Thromboprophylaxis in Neuro Intensive Care Unit

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J Neuroanaesthesiol Crit Care 2019;6:284–291

Abstract

The propensity for venous thromboembolism in patients admitted to neurocritical care setups is high because of predilection toward venous stasis as well as pathological processes favoring embolus formation and dissemination. The application of routine thromboprophylaxis guidelines in the various subsets of neurologically injured patients is limited by the fear of bleeding inside neurologically significant closed locations. The aim of this review is to lay out thromboprophylaxis guidelines in various subsets of patients admitted to neurocritical care setups according to recent evidence base, which is still an evolving process.

Keywords
► thromboprophylaxis
► neurocritical care
► craniotomy

Introduction

Among the plethora of factors contributing to morbidity and mortality of neurosurgically injured patients in neurocritical care setups, venous thromboembolism (VTE) remains an innocuous yet significant factor. The fact that the neurosurgical procedures are lengthy, associated with delayed ambulation and prolonged hospital stay, and the concomitant predisposing comorbidities make neurologically injured patients more prone for development of VTE. Without thromboprophylaxis, deep vein thrombosis (DVT) rates have been found to be significantly high and previous studies have also shown increased incidence of an alarmingly high rate of a major killer, that is, pulmonary embolism.[1]

There is irrefutable evidence to suggest that patients admitted to an intensive care setup are prone for VTE irrespective of the systemic subset they belong to.[2,3] While thromboprophylaxis has shown to reduce thromboembolism rates in both surgical and medical subsets, an interesting fact is that it reduces mortality only among surgical patients.[4,5] Considering the aforementioned background detailing the propensity of neurologically injured patients for VTE and the proven role of thromboprophylaxis in reducing mortality among surgical patients in particular and VTE in general, application of thromboprophylaxis to neurologically injured patients in neurocritical patients should be a no brainer. However, the level of evidence for thromboprophylaxis in neurologically injured patients is still a work in progress and is majorly confounded by the probability of hemorrhage and its effects on closed spaces such as cranium and spinal canal. There have been various systematic reviews in the last two decades on the topic of efficacy of thromboprophylaxis to include pharmacological methods in addition to the widely prevalent mechanical modalities.[6] Various subsets of neurological injury are relevant in present day neurocritical care (►**Table 1**).

The aim of this review is to elucidate evidence-based recommendations for thromboprophylaxis of various subsets of neurologically injured patients, surgical and otherwise, as well as the clinical caveats of such use. These recommendations are majorly drawn from a comprehensive evidence-based guideline published by the neurocritical care society in 2016.[7]

Table 1 Various major subsets of patients in neurocritical care

Cranial pathologies	Spinal pathologies
Postcraniotomy patients Patients of aneurysmal subarachnoid hemorrhage Stroke Traumatic brain injury Patients undergoing endovascular procedures Patients with intracranial hemorrhage	Post spine surgery Spinal injury patients Patients with neuromuscular diseases

received
August 15, 2019
accepted after revision
September 4, 2019
published online
November 20, 2019

DOI https://doi.org/10.1055/s-0039-1698725
ISSN 2348-0548.

Table 2 Risk factors for venous thromboembolism in patients undergoing craniotomy and spine surgery

High risk	Inconsistent/additional risk factors
Malignancy Poor mobility Prolonged procedure Complicated surgery involving more than one level Advanced age	Previous thromboembolism Renal compromise Obesity Cervical and thoracolumbar surgery Open surgical technique Poor compliance to thromboprophylaxis protocols

Postcraniotomy Patients

Neurosurgical patients undergoing craniotomy have demonstrated a clinically significant increased risk of DVT, pulmonary embolism (PE), and VTE, especially in the setting of perioperative neurocritical care which plays an integral part in the hospital course of majority of such patients. Various reasons such as concomitant malignancy, long procedural duration, and release of procoagulant factors have been established while some risk factors have proven inconsistent.[8-10] The risk factors associated with increased risk of DVT is the same as those undergoing spine surgeries and are set out in ►**Table 2**. The incidence of DVT and PE with or without thromboprophylaxis in patients undergoing craniotomy has shown marked variation in various study populations.[8,11-13] The American College of Surgeons - National Surgical Quality Improvement Program (ACS-NSQIP) data from 2006 to 2012 for VTE in craniotomy patients vary from 1.7 to 3.2% with PE rates of 1.4% and DVT rates of 2.6%.[8,11,12] Recent studies have shown higher rates of VTE, especially in patients undergoing neurosurgical removal of brain tumors with rates of DVT as high as 14%.[1,9,10,14-16]

There have been several studies examining the virtues of implementing chemical DVT prophylaxis in patients undergoing craniotomy.[17-20] Moreover, there have been several meta-analyses that have attempted choice of techniques and the commensurate level of evidence of such maneuvers.[21-23] However, the drawbacks of many of the trials included in the meta-analyses is that they are old and do not include mechanical thromboprophylaxis, which is a matter of routine these days.

Intermittent pneumatic compression (IPC) stockings are a form of mechanical thromboprophylaxis, which obviates the risk and harmful effects of bleeding inside a closed skull cavity.[24] IPC has shown significant effect in decreasing incidence of DVT and related complications in patients undergoing neurosurgical procedures in the brain.[25] However, the fact that these devices are not very well tolerated by patients and are cumbersome to use by critical care staff means that they are yet to achieve their full potential.[26,27] A study in China among the staff in the intensive care unit (ICU) showed that while only half of them practiced mechanical thromboprophylaxis, a quarter of people working in the ICUs (nearly 25%) had never heard of the same.

Present-day evidence suggests that whenever IPC is used in patients undergoing craniotomy, their use should be commenced in the pre-surgery phase as soon as the patient is admitted to the hospital and continued in the postoperative intensive care setups with frequent monitoring to improve compliance.[1,28-31]

The theoretical risk of intracranial bleeding notwithstanding pharmacological thromboprophylaxis with low molecular weight heparin (LMWH) or low-dose heparin (LDH) has proven effective both in conjunction with mechanical methods and standalone therapy in patients undergoing neurosurgical procedures and craniotomies.[21-23] There is ample evidence to suggest that pharmacological thromboprophylaxis with LMWH and LDH is not associated with increased bleeding risk in patients undergoing craniotomies, especially when such therapy is started after the first postoperative day when surgical hemostasis has been more or less achieved.[16,32-34]

Thromboprophylaxis recommendation in craniotomy (strong recommendation, moderate quality of evidence)

- Mechanical thromboprophylaxis[1,7]
  - IPC or gradient compression stockings should be used before surgery and following admission in elective and emergency craniotomies, respectively.
- Pharmacological thromboprophylaxis (LMWH/LDH).[1,7]
  - Should be ideally deferred till 24 hours after surgery.
  - Preferably used in high-risk population after radiologically confirming hemostasis.
- Duration of thromboprophylaxis till discharge.[1]

Thromboprophylaxis in Patients Undergoing Spine Surgery

The incidence of DVT and VTE is radically less in patients undergoing surgery on the spine vis-a-vis patients in whom surgery is done on the brain. The DVT rates in this aforementioned subgroup of neurosurgical patients is 0.7% and thromboembolic complications is around 0.4%.[11,35-37] Another interesting fact noted in these patients is that almost 50% of these patients manifest the signs and symptoms of DVT after they are discharged from the hospital.[38]

Just like patients undergoing craniotomy, certain patients have demonstrated higher risk of thromboembolic complications in patients undergoing spinal procedures.[35,37,39-41] However, the predictive models based on these risk factors are yet tbe validated.

Systematic reviews of effect of thromboprophylaxis on patients undergoing spinal surgeries have revealed rates of DVT in the range of 2.7 to 5.8% in patients not receiving thromboprophylaxis. Patients with mechanical thromboprophylaxis in spine surgery have revealed DVT rates of around 1.8% (both GCS and IPC combined). Patients receiving a combination of mechanical and pharmacological thromboprophylaxis fared the best, they had a pooled DVT rate of less than 0.01%.[40,42,43] There is a fear of development of a spinal hematoma in patients receiving pharmacological thromboprophylaxis in patients undergoing surgery on the spine.[44,45]

The said premise has thankfully been proven to be a theoretical one and even the reported rates of epidural hematoma are highly insignificant (~0.2%).[40,42,46-48] Bodies of repute such as the North American Spine Society as well as the ACCP guidelines recommend mechanical thromboprophylaxis (IPC preferred) only in patients with additional high-risk factors throughout the perioperative period (►**Table 2**). In these patients, pharmacological thromboprophylaxis in the form of LMWH can be started in the postoperative period after 24 hours, especially when probability of bleeding is minimal.[44,49] Like in patients with craniotomy, mechanical thromboprophylaxis should be initiated as soon as possible after hospital admission and steps are desirable to establish protocols which would encourage proper use and compliance to protocol.[1]

Thromboprophylaxis recommendations in spine surgeries

- Standard elective surgery without additional risk factors, ambulatory surgery (weak recommendation, low quality of evidence)[1,7]
  - early mobilization
  - no active thromboprophylaxis /IPC only
- Standard elective surgery with risk factors, complicated spinal surgery (strong recommendation, moderate quality of evidence)[1,7]
  - IPC preoperatively
  - Add LMWH/UFH in postoperative phase when risk of bleeding is low (24 hours when hemostasis occurs)
- IVC filter (weak recommendation, low quality of evidence)[7]
  - Not to be used routinely
  - Temporary measure only in patients with DVT with contraindication to anticoagulants or in patients with proven DVT and PE

Thromboprophylaxis in spinal cord injury

- Start within 72 hours of injury (strong recommendation, high quality of evidence)[7]
- If bleeding risk is low or hemostasis is achieved—LMWH/UFH (Strong recommendation, moderate quality of evidence)[7]
- If bleeding risk is high (patient on chronic anticoagulant and antiplatlet therapy, patients with coagulopathies, severe liver disease)[7]
  - IPC (weak recommendation, low quality of evidence)
- Continue till discharge[7]

Thromboprophylaxis in Aneurysmal Subarachnoid Hemorrhage

Incidence of DVT ranges from 1.5 to 2.4% while the incidence of PE ranges from 1.2 to 2% in patients with aneurysmal subarachnoid hemorrhage (SAH).[50-52] Evidence suggests that use of LMWH is associated with increased risk of intracranial bleeding in patients with cerebral aneurysms undergoing surgical occlusion.[53,54] Mechanical methods seem to be more efficacious and safe in patients with aneurysmal SAH.[55] Present recommendations advocate use of either or combination of pneumatic compression device and compression stockings before occlusion of aneurysm (level class II B).[29,56] This form of mechanical thromboprophylaxis normally suffices for patients with low risk of DVT in postoperative periods. However, in patients with high risk of DVT, LMWH therapy can be started after 12 hours of surgical occlusion and immediately after endovascular coiling (level class II B).[56]

Thromboprophylaxis recommendation in intracranial aneurysm

- In all patients with aneurysmal SAH other than ruptured aneurysm, for surgery—UFH (better than LDH) (strong recommendation, low quality of evidence)[1,7]
  - Use of mechanical thromboprophylaxis—IPC as soon as patient is admitted to the hospital (strong recommendation, moderate quality of evidence)
- Patients undergoing clipping or coiling of ruptured aneurysm—UFH (weak recommendation, low quality of evidence)[1,7]
  - 24 hours after clipping
  - Immediately after coiling

Patients Undergoing Neuroendovascular Procedures

There has been an advent of neurointerventional endovascular techniques such as coil embolization of intracranial aneurysms as well as the proliferation of adjunctive techniques such as balloon and stent-assisted techniques.[57] Such patients exhibit high propensity for thromboembolic complications with reported periprocedural stroke in the range of 2.3 to 10.4%.[57] The postulated mechanisms for a greater tendency toward thromboembolic complications in this patient subgroup include trauma to the cranial vascular tree with resultant thrombosis, migration of coil, and embolization and dislodgement of thrombus in the aneurysm.[58]

Periprocedural heparin administration is especially being favored in patients undergoing coiling for unruptured aneurysms.[58,59] In patients with ruptured aneurysms, bleeding risks outweigh the potential benefits. Antiplatelet agents (clopidogrel and aspirin) have also been explored in subjects undergoing coiling- and device-assisted procedures to treat cerebral aneurysms.[60,61] The general consensus for the use of these agents is to employ dual antiplatelet therapy (aspirin 100 mg per day and clopidogrel 75 mg per day), especially in patients with challenging aneurysm anatomy necessitating the use of multiple catheters and stent assistance during the procedure.[62,63] There has been conflicting evidence for the potential of bleeding complications due to antiplatelet therapy in patients presenting with ruptured aneurysms.[63,64]

Present-day recommendations for patients undergoing endovascular coiling of cerebral aneurysms are elucidated below:

Thromboprophylaxis recommendation in neuroendovascular procedures (weak recommendation, low quality of evidence)

- Patients without hemiparesis (elective procedure) (weak recommendation, very low quality of evidence)[7]
  - Early ambulation
  - Mechanical thromboprophylaxis—nneed of UFH/LDH
- Patients with hemiparesis (stroke/other neurological insult) (weak recommendation, low quality of evidence)[7]
  - UFH with/without mechanical thromboprophylaxis—within 24 hours (measure ATT)
- Elective intracranial/intra-arterial procedures (weak recommendation, low quality of evidence)[7]
  - IPC or GCS until patient ambulates plus LMWH/UFH
- Coiling of unruptured aneurysm[62,63]
  - Dual antiplatelet therapy to be started 4 days before procedure
  - After placement of sheath, administer intravenous heparin with target ACT of 250 to 300 seconds.
- Coiling of ruptured aneurysm[62,63]
  - Withhold dual antiplatelet therapy (DAT) before the procedure, can be considered in the postoperative period.
  - Heparin therapy (femoral)
    - Half dose after sheath insertion
    - Remaining dose after coil placement

Thromboprophylaxis in Stroke

Incidence of DVT in patients with stroke is high and variable (10–75%).[65,66] Clinical manifestations of DVT appears in 2 to 10% of patients in acute stroke with peak onset between days 2 and 7.[67-69] The importance of thromboprophylaxis in patients with stroke can be gauged by the fact that PE accounts for as much as 13 to 25% early deaths in stroke and is overall the most common cause of mortality in stroke.[67] Known risk factors for DVT in acute stroke consists of old age, hemiparesis, lack of mobility, a high National Institutes of Health Stroke Scale (NIHSS) score, female sex, and patients of intra-arterial tissue plasminogen activator.[67]

Several trials, such as CLOTS, PREVAIL, and the International Stroke Trial, as well as several comprehensive reviews have attempted to script guidelines for use of mechanical and pharmacological thromboprophylaxis in patients suffering stroke during the acute as well as the rehabilitation phase.[67,68,70-75] While considering pharmacological thromboprophylaxis it is worthwhile to note that while aspirin has been shown to be ineffective as a single therapy, newer agents such as anti Xa danaproid and rosuvastatin have shown promise.[76-78]

Various international bodies have come up with guidelines for thromboprophylaxis in patients with acute stroke. They are summarized below along with the relevant level of evidence.[67]

Thromboprophylaxis recommendations in ischemic stroke

- Early mobilization and good hydration (strong recommendation, low quality of evidence)[7,67]
  - All patients with stroke
- Stroke patients with restricted or no mobility (strong recommendation, high quality of evidence)[7,67]
  - Pharmacological prophylaxis—LMWH/LDH started immediately (unless contraindication to anticoagulants)[7,67]
  - LMWH preferred to UFH[7,67]
    - In patients with renal failure—prefer LDH—grade B[67]
    - Pharmacologic prophylaxis should be started within 48 hours of stroke and continued till 2 weeks[67]
    - Watch for hemorrhagic transformation in CT scan—indication to stop anticoagulation—grade D[67]
    - Aspirin[67]
      - Can be used concomitant to other pharmacological thromboprophylaxis
      - Should not be used as sole therapy in Stroke patients undergoing decompressive proceure[7]
  - UFH/LMWH with/without IPC—immediate postsurgery or postprocedure state—except when patient has received rTPA
  - If rTPA started—delay pharmacological methods for 24 hours

Mechanical thromboprophylaxis in patients with stroke (strong recommendation, moderate quality of evidence)[67]

- Should not be used as standalone therapy in patients with stroke (grade B)
- Can be used as standalone therapy in patients with contraindication to pharmacological methods (grade B)
- In such patients (contraindication to pharmacological thromboprophylaxis) IPC along with GCS is preferred

Thromboprophylaxis in Traumatic Brain Injury

Incidence of DVT in traumatic brain injury (TBI) could be as high as 54%.[79] The Brain Trauma Foundation has suggested that LMWH along with mechanical thromboprophylaxis be used in TBI to prevent DVT.[80]

The primary concern in a TBI is the expansion of the intracranial hematoma.[81] Phelan et al have found that mostly all low-risk ICH patients experience a spontaneous expansion of the hematoma at 48 hours of injury, and most patients with moderate- to high-risk ICH experienced an expansion at 72 hours.[82] Thus, it would seem logical that thromboprophylaxis should start after 48 hours of low-risk and 72 hours of moderate- to high-risk hemorrhages. What confounds matters is the fact that thromboprophylaxis during the 72 hours post injury was associated with hematoma expansion in patients with a pre-existing ICH.[83] It has also been shown that ICH expansion was more when chemoprophylaxis was done with unfractionated heparin, than LMWH, making the latter the preferred agent.[83] It is pertinent to note that spontaneous expansion of hematoma may occur, which is not related to DVT prophylaxis with drugs.[84]

Thromboprophylaxis recommendations in patients with TBI (weak recommendation, low quality of evidence)

- LMWH/LDH to be used in combination with mechanical thromboprophylaxis—watch for signs and symptoms of expansion in hemorrhage[1,7]
- Pharmacological thromboprophylaxis to be used if brain injury is stable and benefits of such treatment outweigh the risk of intracranial hemorrhage[1,7]
- IPC—within 24 hours of TBI or within 24 hours after craniotomy[1,7]
- LMWH/UFH—24 t48 hours after TBI or 24 hours after craniotomy[1,7]

Thromboprophylaxis in ICH

Prevalence of symptomatic DVT in patients with ICH is estimated to be 1 to 5% with PE rates of 0.5 to 2%.[85,86] Several trails have established the effectiveness of mechanical methods.[28,75]A comprehensive meta-analysis has established advantages of pharmacological thromboprophylaxis without significant effects on hematoma expansion and outcome in patients with ICH.[87]

Thromboprophylaxis recommendations in patients with ICH

- Mechanical thromboprophylaxis (IPC and or GCS)—start at hospital admission (strong recommendation, high quality of evidence)[1,7]
- Stable hematoma or normal coagulation status—prophylactic UFH/LMWH (weak recommendations, low quality of evidence)[1,7]

Thromboprophylaxis in Neuromuscular Diseases

Immobility, prolonged hospitalization in critical care, and respiratory failure are the reasons for high propensity of these patients to develop DVT and its complications (rates of DVT = 4–7%, risk of PE = 3–7%).[88-91] Available recommendations in this subgroup are basically an extrapolation of evidence of critically ill patients and patients with spinal cord injury and are enumerated as follows:

Thromboprophylaxis recommendations in patients with neuromuscular disorders7

- Pharmacological prophylaxis (UFH/LMWH/ Fondaparinux) preferred (strong recommendation, moderate quality of evidence)[7]
- Bleeding risk high (patients on anticoagulants, coagulopathies, liver disease, etc.)
    - IPC preferred (strong recommendation, moderate quality of evidence)[7]
- Combination of pharmacological and mechanical thromboprophylaxis, whenever possible (weak recommendation, low quality of evidence)[7]
- Duration of VTE prophylaxis[7]
    - Minimum for duration of hospitalization during acute phase
    - Patient is able to ambulate

Conclusion

With burgeoning evidence in neurologically injured patients it is becoming increasingly clear that thromboprophylaxis has got a significant role in prevention of VTE and the attendant complications and has a potential to improve outcome in various neurocritical patient subgroups. The fear of hemorrhage notwithstanding, especially in high-risk population, the beneficial effects are far more remarkable. There are still areas where focused research would be required, especially to facilitate guideline synthesis in specific patient subgroups.

Funding
This review received the department and institutional support.

Conflict of Interest
None declared.

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