What is the best prophylaxis for venous thromboembolism in the critically ill?

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Abstract - The question 'What is the best prophylaxis for venous thromboembolism in the critically ill?' is clinically relevant. The answer is formulated based upon the best available evidence with a focus on pharmacological prophylaxis and symptomatic venous thromboembolism. Four randomized controlled clinical trials with a grade I level of evidence are discussed in detail. Unfractionated heparin is the best studied pharmacological prophylaxis in addition to enoxaparin and nadroparin. The endpoints in these studies all concerned deep venous thrombosis detected by imaging techniques and unrelated to symptoms. The clinical relevance of these endpoints is debatable. No firm conclusions can be drawn on the efficacy and safety of unfractionated heparin, enoxaparin and nadroparin in the prevention of symptomatic venous thromboembolism in the critically ill. As a consequence, no true recommendations can be given for the prevention of venous thromboembolism in these patients.

Keywords - deep venous thrombosis, pulmonary embolism, venous thromboembolism, prevention, prophylaxis, critically ill

Introduction

The question 'What is the best prophylaxis for venous thromboembolism in the critically ill?' is clinically relevant. To date the answer to this question can be found in three guidelines concerning critically ill patients [1-3]. These guidelines differ in the studies included to determine the evidence, and in the grading systems for the levels of evidence and the levels of recommendation.

First, the guideline ‘Prevention of venous thromboembolism in the critically ill’ of our Dutch Society of Intensive Care (Nederlandse Vereniging voor Intensive Care abbreviated as NVIC), which was published in 2000, recommends the use of pharmacological prophylaxis for venous thromboembolism in all critically ill patients [1]. This recommendation was based upon the evidence from two large randomized controlled trials [4,5]. Nadroparin calcium 2850 anti-Xa IU once daily subcutaneously (sc) or a comparable dose of another low-molecular-weight heparin (LMWH), such as enoxaparin, dalteparin or tinzaparin, was advocated as the drug of first choice. Nadroparin was not the drug of investigation in the two trials, but was chosen as the in The Netherlands generally accepted alternative for unfractionated heparin (UFH) 5000 IU 2-3 daily sc (so-called low dose UFH), since the introduction of LMWHs in the early 1990s.

Second, the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy in the guideline ‘Prevention of venous thromboembolism: Critical Care’, which was published in 2004, recommends that on admission to a critical care unit, all patients be assessed for their risk of venous thromboembolism (VTE) and accordingly, most critically ill should receive thromboprophylaxis [2]. This recommendation was based upon the high level of evidence from four large randomized controlled trials [4,6-8]. The selection of prophylaxis, in a heterogeneous case-mix, involves the consideration of the VTE and bleeding risks and, ideally, should be individualized. For critically ill patients at moderate risk for VTE, such as medically ill or postoperative patients, low dose UFH or LMWH is recommended. For critically ill patients at high risk for VTE, such as after major trauma or orthopedic surgery, LMWH prophylaxis is recommended. For patients at high risk for bleeding, mechanical prophylaxis is recommended until the bleeding risk decreases.

Third, the Surviving Sepsis Campaign guidelines have been updated in January 2008 [3]. It was recommended that patients with severe sepsis receive deep vein thrombosis (DVT) prophylaxis with either low dose UFH or LMWH unless there are contraindications (thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage). These guidelines also recommend that septic patients with a contraindication for heparin use should receive mechanical prophylactic devices, such as graduated compression stockings or intermittent compression devices, unless contraindicated. The guidelines suggest to use a combination of pharmacologic and mechanical therapy in very high risk patients, such as those who have severe sepsis and history of DVT, trauma, or orthopedic surgery, unless contraindicated or impractical. It is recommended that in very high risk patients, LMWH be used rather than UFH as LMWH has been proven superior in other high risk patients.

To formulate an appropriate answer to the question above, based on current knowledge, a renewed literature search was performed with a focus on pharmacological prophylaxis and symptomatic venous thromboembolism. The available best evidence is discussed in detail and – if possible - recommendations are made.
Literature search
For the NVIC guideline ‘Prevention of venous thromboembolism in the critically ill’ an extensive search of the literature was performed by means of MEDLINE database over the period of 1966 until September 2000. We carried out a new literature search using the MEDLINE database covering the period from October 2000 to December 2008. The following search strategy was used. The MeSH terms, key words and text words used were ‘deep venous thrombosis’, ‘deep vein thrombosis’, ‘pulmonary embolism’, ‘venous thromboembolism’, ‘prevention’, ‘prophylaxis’, ‘critical care’, ‘intensive care’, ‘intensive care unit’, and ‘critically ill’ and combinations of these. The articles were selected on ‘humans’ and ‘clinical trials’. The references of the selected articles were reviewed for further possibly relevant studies. Articles were included notwithstanding the type of publication or the language. For the definite analysis, those studies were selected in which the clinically relevant endpoints DVT, pulmonary embolism (PE), bleeding complications, heparin-induced thrombocytopenia (HIT) and mortality had been investigated by objective methods in populations of critically ill patients. Only randomized controlled trials with a grade I level of evidence were considered best evidence. If data were lacking, the authors were contacted to obtain more detailed information.

Quality assessment of the selected studies was performed by Jadad’s scale [9]. The analysis of the literature and formulation of recommendations was performed in accordance with the NVIC Committee Guideline Development procedure [10].

Results
The best available evidence found is still based on the already mentioned four trials [4,6-8]. One study was now deselected [5].

In retrospect, this study concerned trauma patients and it was unclear if all had been admitted in the ICU. Of the four selected studies, two trials were published as full papers [4,6] and two trials have been published as abstract only [7,8]. Since 2004 no new randomized controlled trials have been published. Table 1 depicts the quality assessment of the selected studies according to Jadad’s scale [9]. Table 2 shows the four trials in detail, including their limitations.

The specific anticoagulant drug, dose and way of administration in the strategies investigated are depicted in Table 2. No data are available on concurrent alternative treatments in the study groups and controls.

In his landmark study of 1982, in a population of critically ill patients in a general ICU, Cade demonstrated an incidence of 29% of DVT in patients treated with placebo and of 13% in patients treated with UFH 5000 IU sc twice daily [4]. This difference was statistically significant (p<0.05). It was concluded that the critically ill are at high risk of VTE, and that low dose UFH should be recommended as a prophylactic measure, provided that hemostasis is intact. Pulmonary embolism, bleeding complications, HIT and mortality were not reported.

In 57% of cases, Cade detected DVT confined to one calf, nearly one-third were bilateral calf DVT and one-fifth extended to the knee or above. It was not reported if the cases of DVT were symptomatic or asymptomatic nor if DVT was complicated by PE. The authors did not describe a power calculation, nor consecutive inclusion of patients and their follow-up.

In 2000, Fraisse and co-workers published the results of a prospective, randomized, double-blind comparative trial in critically ill patients with acute decompensated chronic obstructive pulmonary disease (COPD) who required mechanical ventilation [6]. The efficacy and safety of nadroparin adjusted for body weight was compared to physiological saline as placebo in the prevention of VTE. Power calculation was based upon the estimated potential incidence of symptomatic DVT without prophylaxis ranging between 8% and 25%. With a beta error of 10% and an alpha error of 5%, 200 patients were required in each group to show a reduction of these estimated incidences to 3% and 8%, respectively. An interim analysis was performed after the first 100 patients had been enrolled in each group. As a result, the study was stopped after enrollment of 223 patients. Two patients did not receive any treatment and 52 patients were not assessed by venography yielding 169 evaluable patients.

Patients with a body weight between 45 and 70 kg received 3,800 anti-Xa IU sc once daily and patients with a body weight between 71 and 110 kg received 5,700 anti-Xa IU sc once daily. The authors demonstrated a significant difference between the incidence of DVT of 15.5% in patients treated with nadroparin and of 28.2% in patients treated with placebo (p=0.045).

No PE was observed, although it was not systematically investigated by objective testing. In two patients in the nadroparin group, PE was suspected clinically. In one patient, PE was ruled out by normal venography and pulmonary angiography results, and in the second patient who died, PE could not be confirmed.

Table 1. Quality assessment of the selected studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POWER CALCULATION</th>
<th>RANDOMIZATION</th>
<th>METHOD OF RANDOMIZATION</th>
<th>DOUBLE-BLINDING</th>
<th>FOLLOW-UP (DESCRIPTION OF WITHDRAWALS AND DROPOUTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cade</td>
<td>no</td>
<td>yes</td>
<td>not described</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Fraisse</td>
<td>yes</td>
<td>yes</td>
<td>not described</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Kapoor</td>
<td>no</td>
<td>yes</td>
<td>not described</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Goldhaber</td>
<td>no</td>
<td>yes</td>
<td>not described</td>
<td>no (open label)</td>
<td>no</td>
</tr>
</tbody>
</table>
in a study, Goldhaber and colleagues demonstrated the equal efficacy and safety of enoxaparin 30 mg sc twice daily and UFH 5000 IU sc twice daily [8]. The incidence of all DVT were 16% versus 13%, respectively, and the incidence of proximal DVT were 7% versus 5%, respectively. There was no difference in all bleeding (12% versus 11%, respectively) and major bleeding (2% versus 2%, respectively) between the groups. The authors concluded equal efficacy and safety of enoxaparin and UFH among critically ill medical patients, but this trial may not have enrolled patients with a high acuity in view of a high exclusion rate and low mortality rates (1% versus 5%, respectively). PE and HIT were not investigated.

**Discussion**

The best available evidence to answer the clinically relevant question ‘What is the best prophylaxis for venous thromboembolism in the critically ill?’ is embodied by four well known trials and has not been expanded over the recent years. The best studied anticoagulant is UFH in 3 studies in addition to enoxaparin in one study and nadroparin in another study. All levels of evidence are grade I. Due to differences in patient populations, diagnostic methods, efficacy and safety endpoints, it is difficult to draw firm conclusions concerning efficacy and safety of the anticoagulants studied in the prevention of symptomatic venous thromboembolism in a general ICU population.

Concerning efficacy, we can draw the following conclusions. Low dose UFH significantly reduces all DVT detected by 125I fibrinogen uptake test (FUT), unrelated to symptoms, in general critically ill patients. Low dose UFH significantly reduces all DVT detected by duplex ultra sonography (DUS), unrelated to symptoms, in critically ill medical patients. Efficacy of low dose UFH equals that of enoxaparin in the prevention of all DVT.

**Table 2. Randomized controlled trials in the prevention of venous thromboembolism in the critically ill**

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>POPULATION</th>
<th>NUMBER OF PATIENTS</th>
<th>DIAGNOSIS</th>
<th>PROPHYLAXIS</th>
<th>DVT (ALL)</th>
<th>DVT (PROXIMAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cade 1982</td>
<td>General ICU</td>
<td>119 (total)</td>
<td>FUT</td>
<td>UFH 2 dd 5000 IU sc Placebo sc</td>
<td>13% (29%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Kapoor 1999</td>
<td>MICU</td>
<td>401/390</td>
<td>DUS, V/P</td>
<td>UFH 2 dd 5000 IU sc Placebo sc</td>
<td>44 (11%) 122 (31%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Goldhaber 2000</td>
<td>MICU</td>
<td>325 (total)</td>
<td>DUS</td>
<td>UFH 2 dd 5000 IU sc Enoxaparin 2 dd 30 mg sc</td>
<td>13% (16%)</td>
<td>ns</td>
</tr>
<tr>
<td>Fraisse 2000</td>
<td>Decompensated COPD</td>
<td>108/113</td>
<td>venography</td>
<td>Nadroparin: 3800 aXa IU 1 dd sc (45-70 kg) - 5700 aXa IU 1 dd sc (71-110 kg) Placebo sc</td>
<td>13/84 (15.5%)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

**Legend.** aXa anti-factor Xa; COPD chronic obstructive pulmonary disease; DUS duplex ultrasonography; DVT deep venous thrombosis; FUT 125I fibrinogen uptake test; ICU Intensive Care Unit; MICU medical Intensive Care Unit; nR not reported; nS not significant; PE pulmonary emboli; SICU surgical; sc subcutaneously; V/P ventilation/perfusion scintigraphy

since neither pulmonary angiography nor autopsy were performed.

No significant differences were demonstrated between the incidences of all bleeding complications and major bleeding complications, although there was a trend towards increased major bleeding complications in the nadroparin group (6% versus 3%, p=0.28). It was concluded that nadroparin prophylaxis had a therapeutic benefit with a 45% relative decrease in the incidence of DVT not associated with serious bleeding. HIT was not reported. Mortality rates were similar in both groups.

The majority of cases of DVT (27/37 = 73%) was distal and confined to the calf. Proximal DVT was detected in 3/84 nadroparin treated patients and in 7/85 placebo treated patients (p=1.0). It was not described if the cases of DVT were symptomatic or asymptomatic. DVT was not complicated by PE.

Kapoor and colleagues prospectively investigated the efficacy of UFH 5000 IU sc twice daily versus placebo in the prevention of VTE in critically ill medical patients [7]. They demonstrated a significant reduction of the incidence of DVT in the UFH treated patients (11%) compared with placebo treated patients (31%) (p=0.001). The incidence of PE was significantly reduced in the patients treated with UFH (2.2%) versus the patients treated with placebo (5.1%) (p=0.049). The authors concluded that UFH significantly reduces the incidence of DVT and may reduce the incidence of PE. Bleeding complications, HIT and mortality were not reported.

It was not described if the cases of DVT were proximal or distal nor if they were symptomatic or asymptomatic. DVT was not complicated by PE.

Concerning efficacy, we can draw the following conclusions. Low dose UFH significantly reduces all DVT detected by 125I fibrinogen uptake test (FUT), unrelated to symptoms, in general critically ill patients. Low dose UFH significantly reduces all DVT detected by duplex ultra sonography (DUS), unrelated to symptoms, in critically ill medical patients. Efficacy of low dose UFH equals that of enoxaparin in the prevention of all DVT.
detected by DUS, unrelated to symptoms, in critically ill medical patients. Nadroparin significantly reduces all DVT detected by venography, unrelated to symptoms, in critically ill patients with acute decompensated COPD who require mechanical ventilation, but did not reduce proximal DVT, unrelated to symptoms, in this specific group. UFH may reduce symptomatic PE in critically ill medical patients. The effect of nadroparin in the reduction of symptomatic PE in acute decompensated COPD patients cannot be estimated.

Concerning safety, we can conclude the following. The bleeding risk of UFH versus placebo was not investigated or reported. Safety of low dose UFH equals that of enoxaparin in the prevention of all DVT detected by DUS, unrelated to symptoms, in critically ill medical patients. Nadroparin does not increase the risk of all bleeding or major bleeding in critically ill patients with acute decompensated COPD who require mechanical ventilation.

The risk of development of HIT is not investigated or reported. Mortality is not significantly different between patients treated with UFH or enoxaparin in critically ill medical patients. Mortality is not different between nadroparin or placebo in critically ill patients with acute decompensated COPD who require mechanical ventilation.

The most important limitation of these studies is the fact that the primary efficacy endpoints were DVT detected by imaging techniques and unrelated to symptoms. Considering that most cases of DVT were confined to the calf, clinical relevance can be questioned. Furthermore, in the studies PE was not systematically investigated. Kapoor investigated unexplained respiratory symptoms by V/P scintigraphy and demonstrated a reduction of PE, but without description of localizations. The clinical relevance of subsegmental and peripheral PE can also be questioned. As a consequence, conclusions can not be made on the efficacy and safety of prophylaxis for symptomatic VTE. And thus, no real recommendations can be given for the prevention of VTE in a general ICU population.

Another important feature to take into account is the bioavailability of anticoagulant drugs. Several authors have reported on the decreased bioavailability of subcutaneously administered LMWH in the critically ill as measured by anti-factor Xa activities [11-13]. It is important to realise that these small studies did not study clinical endpoints. At this stage it is unknown how anti-factor Xa activities translate into risks of VTE and bleeding complications.

Finally, the aspect of individualization of venous thromboprophylaxis in critically ill patients balancing thrombosis and bleeding risks as advocated by Geerts deserves full attention [2,14]. However, to date no thrombosis risk score or bleeding risk score is validated for the critically ill.

Table 2.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>PE</th>
<th>BLEEDING (ALL)</th>
<th>MAJOR BLEEDING</th>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cade 1982</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>Kapoor 1999</td>
<td>9 (2.2%)</td>
<td>0.049</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td>20 (5.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldhaber 2000</td>
<td>nr</td>
<td>11% 12%</td>
<td>ns</td>
<td>5% 7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
<td>5% 1%</td>
</tr>
<tr>
<td>Fraise 2000</td>
<td>1 (not possible to test)</td>
<td>25/108 (23%)</td>
<td>0.18 6%</td>
<td>0.28 8</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>18/113 (16%)</td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

In conclusion, it is not possible to answer the question which thromboprophylaxis is the best in the critically ill. Although UFH is the best studied drug for the prevention of VTE detected by imaging techniques, unrelated to symptoms, in the critically ill, it...
is as efficacious and safe as enoxaparin. No conclusions can be drawn on the efficacy and safety of these drugs in real prevention of clinically significant VTE in critically ill patients in a general ICU. And thus, no recommendations can be given for the prophylaxis of VTE in these patients.

Postscriptum

During the writing process of this article, the 8th edition of the ACCP guideline was published [16]. Identical recommendations were now only based on the two published trials [4,6]. No motivation was given about the exclusion of the two other unpublished trials [7,8].

References