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ORIGINAL

Standard subcutaneous dosing of unfractionated heparin for venous thromboembolism prophylaxis in surgical ICU patients leads to subtherapeutic factor Xa inhibition

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Abstract *Purpose:* To assess coagulation status and factor Xa inhibition in surgical intensive care unit (ICU) patients administered prophylactic unfractionated heparin for venous thromboembolism (VTE) prophylaxis. *Methods:* We conducted a randomized, single-blind study at a tertiary academic medical center. Included were patients 18 years and older admitted to the surgical ICU directly after major abdominal surgery. Exclusion criteria included significant bleeding risk, preoperative anticoagulation, or history of heparin-induced thrombocytopenia. Patients were randomized to two regimens for VTE prophylaxis: standard of care unfractionated heparin, 5,000 units subcutaneously three times daily (SQH) versus unfractionated heparin via intravenous infusion, titrated to an activated partial thromboplastin time of 40–45 s (IVH). Blood samples were taken prior to surgical incision on day 0 and daily for 5 days after surgery. Samples were analyzed for factor Xa inhibition and viscoelastic whole blood clotting parameters (Sonoclot analyzer). *Results:* A total of 50 patients were randomized to either SQH or IVH. The majority of patients had cancer. Patients in the SQH group had no detectable peak anti-factor Xa (aFXa) activity for 5 days after surgery, while patients in the IVH group had statistically elevated levels compared to the SQH group on days 3–5. SQH patients demonstrated a hypercoagulable profile on Sonoclot, while IVH patients displayed a normal profile. *Conclusions:* Standard of care subcutaneous dosing of unfractionated heparin for VTE prophylaxis in surgical ICU patients leads to subtherapeutic levels of factor Xa inhibition.

Keywords Intensive care unit · Surgery · Cancer · Anticoagulation · Venous thromboembolism · Prophylaxis · Sonoclot

Introduction

Venous thromboembolism (VTE) comprises two main diagnoses, deep venous thrombosis (DVT) and pulmonary embolism. Surgical intensive care unit (ICU) patients are at high risk of developing VTE due to a high prevalence of risk factors, including the surgical procedure itself, central venous catheterization, mechanical ventilation,

immobility, sepsis, increasing age, obesity, and cancer [1–3].

The two common pharmacologic options for VTE prophylaxis in surgical ICU patients are subcutaneous unfractionated or low molecular weight heparin (LMWH) [1]. Large retrospective analyses [4] and a recently published prospective trial [5] indicate that low molecular weight and unfractionated heparin are equally effective for the prevention of DVT in ICU patients, although LMWH may be better at preventing pulmonary embolism. Emerging data also supports the use of factor Xa inhibitors, such as fondaparinux, in selected ICU patients [6].

Even when standard of care subcutaneous prophylaxis is administered routinely, proximal DVT rates in ICU patients range from 6 to 44% [7, 8]. While failure of prophylaxis may be due to a variety of different mechanisms, several studies in ICU patients suggest that subtherapeutic dosing of prophylaxis may be contributory. An observational study found that a high proportion of ICU patients had subtherapeutic anti-factor Xa (aFXa) levels after receiving standard prophylactic doses of the LMWH enoxaparin [9, 10]. However, it is unknown if standard prophylactic dosing of subcutaneously administered unfractionated heparin, a common alternative to LMWH, is similarly subtherapeutic in ICU populations.

This study aims to assess the dosing adequacy of standard of care subcutaneous unfractionated heparin, which has not been assessed in postsurgical ICU patients. We assess dosing adequacy via measurement of aFXa, for which the range used for VTE prophylaxis is 0.1–0.3 IU/ml. We compare it to a low-dose unfractionated heparin infusion, which is commonly used by surgical oncologists at our institution. As a large proportion of our surgical ICU patients have epidural catheters placed for postoperative pain control, we chose not to include comparison arms for LMWH or fondaparinux, which are contraindicated in patients with epidural catheters due to the risk of epidural hematoma.

Materials and methods

A prospective, single-blind randomized study at a tertiary care academic medical center was conducted. We obtained ethics approval from the Colorado Multiple Institutional Review Board. A signed consent was obtained from each study patient or their designated proxy in general surgery clinic before the elective surgical procedure.

Included were patients over the age of 18 admitted to the surgical ICU directly after major abdominal surgery. Excluded were patients with a lower-extremity DVT on day 0 screening ultrasound, high risk of bleeding, history of heparin-induced thrombocytopenia (HIT), currently anticoagulated, or receiving anti-platelet agents other than low-dose aspirin. High risk of bleeding was defined as platelet count less than 30,000/μl, multi-system trauma, severe hepatic disease, or intracranial/gastrointestinal bleeding within the past 3 months.

Treatment

Consented patients were randomized on the morning of surgery. Treatment assignments were contained inside consecutively numbered, opaque envelopes each listing one in a series of randomly generated allocations. Patients, research nurses, and managing clinicians were not blinded to patient allocation, but the ultrasonographers were blinded.

The two treatment arms were subcutaneous heparin (SQH) and intravenous heparin (IVH). All heparin was porcine in origin (Hospira). The SQH group received 5,000 units of unfractionated heparin subcutaneously three times a day, while IVH patients received a heparin infusion titrated to an activated partial thromboplastin time (aPTT) of 40–45 s (normal range 23.4–34.8 s). Bilateral sequential compression devices were used on all patients. Protocol treatment was started postsurgically within 24 h of admission to the surgical ICU, and continued for a maximum of 5 days. For patients receiving IVH, the infusion was started at 300 units/h without a bolus dose. aPTTs were measured every 6 h, and the infusion rate adjusted. If an IVH patient had an indwelling epidural that required removal, the heparin infusion was stopped. The epidural catheter was removed when the aPTT normalized and the study infusion was resumed 2 h later.

Monitoring

All patients had daily hematocrit and platelet count measured during study treatment. If the platelet count dropped by more than 50% from the previous value, heparin treatment was stopped and a serological assay to detect anti-platelet factor 4 antibodies was ordered to rule out HIT. Heparin was restarted if a diagnosis of HIT was excluded. Patients were monitored daily for major bleeding events. Major bleeding was defined as clinically evident hemorrhage associated with a hemoglobin decrease of at least 2 g/dl, or that led to a transfusion of at least 2 units of whole blood or packed red cells outside of the perioperative period (time from the start of the surgery or procedure and up to 12 h after), or that was intracranial, retroperitoneal, or into a prosthetic joint.

Plasma markers

“Day 0” baseline labs were drawn in the operating room, before surgical incision. Subsequent daily lab draws were timed 4 h after SQH administration to coincide with peak

blood levels of heparin [10–12]. Citrated and heparinized plasma was stored at −80°. aFXa activity and antithrombin were measured in citrated samples using chromogenic assays (Coatest Heparin Assay, product no. K255539 and Coamatic Antithrombin Assay, product no. K821991, both from Chromogenix, Lexington, MA). Standard curves were generated using normal human plasma standardized for these activities (Hemosil, Instruments Laboratory, Lexington, MA).

Measurement of whole blood coagulation profile

Whole blood viscoelastic clotting parameters were measured in citrated blood using the Sonoclot Analyzer (Sienco, Inc., Arvada, Colorado). Samples were drawn at the same time points as the plasma markers.

Screening for lower-extremity DVT

Screening for lower-extremity compression Doppler ultrasound was conducted on days 5 and 10 after surgery. Any patient with confirmed DVT was excluded from the study and treated according to standard of care. Ultrasonographers were blinded to the study treatment.

Statistical analysis

The primary end point was peak aFXa levels. We calculated that 50 patients would be needed to detect an absolute difference of 20% in aFXa levels between the groups, assuming a power of 80% and a significance level of 5%. Continuous variables were compared using two-way ANOVA and Mann–Whitney post-tests. Proportions were compared using Fisher's exact test. A p value of less than 0.05 was considered significant. The intent-to-treat population was defined as all patients who were randomized and received at least one dose of study drug. The per-protocol population was defined as patients who received any study drug within the 8 h prior to blood draw.

Results

Patients

Seventy-six patients were consented at their preoperative visit in surgery clinic. Twenty-six patients were not randomized secondary to no admission to the ICU (20), withdrawal of consent (1), cancelled surgery (1), or newly acquired exclusion criteria (4). Fifty patients were randomized, 25 to SQH and 25 to IVH. No patients were lost to follow-up.

The baseline characteristics of the two study groups are described in Table 1. Both groups were predominantly male and carried a cancer diagnosis. There was no statistically significant difference in surgical procedures between groups. A total of 28% required postoperative mechanical ventilation and 14% required postoperative vasopressors. The mean APACHE II score was approximately 13 in both groups. The percentage of study days that patients received drug per protocol was 94% for the SQH group and 90% for the IVH group.

Laboratory studies

Peak aFXa activity was analyzed in the per-protocol population. Mean times between previous SQH dose and blood draws ranged between 3.9 and 6.6 h (Fig. 1). aFXa activity was predominantly undetectable in patients who received SQH according to protocol (Fig. 1) on days 1–5 after surgery. Patients who received IVH according to protocol had a statistically significant increase of aFXa activity on days 3–5 after surgery when compared to patients in the SQH group.

Heparin administration in the IVH group was titrated to a target aPTT of 40–45 s (Fig. 2a); however, there was no statistical difference in mean daily aPTT between groups. The average IVH dose on day 5 after surgery (at which mean aFXa levels were within therapeutic range) was approximately 15 IU/kg/h, compared to 8.4 IU/kg/h for patients receiving SQH (Fig. 2b).

Heparin anticoagulation depends on heparin binding to and catalytically activating antithrombin. In order to assess if antithrombin deficiency was present in this postsurgical population, we measured antithrombin levels in study patients for 5 days after surgery. There were no differences in mean antithrombin levels between SQH and IVH groups at any time point, and the majority of patients had antithrombin levels over 40%.

Sonoclot analysis, a measure of whole blood coagulation, was used to compare activated clotting times and clot rates were compared between groups (Fig. 3). Activated clotting times represent the time elapsing from addition of glass bead activator to clot initiation, while clot rate indicates the speed of thrombin generation. Statistically significant differences were observed in activated clotting times and clot rate between treatment groups. In the intent-to-treat population, activated clotting times were prolonged and clot rates shortened in the IVH group when compared to the SQH group ($F = 10.56$; p value $= 0.001$ and $F = 2.726$; $p = 0.044$) (Fig. 3); the direction and statistical significance of these results were maintained in the per-protocol analysis (data not shown). Activated clotting times and clot rates for the IVH group were within the normal range, while the SQH group showed evidence of hypercoagulability as shown by shortened activated clotting times and increased clot rates when compared to the normal range.

No patients in either study group developed de novo proximal DVT during the 10-day screening period.

Table 1 Baseline characteristics of the intention-to-treat population

	SQH ($N = 25$)	IVH ($N = 25$)
Baseline characteristics of intent-to-treat population		
Age (years)	61 ± 9.4	62 ± 8.3
Male sex, no/total no. (%)	13/25 (52%)	15/25 (60%)
APACHE II score[a]	13.1 ± 4.6	12.9 ± 5.2
Cancer diagnosis	25/25 (100%)	19/25 (74%)
Body mass index[b]	28.9 ± 6.5	26.4 ± 4.4
VTE, personal history	1/25 (4%)	1/25 (4%)
Surgical type		
Hepato-pancreatico-biliary	5/25 (20%)	9/25 (36%)
Esophago-gastric	4/25 (16%)	6/25 (24%)
Colorectal	3/25 (12%)	2/25 (8%)
Abdominal debulking with or without intraperitoneal chemotherapy	11/25 (44%)	4/25 (16%)
Sarcoma resection	2/25 (8%)	0/25 (0%)
Other	0/25 (0%)	4/25 (16%)
Life support (no./total no.) (%)		
Mechanical ventilation[c]	7/25 (28%)	7/25 (28%)
Vasopressors[c]	4/25 (16%)	3/25 (12%)
% of study days received heparin per protocol	127/135 (94%)	121/135 (90%)
Safety outcomes		
HIT tests sent[d]	2/25 (0.02–0.23)	2/25 (0.02–0.23)
HIT tests positive[d]	0/2	0/2
Major hemorrhage[e]	0/25 (0–0.13)	0/25 (0–0.13)
Severe adverse events[d]	0/25 (0–0.13)	1/25 (0.01–0.19)
Indwelling epidural for postoperative pain	15/25	11/25
Epidural hematoma[d, f]	0/15 (0–0.21)	0/11 (0–0.26)

Plus-minus values are means ± SD

[a] APACHE (Acute Physiology and Chronic Health Evaluation) II score ranges from 0 to 71, with higher scores indicating more severe disease

[b] Body mass index is the weight in kilograms divided by the square of the height in meters

[c] These categories were satisfied if the patient was on mechanical ventilation or vasopressor therapy at any time during the first 5 postoperative days. Safety outcomes: proportions and 95% confidence intervals are shown

[d] Assessed during duration of hospital stay

[e] Assessed if within 24 h of receiving study drug

[f] Assessed if patient had an in-dwelling epidural for postoperative analgesia at any time during their hospital stay

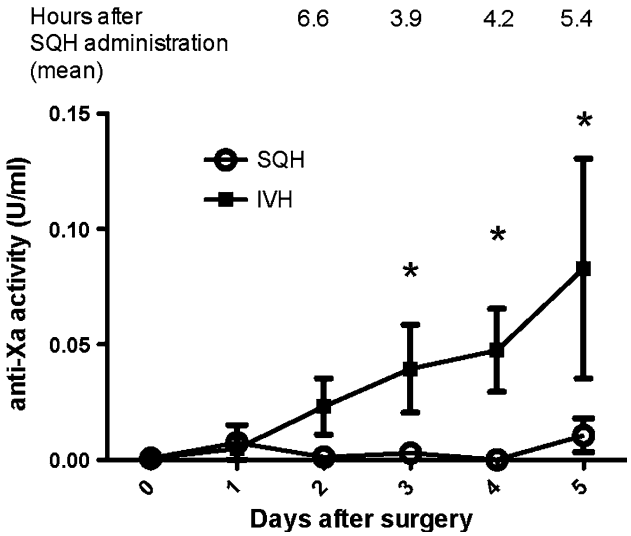

Fig. 1 Peak aFXa activity in per-protocol analysis. Values are plotted as mean ± SEM. SQH patients had largely undetectable aFXa activity, while IVH patients had statistically elevated levels of aFXa activity when compared to SQH patients on the same day. *$p < 0.05$, two-tailed Mann–Whitney test

Adverse events were carefully monitored (Table 1). No major bleeding was observed in either study group. Serotonin-release assays to test for HIT were conducted in 2/25 (8%) of SQH and 2/25 (8%) of IVH patients; no cases were positive in either group. Over half of the patients had epidural catheters for postoperative pain control, and none of these patients developed epidural hematomas. Severe adverse events were reported to the Data Safety Monitoring Board for no patients in the SQH group and 1 patient in the IVH group. After review of this event, in which the patient developed respiratory distress from an acute pulmonary embolism, the Data Safety Monitoring Board deemed it unrelated to the study drug since the patient was receiving more aggressive VTE prophylaxis than the recommended standard of care.

Discussion

All the patients in this trial underwent major abdominal surgery and were admitted to the surgical ICU, and the

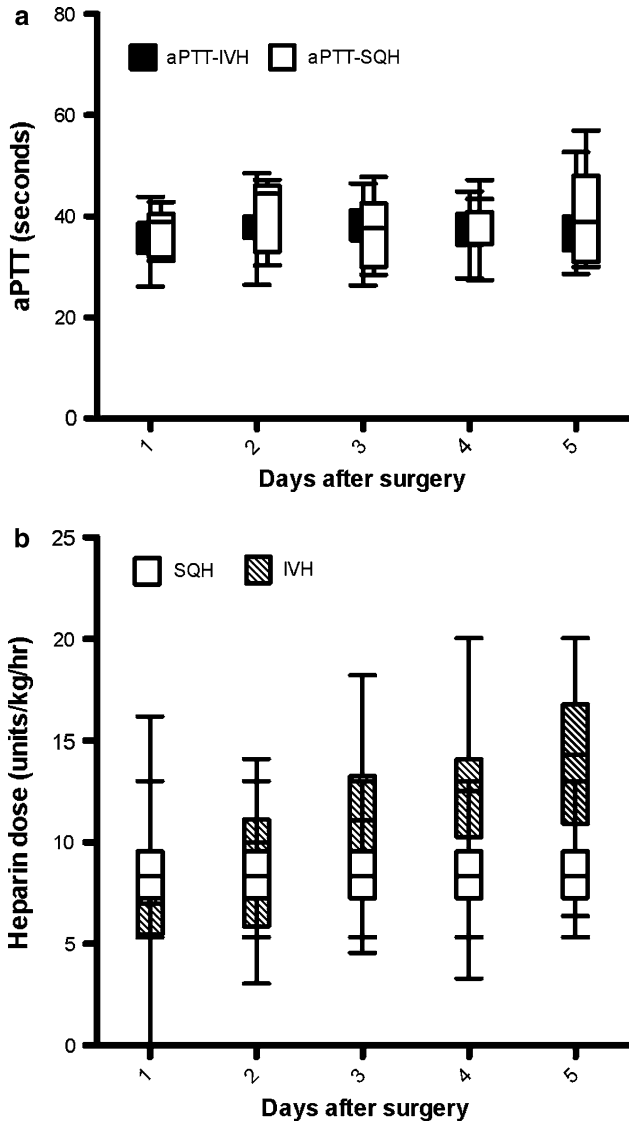

Fig. 2 Average aPTT and heparin dosing in per-protocol analysis. **a** aPTT in IVH and SQH groups, plotted as box and whisker quartiles. **b** Heparin dose in SQH and IVH patients. A large variation in heparin dosing was seen in the IVH group patients, although the aPTT varied very little

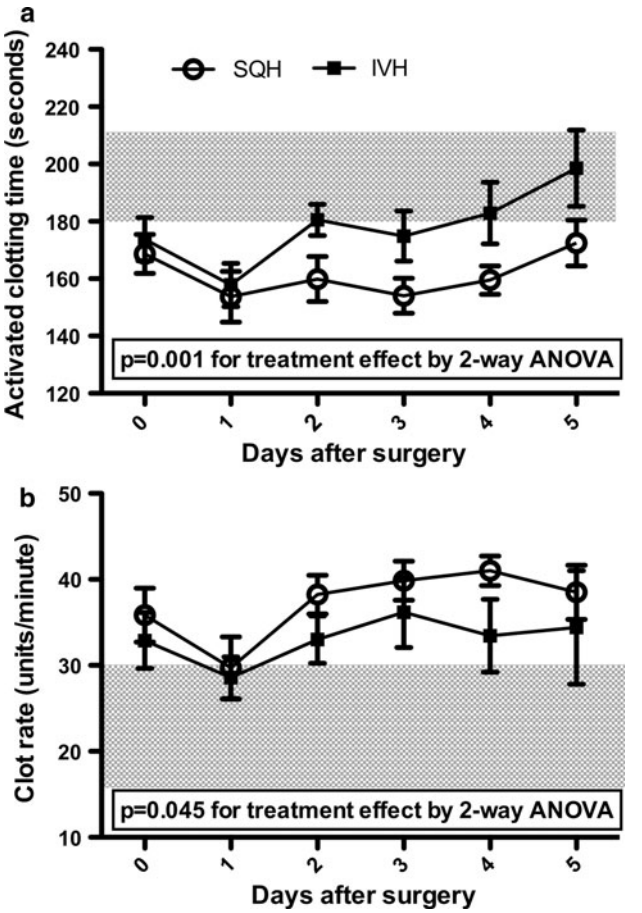

Fig. 3 Whole blood coagulation parameters in per-protocol analysis. **a** Activated clotting time in seconds (mean ± SEM) and **b** clot rate in gel units/min (mean ± SEM) were measured after addition of a glass bead activator. Normal ranges are depicted in *gray*. SQH patients displayed a hypercoagulable response after major surgery as evidenced by shortened activated and increased clot rate. In IVH patients, these hypercoagulable changes were largely attenuated by day 5 after surgery

majority of them had cancer. There is a widely acknowledged need for evidence-based guidelines for VTE prophylaxis in surgical ICU patients. Despite the high-risk status of these patients, high-quality evidence regarding optimal VTE prophylaxis is lacking. Only three randomized prospective trials have been performed in ICU patients, and none of these trials were performed in a surgical population [13–15]. This is important, since autopsy data suggests that VTE may be responsible for 16% of in-hospital deaths in surgical patients [16].

This study adds to the current literature by demonstrating in a surgical population that the recommended dosage of unfractionated SQH yields subtherapeutic levels of aFXa activity. SQH patients displayed a hypercoagulable whole blood coagulation profile. In contrast, this hypercoagulable profile was corrected in IVH patients. As there was no placebo control group in this trial, no conclusions can be made about whether SQH had any anticoagulant effect.

A variety of ICU conditions, including sepsis, multiple organ dysfunction, high body weight, peripheral edema, and vasopressor requirement, have all been identified as risk factors for subtherapeutic anticoagulation with subcutaneously administered drugs [9, 17–19]. By corollary, peripheral vasoconstriction from hypovolemia, hypotension, hypothermia, or sepsis may contribute to decreased absorption of subcutaneous drugs such as unfractionated heparin.

There are several limitations to this study. First, this study involved a small number of patients. This resulted

in chance imbalances in several patient characteristics, including gender, cancer diagnosis, and vasopressor use. While the magnitudes of these differences were small, there is a chance these imbalances may cumulatively render the SQH group more prone to hypercoagulable state than the IVH group. However, the basic observation of this study—that SQH yields subtherapeutic aFXa levels in surgical ICU patients—is likely unaffected by the observed differences.

Viscoelastic point-of-care devices such as the Sonoclot have found increasing use in guiding pro- and anticoagulant therapy [20], particularly in the setting of cardiac and hepatic surgery. However, there is limited data available regarding the use of the Sonoclot analyzer for the detection of hypercoagulable state. The Sonoclot findings presented here may not be comparable to results obtained with more widely available viscoelastic tests such as the thromboelastogram or rotation thrombelastometry.

This small study was not powered to detect differences in VTE rates between groups. Therefore, conclusions about the relative efficacy of IVH vs. SQH for in-hospital VTE prophylaxis cannot be drawn at this time. The drawbacks of an IV heparin infusion for VTE prophylaxis include increased laboratory costs and nursing time. Therefore, it would be prudent to study in a patient population at very high risk of VTE, for whom the possible benefits may outweigh the costs.

Conclusions

SQH administration in surgical ICU patients following major abdominal operations did not lead to measurable aFXa activity for the first 5 postoperative days and did not correct the postoperative hypercoagulable state. The main implication of this study is that current subcutaneous dosing schedules of unfractionated heparin for VTE prophylaxis may be inappropriate in postsurgical ICU patients with cancer. Studies are needed to test the efficacy of higher doses of heparin, administered either subcutaneously or intravenously, for the prevention of VTE in this patient population.

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Conflicts of interest None.

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