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INFOGRAPHIC

GUIDELINES

European guidelines on peri-operative venous thromboembolism prophylaxis: first update.

Chapter 11: Trauma

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Monitoring hypercoagulation in trauma patients

Rationale

It is now well recognised that in the acute phase, after major trauma, the coagulation system is dynamic and, particularly in bleeding patients with trauma-induced coagulopathy or severe brain injury, a hypercoagulable phenotype develops universally within 24 to 48 h.[1] Achieving adequate venous thromboembolism prophylaxis (VTEp) in trauma patients remains challenging for several reasons and despite standardised protocols to administer low-molecular-weight heparin (LMWH), up to 18% of critically injured patients will develop deep venous thrombosis (DVT) or pulmonary embolism despite pharmacoprophylaxis.[2]

Measuring serum anti-Xa levels has been proposed to help titrate VTEp, with consensus defining prophylactic anti-Xa levels as 0.2 to 0.4 IU ml^{-1} for peak measurements or 0.1 to 0.2 IU ml^{-1} for trough levels, with values below this being subprophylactic.[3] Studies have shown that prophylactic anti-Xa levels compared with subprophylactic levels predict the risk of a clinically significant VTE in trauma patients.[4–6] Two studies have reported that anti-Xa-guided dosing of LMWH reduces the rate of VTE after trauma compared with a standard fixed dose of enoxaparin.[7,8] However, a more recent large single centre study has failed to show any benefit of anti-Xa guided dosing for VTEp.[9] Weight-adjusted protocols for LMWH are used in published guidelines[10] based on a handful of studies demonstrating improved rates of prophylactic anti-FXa levels and overall lower VTE rates. Interestingly some authors have reported no additional benefit of anti-FXa-guided dosing over and above weight-adjusted protocols.[11,12] Interpretation of these studies is confounded by the timing of prophylaxis, a retrospective study design, and screening-detected vs. symptomatic VTE.

A recent systematic review[13] has evaluated the role of anti-FXa levels to predict VTE, and whether dose-adjusted protocols affect anti-FXa serum levels, and crucially whether the rates of clinically significant VTE are reduced when such protocols are implemented. Paradoxically, although anti-FXa levels were found to be correlated with VTE events, and dose-adjusted protocols improved the rate of prophylactic anti-FXa levels, there was no effect on the incidence of VTE compared with standard LMWH-dosing regimens. One explanation may be the delay in achieving the prophylactic anti-FXa range with dose optimisation: some studies reported a lag of 3.5 days[14] before achieving an adequate effect. It is unclear whether anti-Xa levels are reflective of VTE risk over the clinical episode or simply the prothrombotic state at a given time. After implementation of the anti-Xa titration protocol in over 3000 patients, a more recent single-centre study found a statistically significant reduction in the VTE and DVT rates but not in the incidence of pulmonary embolism ($P = 0.21$).[15]

The prothrombotic risk is unlikely to be determined by a single factor level, and novel biomarkers evaluating platelet function, for example, platelet factor 4, are active areas of research and preliminary studies have found it to be closely related to VTE risk.[16] In summary, the evidence base to determine optimal risk profiling of the hypercoagulable state after major trauma is limited to observational cohort studies and it is unclear whether weight or anti-FXa level-adjusted protocols reduce VTE

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rates. High-level evidence is lacking, and randomised controlled trials to evaluate alternative dosing strategies are required.

Recommendations

(1) We suggest that dose adjustment of LMWH is associated with reduced VTE in severe trauma patients, but there is inconclusive evidence to support one method over another (i.e. weight-adjusted vs. anti-Xa levels) and further research is required. (Grade 2B)
(2) We do not recommend the use of thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to stratify VTE risk for adjusting prophylaxis. (Grade 1C)

Polytrauma without neurotrauma

Rationale

In 2019, three retrospective studies were published.[17–19] Kingdon *et al.* performed a retrospective comparison of propensity-matched patient cohorts ($n = 2106$) with multisystem injuries, receiving either rivaroxaban or enoxaparin as thromboprophylaxis. They found no difference in DVT, pulmonary embolism or bleeding. Hospital length of stay (LOS) and mortality was higher in the enoxaparin group.[17] Hamidi *et al.* performed a comparison between matched groups of nonoperatively managed isolated pelvic injuries from the Trauma Quality Improvement Programme of the American College of Surgeons database (ACS TQUIP), with 284 patients receiving direct oral anticoagulants (DOAC) vs. 568 receiving LMWH. The DOAC group had significantly fewer DVTs (1.8 vs. 6.9%), no difference in pulmonary embolism, without increasing the risk of bleeding complications, evaluated as packed red blood cell (pRBC) transfusion, postprophylaxis surgery and/or angioembolization for bleeding complications, or mortality[18]. The same group published results on surgically managed spinal injuries, matching 270 patients receiving DOAC with 540 receiving LMWH. Compared with the DOAC group, DVT (1.8 vs. 7.2%) and pulmonary embolism rates (0.3 vs. 12.1%) were increased in the LMWH group.[19]

Recommendation

(1) We suggest DOAC as an alternative to LMWH in protecting against VTE. (Grade 2C)

Rationale

We identified three large retrospective studies published between 2020 and 2022 in addition to a meta-analysis from 2022, which includes four older RCTs and eight retrospective studies.[20–22] Gaitanidis *et al.* focus on 93 987 elderly trauma patients aged older than 65 years in a retrospective study from the database of the ACS TQUIP: 72.1% received LMWH and the remainder received unfractionated heparin (UFH). After propensity score matching, LMWH showed significantly lower rates of DVT (1.7 vs. 2.1%), pulmonary embolism (0.6 vs. 1.0%), blood product transfusions (2.8 vs. 3.5%) and surgical procedures (0.7 vs. 0.9%).[20] Krantz *et al.* also focused on high-risk elderly trauma patients older than 65 years of age ($n = 1090$). VTE occurred in 3.6% with no statistical difference between LMWH and UFH based on logistic regression analyses.[22] A review by Tran *et al.*[23] from 2022 included four RCTs, the most recent from 2015, three others from the 1990s, and eight observational studies: these authors concluded that LMWH is superior to UFH in protecting against DVT, and potentially protecting against PE and mortality.

Recommendation

(1) We recommend that LMWH be used rather than UFH as thromboprophylaxis after severe trauma. (Grade 1C)

Rationale

Schroeppel *et al.* [24] describe a cohort of 1597 patients with absence of active ongoing haemorrhage. Over a 12-month study period, 53% were admitted during the first 6-month period before implementing an early thromboprophylaxis protocol, and 47% in the second 6-month period after the protocol implementation. The time to thromboprophylaxis diminished from 23.3 to 13.9 h. Linear regression identified time to thromboprophylaxis to be a significant predictor of VTE without increasing the risk of bleeding.[24] Hecht *et al.*[25] analysed data from 32 level I and II trauma centres including only severely injured patients ($n = 14\,096$) and found a significantly lower incidence of VTE when thromboprophylaxis was initiated within 24 h. The same group analysed data for 79 386 patients from 34 level I and II trauma centres with initiation of VTE-prophylaxis at different time intervals. Risk-adjusted rates for VTE were calculated (type of prophylaxis and patient characteristics). Compared with those receiving prophylaxis within 24 h, VTE rates were significantly higher in patients receiving VTEp between 24 and 48 h and more than 48 h: odds ratio (OR) [95% confidence interval (CI)] 1.26 (1.09 to 1.47) and 2.34 (2.04 to 2.70), respectively.[26]

In a retrospective analysis of ACS TQIP involving 36 187 patients with blunt solid organ injury and nonoperative management (NOM), patients receiving early thromboprophylaxis (≤48 h) had lower rates of DVT ($P = 0.01$) and pulmonary embolism ($P = 0.01$) compared with the late thromboprophylaxis groups (>48 h) or those who did not receive any VTEp.[27] There was no difference between the three groups regarding the postprophylaxis pRBC transfusions, failure of NOM or mortality.[27] In another retrospective analysis of 25 118 patients from ACS TQIP, Gaitanidis *et al.*[28] confirmed that early thromboprophylaxis initiation (<48 h) should be considered in patients with blunt abdominal solid organ injuries

undergoing NOM who are at low likelihood of bleeding. At increased risk of bleeding in NOM for solid organ injuries are patients with a history of diabetes mellitus, patients with severe splenic injuries [Abbreviated Injury Score (AIS) 3 to 5] or severe liver injuries (AIS 3 to 5]. For these patients, the author recommends an intermediate delay of 48 to 72 h before starting VTEp.[28] A recent meta-analysis was conducted in trauma patients who underwent NOM of blunt solid organ injuries.[29] Twelve retrospective cohort studies, comprising 21 909 patients, were included. Pooled adjusted analysis demonstrated that initiation of prophylaxis before 48 h was associated with lower VTE rates without higher risk of failure of NOM.

Recommendation

(1) We recommend thromboprophylaxis should be initiated early (<24 h) after severe trauma without traumatic brain injury and absence of active haemorrhage. (Grade 1C)
(2) Statement: For nonoperative management (NOM) of blunt solid organ injuries, VTE rates decrease consistently with early thromboprophylaxis but, based on conflicting results concerning delayed bleeding risk, some high-risk patients might benefit from a 48-h delay.

Traumatic brain injury/spinal cord injury

Rationale

Patients with spinal cord injury are at very high risk of venous thromboembolic events. There are very few data comparing mechanical prophylaxis alone with pharmacological prophylaxis. However, several large retrospective studies report fewer VTE and pulmonary embolism when patients receive UFH or LMWH within 48 h following injury, without a significant increase in bleeding complications.[30–33] Although a few studies suggest fewer VTE with LMWH compared with UFH, the strength of the evidence is too low to recommend one pharmacologic method.

One large population study of patients with nonoperatively managed spinal fractures showed a high risk of VTE for 6 months after the injury, even in the absence of a neurological deficit.[34] Hence, a 6-month duration of anticoagulation seems reasonable in patients still hospitalised in a rehabilitation centre, and presumably even more so in presence of a motor deficit.

There is very low evidence that intermittent pneumatic compression (IPC) added to pharmacological prophylaxis is beneficial. In stroke patients, one prospective randomised study demonstrated the efficacy of IPC in reducing the risk of DVT, especially in patients with a leg motor deficit.[35] Accordingly, this might apply to patients with spinal cord injury (SCI) and motor deficits. However, a study on critically ill patients, not limited to trauma patients, did not show any benefit of adding IPC.[36] Considering the low risk associated with IPC (skin breaks in only 1 study), IPC may be considered in patients with a motor deficit due to SCI, both combined with pharmacological VTEp or in patients with contraindication to anticoagulants.

Patients with traumatic brain injury (TBI) are at high risk of VTE. At the same time, they are also at risk of intracranial bleeding or progression of intracranial haemorrhage. Several retrospective studies have shown that early pharmacological prophylaxis (< 48 h) is effective in reducing VTE without increasing the risk of intracranial haemorrhage in patients where progression of intracranial haemorrhage has been excluded.[37–41] In patients needing urgent neurosurgery (craniotomy, craniectomy or intracranial monitor or drain insertion), the probability of VTE increased with longer delays in pharmacological prophylaxis, but earlier prophylaxis was associated with a greater probability of repeated neurosurgery.[42] Hence, the risk/benefit ratio of pharmacological prophylaxis is uncertain and needs individual assessment of VTE and intracranial bleeding risks. The risk of intracranial bleeding is particularly high in the first 3 days following neurosurgery, suggesting a case for delaying prophylaxis for 72 h. In retrospective studies, the benefit of LMWH is either comparable or better than UFH.[39,43]

Recommendations

(1) In nonoperated patients with TBI and no progression of intracranial haemorrhage on the CT scan 24 h after the injury, we suggest early prophylaxis with LMWH within 48 h after injury. (Grade 2C)
(2) In patients having urgent neurosurgical interventions after TBI or in those at high risk of intracranial bleeding, we suggest delaying pharmacological prophylaxis on a case-by-case basis, balancing the risk of haemorrhage and the risk of VTE. (Grade 2C)
(3) For trauma patients with TBI and a contraindication to pharmacological prophylaxis, we recommend IPC (Grade 1C). We suggest adding LMWH when the risk of bleeding decreases. (Grade 2C)
(4) In patients with spinal cord injury, we suggest starting pharmacological prophylaxis within 48 h following trauma or surgery. (Grade 2B)
(5) We suggest a total duration of pharmacological prophylaxis of 3 to 6 months after spinal cord injury with neurological deficit. (Grade 2C).
(6) We suggest associating pharmacological and IPC in patients with spinal cord injury and a motor deficit. (Grade 2C)

Vena cava filter in trauma patients

Rationale

In the largest RCT published on inferior vena cava filters (IVCF) in trauma patients, 240 severely injured patients, showed no clear effect on symptomatic pulmonary embolism or death at 90 days: hazard ratio (95% CI) 0.99

(0.51 to 1.94).[44] In a subgroup of patients who did not receive pharmacologic VTE prophylaxis within the first 7 days after the injury, IVCF use reduced the risk of symptomatic pulmonary embolism: relative risk (RR) 0 (0.00 to 0.55). However, only symptomatic VTE and pulmonary embolism were recorded in this study, and no systematic screening was performed.

Three observational retrospective studies of acceptable to low quality indicated more DVTs in patients with IVCFs,[45–47] and one of these observed more pulmonary embolisms in patients with an IVCF.[45] None of these studies screened patients routinely for DVT or pulmonary embolism and none showed a significant difference in survival.

Considering the lack of evidence for a clear effect of IVCFs on pulmonary or DVT occurrence, we cannot recommend the routine use of prophylactic IVCFs as VTE-prophylaxis in severely injured patients.

Recommendation

- In trauma patients, we recommend against the routine use of IVC filters for the primary prevention of VTE. (Grade 1C)

Supplementary Table 1, http://links.lww.com/EJA/A975 lists the manuscripts related to this chapter.

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GRAPHICAL ABSTRACT