprophylaxis.[28] Among 196 patients who survived more than 72 h after SAH who were given thromboprophylaxis with IPC and LDH and had Doppler ultrasound screening on day 4 and weekly thereafter, DVT was detected in 10%.[25]

The risk factors for VTE appear to be similar to those in other patients undergoing craniotomy (except that active cancer is much less common in the ICH patients) and include increasing age, immobility or paresis, length of hospital stay and reduced or delayed use of anti-coagulant thromboprophylaxis.[26,28] Although there are very few studies of the prevention of VTE specifically in patients with ICH, the approach to thromboprophylaxis is similar to other patients undergoing craniotomy whereas concern about recurrent bleeding generally leads to delayed initiation of anti-coagulant thromboprophylaxis.[19,25,26] We were able to identify only two randomised controlled trials of thromboprophylaxis in patients with ICH, both of which assessed mechanical options.[19,29] The first randomised 151 traumatic or spontaneous ICH patients to GCS alone or combined with IPC.[19] Ultrasound screening detected asymptomatic DVT in 16% of the former patients and in 5% of the combined mechanical thromboprophylaxis group ($P = 0.03$). In the multi-centre CLOTS 3 trial, 376 of the immobile patients with a haemorrhagic stroke were randomised to thigh-length IPC or no IPC and had a screening ultrasound on days 7 to 10.[29] Proximal DVT was detected in 17% of the patients who did not have IPC and 7% in those who did (OR 0.36; 95% CI, 0.17 to 0.75).

Although there is a generally conservative approach to using anti-coagulant thromboprophylaxis in patients with ICH, there is no strong evidence that re-bleeding is increased with this approach. In a retrospective study of 247 patients with subdural haematoma, the use of enoxaparin 40 mg once daily beginning on postoperative day 1 was not an independent predictor of recurrent chronic subdural haematoma (SDH).[30] Finally, a retrospective study of low-dose intravenous heparin versus low-dose subcutaneous heparin in 86 patients with SAH did not detect new bleeding in any patient.[31]

For patients with ICH and reduced mobility, mechanical thromboprophylaxis with IPC is recommended as soon as possible after admission. The addition of (or replacement with) anti-coagulant thromboprophylaxis at least a few days later is reasonable for patients with additional risk factors, although there is no prospectively derived evidence to guide the decisions about when this should be initiated. Among patients with SAH secondary to ruptured intra-cranial aneurysm, anti-coagulant thromboprophylaxis should be withheld until the aneurysm has been clipped or coiled. Clinical practice guidelines by the American Heart Association/American Stroke

Association, Neurocritical Care Society and European Stroke Organisation also recommend the routine use of IPC and/or GCS from admission.[32–35] Delayed initiation of LMWH or LDH in immobile patients after an ICH or after an aneurysm has been secured is also recommended.[32,33,35] Clearly, there is a need for methodologically rigorous trials to address the relative effectiveness and safety of various thromboprophylaxis options, the optimal time to initiate thromboprophylaxis and the optimal duration of therapy.

Spinal surgery

Patients who undergo spinal surgery are generally at low risk for VTE compared with craniotomy patients.[4] Among 27 730 patients undergoing spinal surgery and included in the 2005 to 2011 ACS-NSQIP database, DVT was reported in 0.7% and pulmonary embolism in only 0.4% at 30 days postoperatively.[36] Similarly, among 430 000 patients who underwent spinal fusion, in-hospital VTE was identified in only 0.4%.[37] Symptomatic DVT was diagnosed within 30 days of spine surgery in 1.1% of 1346 patients (0.6% after elective surgery and 4.2% after emergency surgery).[38] Almost half of all thromboembolic events in spinal surgery patients occur after hospital discharge.[39] With routine ultrasound screening of 459 patients 7 to 10 days after surgery for degenerative spine disease and who received mechanical thromboprophylaxis only, there were no symptomatic DVTs, one symptomatic pulmonary embolism and fewer than 1% of patients had proximal DVT.[40]

Risk factors for VTE in spinal surgery patients appear to be cancer, limited preoperative or postoperative mobility, a complex or multi-level and prolonged procedure and advanced age.[37,41–43] Additional potential risk factors, inconsistently identified, include previous VTE, obesity, renal dysfunction, vertebral trauma, thoracolumbar versus cervical surgery, open versus minimally invasive techniques and low use of thromboprophylaxis.[37,38,40,43] Predictive models for VTE after spinal surgery have been proposed but not validated.[44,45]

Our literature search identified only five published randomised trials of thromboprophylaxis in spinal surgery (none since 1997). All of the studies were small, had serious methodological limitations and used various methods to screen patients for asymptomatic DVT. A systematic review of thromboprophylaxis studies in 4383 elective spinal surgery patients determined the prevalence of DVT in relation to methods of prophylaxis as follows: no thromboprophylaxis 5.8%, mechanical thromboprophylaxis 1.8% and mechanical thromboprophylaxis and LMWH less than 0.01%.[42] Another systematic review of 25 thromboprophylaxis trials (of variable quality) in spinal surgery reported pooled DVT rates as follows: no thromboprophylaxis 2.7%, GCS 2.7%, IPC 4.6%, GCS and IPC 1.3% and anti-coagulant thromboprophylaxis 0.6%.[46] A retrospective study among 1919 spinal surgery patients who were given LMWH reported symptomatic DVT in only 0.05%.[41] In a before-and-after study of the implementation of routine thromboprophylaxis, Cox *et al.*[47] detected DVT in 2.7% of 941 spine surgery patients who received inconsistent thromboprophylaxis and in 1.0% of another cohort of 992 patients who received consistent thromboprophylaxis with IPC and LDH.

The issue of perispinal haematoma after anti-coagulant thromboprophylaxis remains controversial in the face of very limited evidence.[44,48] However, the reported rates of epidural haematoma are very low (≈0.2%) and do not appear to be related to the modality of thromboprophylaxis.[41,42,47,49,50] Currently, many elective spinal procedures are performed as day surgery or a single overnight stay, and the patients are mobilised shortly after surgery. There are no clinical trials of thromboprophylaxis in this subset of spinal surgery patients. For these patients, no thromboprophylaxis measures are recommended other than early mobilisation. The North American Spine Society recommends mechanical thromboprophylaxis alone with consideration of anti-coagulant thromboprophylaxis only if additional risk factors for VTE are present, such as long and complex operations, paralysis, cancer, spinal cord injury or hypercoagulable states.[44] The ACCP guidelines also recommend the use of mechanical thromboprophylaxis, preferably with IPC, over anti-coagulant methods in spinal surgery.[1] For higher risk patients, the ACCP suggests adding LMWH or LDH once haemostasis is established, a strategy in which we are in agreement. In addition to early mobilisation, for patients at increased risk for VTE (because of cancer, motor deficits, prolonged immobilisation or a complex surgical procedure) and who will remain in hospital for at least 2 days, we recommend in-hospital thromboprophylaxis starting with IPC and/or GCS followed by delayed use of LMWH (generally started 24 h postoperatively). If mechanical thromboprophylaxis is used, it should be started just prior to surgery (or on admission for emergency cases) and efforts should be made to ensure proper fitting and compliance with their continual use. If anti-coagulant thromboprophylaxis is used, it should be started postoperatively once there is clinical evidence that primary haemostasis has taken place. Further delay is recommended if there are intraoperative or postoperative circumstances that substantially increase bleeding risk.

Recommendations

Patients undergoing craniotomy

- We recommend that if IPC is used, it should be applied before the surgical procedure or on admission, used continuously (except when the patient is actually walking) and monitored frequently to optimise compliance (Grade 1C).

- If LMWH or low-dose unfractionated heparin (LDUH) are used, we suggest delayed initiation until at least 24 h after surgery (Grade 2C).
- In craniotomy patients at particularly high risk of VTE (additional risk factors including malignancy, motor impairment, prolonged operative time), we suggest considering the initiation of mechanical thromboprophylaxis with IPC preoperatively with addition of LMWH or LDUH postoperatively when the risk of bleeding is presumed to be decreased (Grade 2C).
- We suggest that thromboprophylaxis should be continued until discharge (Grade 2C).

Patients with non-traumatic intracranial haemorrhage

- We suggest thromboprophylaxis with IPC (Grade 2C).
- We recommend the application of IPC on admission, used continuously (except when the patient is actually walking) and monitored frequently to optimise compliance (Grade 1C).
- For patients who have had non-traumatic ICH, we suggest giving consideration to commencement of LMWH or LDUH when the risk of bleeding is presumed to be low (Grade 2C).
- We suggest continuing thromboprophylaxis until full mobilisation of the patient (Grade 2C).

Spinal surgery

- For patients with no additional risk factors, we suggest no active thromboprophylaxis intervention apart from early mobilisation (Grade 2C).
- For patients undergoing spinal surgery with additional risk factors (limited mobility, active cancer, complex surgical procedure), we recommend starting mechanical thromboprophylaxis with IPC preoperatively (Grade 1C) and we suggest the addition of LMWH postoperatively when the risk of bleeding is presumed to be decreased (Grade 2C).
- If LMWH is used, we recommend delayed initiation at least until 24 h after surgery and only when haemostasis occurs (Grade 1C).
- We suggest continued thromboprophylaxis until discharge in high-risk patients (Grade 2C).
- In patients with spinal cord injury or significant motor impairment, we suggest extending the thromboprophylaxis into the rehabilitation phase of hospital care (Grade 2C).

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