How to Safely Prevent Venous Thromboembolism in Severe Trauma Patients
A Novel Protocol to Prevent Trauma-Related Venous Thromboembolism

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Summary
Venous thromboembolism (VTE) is a life-threatening complication after trauma. Several studies have reported VTE prophylaxis using low-molecular-weight heparin; however, there is no consensus for prophylaxis after trauma. This study aimed to assess the efficacy and safety of our new anticoagulation therapy protocol using unfractionated heparin (UFH) plus intermittent pneumatic compression (IPC) to prevent post-traumatic VTE in high-risk trauma patients.

This study enrolled 70 trauma patients who were admitted to the emergency medical center of Nagasaki University Hospital and had Risk Assessment Profile (RAP) scores ≥ 5. After stopping bleeding at the trauma site, all patients received intravenous UFH (10,000 U/day) plus IPC, which was continued for 14 days or until the patients could walk. On days 7 and 14, all patients underwent lower extremity sonography for deep-vein thrombosis screening. VTE incidences between patients with the above intervention and historical controls with IPC alone were compared.

No significant differences in age, sex, and the RAP score were observed between the 105 controls and intervention patients. VTE occurrence was fewer in patients with the intervention (14.3%) than in the controls (28.6%; P = 0.029). No hemorrhagic complications occurred after UFH administration. Multivariable logistic analysis revealed a significant association between the intervention and low incidence of VTE (odds ratio: 0.390; 95% confidence interval: 0.163-0.913; P = 0.030).

Routine UFH administration with IPC may prevent post-traumatic VTE without adverse events.

Key words: Preventable trauma death, Pulmonary embolism, Deep-vein thrombosis, Unfractionated heparin, Prevention

Of the 900,000 patients who develop venous thromboembolism (VTE) annually, including pulmonary thromboembolism (PTE) and deep-vein thrombosis (DVT), in the United States, approximately 300,000 succumb to the disease. As coagulation reactions occur rapidly after trauma, trauma patients can be at a high risk of VTE. In fact, VTE is considered as the leading cause of preventable trauma death. A study has shown that the incidence rate of VTE is high (approximately 5-63%) in trauma patients during hospitalization. Despite standard prophylaxis, the incidence of VTE during hospitalization remains high (up to 15%), particularly in critically ill patients. Based on our experience, approximately 30% of trauma patients who receive prophylaxis using intermittent pneumatic compression (IPC) of the lower extremity develop VTE. VTE occurrence after trauma is not only life-threatening but also results in delayed rehabilitation, requiring frequent imaging and prolonged hospitalization. Therefore, its early detection and prevention are imperative. For prophylaxis, it is necessary to assess the risk of VTE occurrence in trauma patients. The Risk Assessment Profile (RAP) score has been used widely to predict VTE risk after trauma. The RAP score comprises the following four factors: (1) underlying conditions such as obesity or malignancy; (2) iatrogenic factors such as transfusion or operation; (3) injury-related conditions...
factors; and (4) age. A previous study has shown that the VTE risk increases threefold in patients with RAP scores ≥ 5.12)

The American College of Chest Physicians (ACCP) recommends a combination of mechanical and pharmacologic prophylaxis in trauma patients, except for those with severe trauma who cannot adapt to the prophylaxis with IPC owing to lower limb fractures. Low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) has been used for drug prevention, although the recommendation is still weak (Grade 2C).10,11) According to the Japan Circulation Society joint guidelines, regarding fractures of the thigh and lower legs, anticoagulation therapy is considered when early operation or early ambulation cannot be performed. However, no safe and effective method to prevent VTE after severe trauma and pelvic fracture has been established yet. Given the absence of a consensus regarding VTE prevention in severe trauma, a preventive anticoagulant therapy for trauma patients, particularly those at a high risk of VTE, is necessary.

Trauma patients are also at a constant risk of bleeding, suggesting that anticoagulants of VTE prophylaxis need to be administered carefully to these patients. Intravenous UFH has clinical benefits, such as a relatively short half-life (60 minutes), and UFH has an antagonist protamine sulfate, which is used when adverse events due to heparin occur. Moreover, the effects of UFH can be examined by measuring the activated partial thromboplastin time (APTT). On the other hand, the half-life of subcutaneous LMWH is longer, that is, approximately 3.2 hours. Although LMWH promotes lower frequencies of hemorrhagic complications than UFH, protamine sulfate can antagonize only approximately 60% of its effect. Therefore, UFH may be superior in managing severe trauma with a high risk of bleeding. Moreover, a meta-analysis study revealed no significant differences between UFH and LMWH with preventing VTE in patients with acute spinal cord injuries.12) Furthermore, UFH is much cheaper than LMWH. The present study aimed to evaluate the efficacy and safety of our new prophylactic anticoagulation therapy protocol with UFH and IPC in trauma patients at a high risk of VTE.

Methods

Study population: Adult trauma patients who were admitted to the Acute and Critical Care Center of Nagasaki University Hospital from April 2016 to February 2019 and had a RAP score ≥ 5 were included in this study. The exclusion criteria were as follows: severe head trauma requiring invasive interventions, such as craniotomy or placement of intracranial pressure monitor; severe liver or renal dysfunction; a medical history of heparin-induced thrombocytopenia (HIT); severe allergies; pregnant or lactating women; and those with the severest trauma, such as those expected to die within hours or those in a moribund condition.

A total of 161 adult trauma patients were admitted to our hospital during the study period. Among them, 33 patients met the exclusion criteria, 39 patients did not consent to study participation, and two patients had a clinically significant risk of bleeding. One of the patients with high bleeding risk was a 74-year-old male who had marked hematoma around the airway due to a cervical spine fracture and was excluded, given the possibility of airway emergency when bleeding occurred. The other was a 51-year-old male who was excluded because of traumatic subclavian artery dissection and intercostal artery injury. Hence, 87 patients received our prevention protocol. After excluding patients with incomplete data and patients withdrawing without following the protocol, 70 patients were eventually included in the analysis of the intervention group (group I) (Figure 1). We compared the effects of VTE prevention between group 1 and 105 historical controls (group C) who met the aforementioned criteria and received only IPC to prevent VTE from January 2014 to December 2015 at our hospital.

This study complies with the Declaration of Helsinki regarding ethical human investigations, and the Ethics Committee of Nagasaki University Hospital approved the protocol (approval number: 16020803). All patients provided written, informed consent to participate in the study before enrollment.

Prevention protocol: After confirming the absence of active bleeding, a continuous UFH infusion was initiated at a dose of 10,000 units/day together with IPC. UFH administration was continued for up to 14 days or was discontinued when the patient was able to walk alone within 14 days. Blood tests were conducted daily during the first week of the study and when needed thereafter. When the APTT was ≥ 50 seconds, the UFH dose was reduced or the administration was discontinued by the physician in charge. Hypercoagulability after trauma becomes remarkable during the acute phase and resolves within approximately two weeks.13) Given that VTE onset in our previous study was detected on the 12th hospitalization day (median) using our screening criteria, lower extremity vein ultrasonography was performed to assess DVT on the
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7th and 14th days after UFH in the present study. Moreover, VTE occurrence was evaluated by measuring D-dimer levels; when VTE was suspected, ultrasonography and/or contrast-enhanced computed tomography (CE-CT) was performed accordingly. VTE screening was performed according to the method described in our previous study.15 Briefly, our criteria to conduct imaging tests were as follows: (1) ≥ 5 days of hospital stay; (2) increasing D-dimer levels in three measurement days; and (3) D-dimer levels ≥ 15 μg/mL. These screening criteria allowed the diagnosis of asymptomatic VTE in patients, of whom 92% met the criteria within 14 days of hospitalization.16

Statistical analysis: The following variables were included in the analysis: patient background (age and sex); D-dimer and APTT levels at admission; the RAP score; the Injury Severity Score (ISS), which is a score to evaluate the severity of trauma;17 and the start date and duration of UFH administration in group I.

Continuous and categorical data were presented as the medians (interquartile range) and proportions and were analyzed using the Wilcoxon rank sum test and Fisher’s exact test, respectively. Moreover, univariate regression analyses were performed, from which independent variables were extracted (P < 0.20) and included in multivariable logistic regression analysis. All statistical analyses were performed using JMP Pro 14 (SAS Institute, Inc., NC, USA), with the significance level set at 0.05.

Results

The characteristics of the patients in groups C (n = 105) and I (n = 70) are shown in Table I. Between groups C and I, age [67 (57.5-77.0) versus 64 (55.5-74.0) years, respectively, P = 0.230], sex (proportion of female, 36.2% versus 24.3%, respectively, P = 0.134), RAP scores [10 (8.0-14.0) versus 11 (9.0-14.0), respectively, P = 0.061], ISS [24 (16.0-29.5) versus 24.5 (17.0-33.3), respectively, P = 0.440], and IPC period [18 (10.0-31.0) versus 16 (10.0-22.5) days, respectively, P = 0.230] were comparable. Among the four factors in the RAP score, the score of iatrogenic factors was significantly lower in group I (14.3%) than in group C (28.6%; P = 0.029; Figure 2). The number of patients diagnosed by CE-CT or lower extremity vein ultrasonography was as

Table I. Characteristics of the Control and Intervention Groups

<table>
<thead>
<tr>
<th></th>
<th>Control group (Group C)</th>
<th>Intervention group (Group I)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>105</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 (57.5-77.0)</td>
<td>64 (55.5-74.0)</td>
<td>0.230</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>38 (36.2)</td>
<td>17 (24.3)</td>
<td>0.134</td>
</tr>
<tr>
<td>RAP score</td>
<td>10 (8.0-14.0)</td>
<td>11 (9.0-14.0)</td>
<td>0.061</td>
</tr>
<tr>
<td>Underlying conditions</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.840</td>
</tr>
<tr>
<td>Iatrogenic factors</td>
<td>0 (0-3)</td>
<td>2 (0-4)</td>
<td>0.034</td>
</tr>
<tr>
<td>Injury-related factors</td>
<td>6 (4-8)</td>
<td>7 (4-9)</td>
<td>0.136</td>
</tr>
<tr>
<td>Age</td>
<td>3 (2-4)</td>
<td>3 (2-3)</td>
<td>0.190</td>
</tr>
<tr>
<td>ISS</td>
<td>24 (16.0-29.5)</td>
<td>24.5 (17.0-33.3)</td>
<td>0.440</td>
</tr>
<tr>
<td>Duration of IPC (days)</td>
<td>18 (10-31)</td>
<td>16 (10-22.5)</td>
<td>0.230</td>
</tr>
<tr>
<td>Duration of hospitalization (days)</td>
<td>27 (18.5-42.5)</td>
<td>23.5 (15.8-35.0)</td>
<td>0.191</td>
</tr>
<tr>
<td>The hospital day of starting UFH (days)</td>
<td>N/A</td>
<td>5 (3.0-7.0)</td>
<td>-</td>
</tr>
<tr>
<td>Duration of UFH administration (days)</td>
<td>N/A</td>
<td>10 (6.5-14.0)</td>
<td>-</td>
</tr>
<tr>
<td>D-dimer on admission (μg/mL)</td>
<td>34.5 (8.8-91.9)</td>
<td>29.0 (7.2-60.4)</td>
<td>0.175</td>
</tr>
<tr>
<td>APTT on admission (seconds)</td>
<td>26.7 (24.3-31.7)</td>
<td>27.0 (24.2-30.4)</td>
<td>0.926</td>
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<tr>
<td>APTT during UFH administration (seconds)</td>
<td>N/A</td>
<td>30.1 (28.4-34.8)</td>
<td>-</td>
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</tbody>
</table>

Values are shown as the medians (interquartile range) or n (%). RAP score indicates Risk Assessment Profile score; ISS, Injury Severity Score; IPC, intermittent pneumatic compression; APTT, activated partial thromboplastin time; and UFH, unfractionated heparin.

Figure 2. Comparison of VTE development between the intervention and historical control groups. The intervention group had a significantly lower incidence of VTE than the historical control group (P = 0.029).
follows: one (10%) versus nine (90%) in group I, respectively, and 26 (87%) versus four (13%) in group C, respectively. The diagnosis dates in groups C and I were 11 (7-16) and 16 (13.75-18) hospital days, respectively (P = 0.063).

The results of the univariate logistic regression analysis are presented in Table II. The presence of intervention (odds ratio (OR): 0.417; 95% confidence interval (CI): 0.189-0.920; P = 0.030), sex (OR of female to male: 3.778; 95% CI: 1.809-7.889; P < 0.001), age (OR: 1.056; 95% CI: 1.023-1.089; P = 0.001), RAP score (OR: 1.149; 95% CI: 1.059-1.244; P < 0.001), ISS (OR: 1.036; 95% CI: 1.004-1.069; P = 0.026), and D-dimer levels on admission (OR: 1.005; 95% CI: 1.001-1.010; P = 0.027) were significantly associated with VTE occurrence. Four significant factors determined by univariate analysis (P < 0.20), that is, the presence of intervention, sex, the RAP score, and ISS, were used for multivariable logistic regression analysis. Age is a parameter of the RAP score, whereas D-dimer levels are related to ISS, suggesting that these variables are confounding factors, and therefore, were not used for multivariable analysis. The results identified that the presence of intervention, sex, and the RAP score were significant factors for VTE occurrence (Table II).

In group I, the initiation of UFH administration was significantly delayed in patients with VTE than in those without VTE [6.5 versus 4 median days, respectively; P = 0.04]. The UFH dose was adjusted in one patient whose APTT value increased to 103.7 seconds on the 10th day and then decreased to 43.9 seconds on the 14th day. No patient developed hemorrhagic complications. VTE was subsequently treated via the intake of direct oral anticoagulants. No patient developed symptomatic VTE during hospitalization after anticoagulant therapy. In addition, 60 patients without DVT did not present with symptomatic VTE during hospitalization.

**Discussion**

We developed a prevention protocol based on the concept of convenience and ease of use so that anyone can use it without specific knowledge or skills. The present study showed that our new protocol for VTE prophylaxis, which involves the routine administration of UFH with IPC, resulted in a lower incidence of VTE in trauma patients with a RAP score ≥ 5 than the use of IPC alone. In addition, multivariable logistic regression analysis showed that the prevention protocol significantly inhibited VTE occurrence without any clinically relevant bleeding.

Trauma itself is a risk factor for VTE. Winchell et al. showed that trauma patients with severe fractures and an Abbreviated Injury Scale ≥ 3 or ISS ≥ 16 were strongly associated with PTE development (OR > 10). However, given that trauma also increases bleeding from fracture sites and head or internal organ injuries, the balance between VTE and bleeding risks should always be considered before anticoagulation prophylaxis, and treatment should be tailored to each individual case. Indeed, the ACCP guidelines have also proposed maintaining a balance between VTE suppression through anticoagulation and serious bleeding risk.

LMWH has been recommended as a prophylactic anticoagulant not only for critically ill patients but also for trauma patients. However, no studies have been dedicated to trauma. The ACCP guidelines recommend adding LMWH or UFH to IPC in patients with trauma, unless a lower extremity fracture exists, as Grade 2C. This indicates that the “recommended” prevention method of VTE for trauma patients has not yet been established. Therefore, a clinically useful VTE prophylaxis method is warranted, which has been undertaken in this study.

Subcutaneous LMWH injections can be an effective prevention method. However, its effects cannot be antagonized completely when hemorrhagic complications occur, as mentioned above. In addition, LMWH has a higher bioavailability (90%) than UFH (29%), with advantages such as predictable pharmacokinetics and the non-requirement of APTT monitoring. Conversely, APTT monitoring is impossible, indicating that its effect is not clinically evaluated even in patients at risk of bleeding during the acute phase. As our subjects were trauma patients who were also at risk of bleeding, we chose continuous UFH infusion rather than subcutaneous LMWH. Moreover, UFH can be used regardless of renal function, although other anticoagulants require dose adjustments based on renal function. In Japan, in the field of orthopedics, patients with health insurance can receive prophylaxis treatment with anticoagulants for VTE up to 14 days. Therefore, the maximum duration for UFH administration was set to 14 days. Although UFH was administered subcutaneously twice or thrice daily (10,000 or 15,000 units/day) in previous studies, we continuously administered UFH intravenously at a dose of 10,000 units/
day in this study because it had a stable effect, could be manipulated easily, and caused less pain in patients.\(^{6,7}\) Subsequently, the APTT during UFH administration was not prolonged drastically with the dose used in this protocol (median value: 30.1 seconds). Leyvraz, et al. reported that the APTT level controlled between 31.5 and 36 seconds could efficiently prevent VTE in patients with total hip arthroplasty.\(^{10}\) Compared with the previous study, the subjects in our study were severe trauma patients at a much higher risk of bleeding. Therefore, we set the dose of UFH to 10,000 units/day and we believe that this protocol may be advantageous in terms of risk benefits.

**Limitations:** This was a single-center study using a small patient cohort. Although CE-CT confirmed the absence of thrombi on admission, UFH intervention was initiated only after 5 days. Previous studies have reported that thrombus formation tended to occur approximately 48-96 hours after trauma,\(^{19,20}\) and a delay in prophylaxis beyond thrombus formation tended to occur approximately 48-96 hours after trauma,\(^{19,20}\) and a delay in prophylaxis beyond 4 days is associated with a threefold greater risk of VTE.\(^{21}\) In addition, some patients did not undergo CE-CT of the lower legs. Therefore, VTE might have already developed before intervention was provided to group I. UFH initiation was delayed in patients with VTE, which might be attributed to conditions requiring frequent surgeries or progressive anemia. As specific criteria and management for active bleeding were not defined in the present study, the decision to start UFH administration depended primarily on the judgment of the attending physician. The assessment of the balance between VTE and the risk of bleeding appears to contribute to the delay, which may vary widely among attending physicians. The delay of UFH administration may have some effects on VTE occurrence. In our prevention protocol, a fixed dose (10,000 units/day) of UFH was administered to the patients regardless of their body weight or the levels of APTT during the infusion. As this study aimed to develop a simple prevention protocol for clinicians as mentioned above, we used this fixed dose. In group C, CE-CT was performed and evaluated only in those patients who met our screening criteria of post-traumatic VTE, and not all patients underwent lower extremity vein ultrasonography. Therefore, VTE incidence may have been underestimated in group C. Nevertheless, VTE incidence was significantly lesser in group I than in group C, suggesting that our prevention protocol was effective. Our investigation was only limited to a single hospital; therefore, long-term outcomes after discharge are uncertain. However, the median duration of hospitalization in group I was 22 days, allowing for sufficient acute phase observation.

**Conclusion**

The present study demonstrated that routine UFH administration after admission can prevent post-traumatic VTE without adverse events in patients with severe trauma. We believe that this study can be a milestone; however, further studies with large cohorts are needed to confirm our results.

**Acknowledgments**

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**Disclosure**

**Conflicts of interest:** The authors declare no conflict of interest.

**References**