Preventing venous thromboembolism in the critically ill – can we do more?

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Pulmonary embolism is the most common preventable cause of hospital death; and of all the different patient groups, the critically ill are particularly at risk of venous thromboembolism. Most critically ill patients have multiple risk factors. Clinical trials have shown that the use of low molecular weight heparin (LMWH) is safer than unfractionated heparin in this population. Further trials are required to look at the risks and benefits of dose adjusting LMWH at the extremes of weight, in patients with renal failure and those on antiplatelet agents. Heparin-induced thrombocytopenia is still a risk with LMWHs so a safer anticoagulant such as fondaparinux and even the new oral anticoagulants merit trials. Further evidence is also needed for the use of graduated compression stockings and pneumatic devices.

Keywords: *inferior vena cava filter; venous thromboembolism; low molecular weight heparin; unfractionated heparin; thromboprophylaxis*

A systematic review by the US Agency for Healthcare Quality and Research of 79 safety interventions for hospital patients, ranked pulmonary embolism (PE) as the most common preventable cause of hospital death, and thromboprophylaxis (TP) as the number one strategy to improve patient safety in hospitals.[1] Of all the hospital patient groups, the critically ill are particularly at increased risk of venous thromboembolism (VTE) which contributes significantly to their morbidity and mortality. PE is frequently seen at post mortem in these patients, the incidence being as high as 27%.[2] The incidence of image-proven deep venous thrombosis (DVT) in critically ill patients ranges from <10% to almost 100% depending upon the screening methods and diagnostic criteria used.

Most critically ill patients have multiple risk factors for VTE. Many risk factors predate intensive care unit (ICU) admission, in particular recent surgery, trauma, sepsis, malignancy, immobilisation, increased age, heart or respiratory failure and previous VTE, so that about 5% have evidence of DVT on ultrasound scanning on admission.[3] Other risk factors are acquired on the ICU including immobilisation, pharmacological paralysis, central venous catheterisation, additional surgical procedures, sepsis, vasopressors and haemodialysis.[4] Hospitalised patients recovering from major trauma have the highest risk of developing VTE; with a risk of DVT exceeding 50% without thromboprophylaxis, explaining why PE is the third leading cause of mortality after the first day.

Mechanical measures of thromboprophylaxis

Immobility increases the risk of DVT tenfold.[5,6] Mechanical methods of thromboprophylaxis act by reducing venous stasis in the leg. The major advantage of these methods is the avoidance of systemic anticoagulation and thus the incumbent risk of bleeding. However studies suggest the benefits of mechanical methods in reducing VTE are small or negligible. A meta-analysis of the only two randomised controlled trials performed, showed both graduated compression stockings (GECs) and intermittent pneumatic compression devices (IPC) produced no benefit.[7]

GECs have been shown to reduce the incidence of post-operative DVT in general surgery and neurosurgery. However there are no good RCTs as yet of GECs in medical patients, apart from the CLOT study[8] which showed no reduction in VTE in stroke patients using GECs, but actual harm due to skin damage. CLOT 3 randomised IPC versus no IPC in over 2800 stroke patients and the rate of proximal DVT decreased from 12.1% to 8.5% and possibly improved survival.[9] In a recent study in 798 intensive care patients using multiple propensity scores adjusted analysis, the use of IPC but not GECs was associated with a lower VTE incidence regardless of type of pharmacological thromboprophylaxis used.[10]

Pharmacological methods of thromboprophylaxis

Aspirin

Aspirin's importance in the primary and secondary prevention of atherosclerotic disease is well established, but it only reduces risk of VTE by about 25%[11] whereas low molecular weight heparin (LMWH) reduces risk by 60-70%, so why would one use such an inferior agent? Furthermore, critically ill patients are more likely to suffer the deleterious consequences of aspirin therapy, including increased risk of haemorrhage, and reduced urinary prostaglandin synthesis decreases glomerular filtration, further restricting its use in critically ill patients.

Unfractionated heparin (UFH) and LMWH

Three randomised clinical trials compared UFH to placebo in intensive care patients.[12-14] The largest by Kapoor *et al*, studied 791 patients; DVT was detected in 31% of the placebo-treated group but only 11% of the UFH group (RRR 65%, p=0.001) and PE was reduced from 5% to 2% in the treated group.[14] Similar trials against placebo have been conducted with LMWH. For example Fraisse *et al* randomised 223 patients receiving mechanical ventilation for exacerbations of COPD to receive nadroparin or placebo.[15] DVT was detected by routine venography in 28% of the placebo group and 15% of those treated with nadroparin, a relative risk reduction of 45% (p=0.045%), with no difference in the major bleeding between the two groups.

UFH has an inferior safety profile when compared to LMWH for it has a tenfold increased incidence of fatal heparin-induced thrombocytopenia (HIT) when compared to LMWH. Prior to the PROTECT study, one study compared UFH to LMWH in 325 medical intensive care patients. DVT was detected by ultrasound in 16% of patients receiving UFH compared to 13% on LMWH, with no differences noted in the rates of proximal DVT or major bleeding.[16] The PROTECT study[17] was a landmark study that randomised 3764 patients to 5,000u dalteparin versus

unfractionated heparin twice daily. The rate of proximal DVT on ultrasound was similar (5.1% with dalteparin *vs* 5.8% with UF heparin), although the rate of PE was significantly lower (1.3% dalteparin *vs* 2.3% UF heparin, hazard ration 0.51, p=0.01). Rates of major bleeding were also similar but as expected HIT was less common with dalteparin.

A previously discussed limitation of LMWH in the intensive care population is the risk of drug accumulation in patients with renal impairment leading to an unpredictable and excessive anticoagulation. Nevertheless in the PROTECT study 6.7% of patients receiving dalteparin 5,000 IU required renal dialysis during their stay. It was noted in a later publication from the PROTECT study that renal replacement therapy was a minor risk factor for bleeding (HR 1.75, 1.2-2.56).[18] Paradoxically there is also concern that the use of vasopressors and the metabolic condition of some critically ill patients may reduce the effectiveness of pharmacological prophylaxis. The putative mechanism is decreased absorption of LMWH from the subcutaneous tissues due to reduced perfusion caused by the vasopressor. Multiple organ dysfunction may alter drug metabolism, distribution and binding to albumin and acute phase proteins.

Vitamin K antagonists

Treatment with adjusted-dose oral vitamin K antagonists with a target INR is not recommended in the critically ill because dosing is difficult and unpredictable with a significant risk of both over- and under-anticoagulation.

Fondaparinux

No studies have been undertaken using fondaparinux in an intensive care population although a study in 849 older acute medical patients versus placebo showed that it is effective in this group and there was no increased bleeding when compared to placebo.[19]

Bleeding risk and side effects

Many critically ill patients have increased risk of bleeding and therefore pharmacological thromboprophylaxis may be relatively or absolutely contraindicated in those with:

- Thrombocytopenia with a platelet count <50 × 10^9/L
- Underlying coagulopathy
- Evidence of active bleeding
- Known bleeding disorder
- Uncontrolled hypertension
- Use of oral anticoagulation
- Lumbar puncture/epidural/spinal analgesia within the previous four hours
- New ischaemic or haemorrhagic CVA.

Due to the risk of HIT with heparin, patients should have regular full blood counts to ensure they are not becoming thrombocytopenic.

The role of IVC filters

These are discussed in detail in other articles in this supplement. Briefly, despite insurance payments in the USA for using inferior vena cava (IVC) filters for primary prophylaxis in trauma patients, a meta-analysis of prospective studies found no difference in the rates of PEs among such patients and bariatric patients with and without prophylactic IVC filters.[20,21]

The main indication for IVC filters is for the prevention of PE in patients with established VTE who have a contraindication to anticoagulation.[22] Most guidelines recommend that anticoagulation be considered in all patients with an IVC filter once a temporary contraindication to anticoagulation has passed and that IVC filter insertion is not indicated in unselected patients with VTE who will receive standard anticoagulant therapy.

The long-term use of IVC filters has been disappointing. Decousus et al 1998[23] studied a mixed population of surgical and medical patients who had a proven DVT and underwent randomisation with regards to insertion of an IVC filter. Both groups were anticoagulated with either heparin or LMWH. Patients with a contraindication to anticoagulation were excluded from the study. At 12 days 1.1% of the patients with an IVC filter had suffered a PE compared to 4.8% in the group without a filter. After two years' follow up however, 20.8% of the filter group and 21% of patients in the non-filter group had gone on to suffer a further PE.

In summary, where possible and whenever the contraindication to anticoagulation is transient, a retrievable filter should be favoured and anticoagulation commenced when it is no longer contraindicated.

Future directions

Many questions around thromboprophylaxis in intensive care patients remain and the absence of evidence supporting this area is striking. The benefits of mechanical thromboprophylaxis remain uncertain, current data suggests IPCs may have some benefit. For the moment the use of LMWHs is the preferred pharmacological agent, but because the risk of VTE is high in intensive care, the question remains as to whether higher doses would reduce the rate of VTE further, or would this lead to an unacceptable bleeding rate? The use of LMWHs at the extremes of body weight, in those with renal insufficiency and on antiplatelet agents remains insufficient and high-quality studies are needed to inform clinicians about dosing in these groups. HIT remains a risk with LMWHs so a safer anticoagulant would be preferable – would fondaparinux fit this role? Will the new oral anticoagulants be suitable for thromboprophylaxis in intensive care patients? There is currently inadequate data on safely reversing the new orals, so perhaps we should await this data before contemplating trials.

After total hip replacement or cancer surgery, extended duration thromboprophylaxis, given for 28-35 days post surgery, usually after 4-6 days admission, ie 3-4 weeks at home, significantly reduce the risk of VTE when compared to standard use of LMWH. It appears reasonable that intenisve care patients who fall into this group should be considered for extended prophylaxis, provided there is no increased bleeding risk. No clinical trials have assessed the benefits of extended duration prophylaxis after other illnesses requiring ICU admission and would be welcomed.

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