Adequacy of Fixed-Dose Heparin Infusions for Venous Thromboembolism Prevention after Microsurgical Procedures

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J Reconstr Microsurg

Abstract

Background In microvascular surgery, patients often receive unfractionated heparin infusions to minimize risk for microvascular thrombosis. Patients who receive intravenous (IV) heparin are believed to have adequate prophylaxis against venous thromboembolism (VTE). Whether a fixed dose of IV heparin provides detectable levels of anticoagulation, or whether the "one size fits all" approach provides adequate prophylaxis against VTE remains unknown. This study examined the pharmacodynamics of fixed-dose heparin infusions and the effects of real-time, anti-factor Xa (aFXa) level driven heparin dose adjustments.

Methods This prospective clinical trial recruited adult microvascular surgery patients placed on a fixed-dose (500 units/h) unfractionated heparin infusion during their initial microsurgical procedure. Steady-state aFXa levels, a marker of unfractionated heparin efficacy and safety, were monitored. Patients with out-of-range aFXa levels received protocol-driven real-time dose adjustments. Outcomes of interest included aFXa levels in response to heparin 500 units/h, number of dose adjustments required to achieve goal aFXa levels, time to reach goal aFXa level, and 90-day clinically relevant bleeding and VTE.

Results Twenty patients were recruited prospectively. None of 20 patients had any detectable level of anticoagulation in response to heparin infusions at 500 units/h. The median number of dose adjustments required to reach goal level was five, and median weight-based dose to reach goal level was 11.8 units/kg/h. Real-time dose adjustments significantly increased the proportion of patients with in-range levels (60 vs. 0%, $p = 0.0001$). The 90-day VTE rate was 5% and 90-day clinically relevant bleeding rate was 5%.

Conclusions Fixed-dose heparin infusions at a rate of 500 units/h do not provide a detectable level of anticoagulation after microsurgical procedures and are insufficient for the majority of patients who require VTE prophylaxis. Weight-based heparin infusions at 10 to 12 units/kg/h deserve future study in patients undergoing microsurgical procedures to increase the proportion of patients receiving adequate VTE prophylaxis.

Keywords
- heparin
- plastic surgery
- microvascular surgery
- venous thromboembolism
- anti-factor Xa

received
December 20, 2017
accepted after revision
March 22, 2018

DOI https://doi.org/10.1055/s-0038-1655735.
ISSN 0743-684X.

Microvascular procedures, including free flap reconstructions, replantantion, and revascularizations, are commonly used in head, neck, breast, and extremity surgery with estimated success rates of 80 to 99%.[1,2] While failure rates are low, flap or replant loss is most commonly caused by thrombosis at the anastomoses.[3,4] Anticoagulant and antiplatelet agents are often administered perioperatively to help minimize the risk for microvascular thrombosis.[5] Such regimens may include aspirin, low-molecular-weight heparin, unfractionated heparin administered subcutaneously and intravenously, and/or dextran.[5] Protocols vary from institution to institution with scarce data to support the use of any particular regimen, although it is reported that 96% of surgeons utilize a chemical prophylaxis regimen for microvascular patency in this patient population.[2,6]

Patients who require microsurgical procedures have recognized risk factors for venous thromboembolism (VTE), including concurrent traumatic injury, need for multiple and lengthy operative procedures, central venous access, and cancer, among others.[7] The presence of multiple risk factors places microsurgical patients among those at highest risk for VTE, in some cases more than 10%.[7] Chemical prophylaxis is known to decrease VTE risk by 50% when provided to plastic surgery patients at high risk for VTE.[8] Some microsurgery patients are started on low-dose (500 units/h), untitrated heparin drips during surgery, in response to an intraoperative finding or event such as friable or delaminated vessels, proximity to the zone of injury, radiation injury, and/or intraoperative microvascular thrombosis. Fixed-dose unfractionated heparin infusion is a strategy that is widely used to keep microvascular anastomoses patent. The low-dose heparin infusion is presumed to provide adequate anticoagulant effect to minimize VTE risk as well, and surgeons generally do not provide additional chemical prophylaxis against VTE.

At our institution, heparin infusions are initiated with or without a bolus dose of 3,000 units and maintained at a fixed dose of 500 units/h, with no monitoring of partial thromboplastic time or anti-factor Xa (aFXa). No additional VTE prophylaxis is provided as the patient is receiving chemical (heparin and aspirin) and mechanical (sequential compression devices) prophylaxis. This is a learned practice based on our clinical experience and prior residency and fellowship training at leading microsurgery institutions.

The goal of this study was to critically examine the extent of anticoagulation provided by a fixed-dose, unfractionated heparin infusion at 500 units/h using aFXa levels, and to determine whether unfractionated heparin infusions provide adequate anticoagulation to minimize risk for VTE. This study also examined the impact of a heparin titration protocol, guided by aFXa level, and the weight-based unfractionated heparin dose typically required for adequate VTE prevention after microsurgical procedures.

Methods

This study was funded through a competitive research grant from the Division of Plastic Surgery at the University of Utah. The study received approval from the University of Utah Institutional Review Board (IRB_00095514) and was registered on ClinicalTrials.gov prior to recruitment (NCT02970032).

Eligible patients were adults (age: 18 years or older) undergoing microsurgical procedures at the University of Utah Hospital and Huntsman Cancer Hospital. During the microvascular procedure, the attending surgeon determined the patient's need for a fixed-dose heparin infusion, which was started with or without a 3,000-unit bolus and maintained at 500 units/h based on our institutional standard of care. Intravenous (IV) heparin infusion is initiated on a case-by-case basis in approximately 15% of our microvascular reconstruction cases. Common reasons for use include close proximity to the zone of injury and on-table microvascular thrombosis.

Study investigators did not dictate any portion of the patient's care intraoperatively, but rather enrolled patients who were placed on the study-specific regimen by their attending surgeon. Eligible patients were approached by one of two investigators (C.M.B. or C.J.P.). Informed consent was typically obtained on the morning after surgery. The dose adjustment protocol in ►**Table 1** was designed with a clinical pharmacist, based on our institution's experience with real-time aFXa monitoring and dose adjustment.[9–11] For prophylaxis, the target steady-state unfractionated heparin aFXa levels were 0.1 to 0.35 IU/mL.[12,13] All consented patients were enrolled in the observational arm of the study and received aFXa monitoring at least 6 hours after initiation of the heparin infusion to determine response. Patients above

Table 1 Dose adjustment protocol

aFXa (unfractionated) (units/mL)	Stop infusion (min)	Rate change
Initial dose	0	X units/kg/h (500 units/h)
< 0.1	0	Increase by 1 unit/kg/h and redraw laboratories in 6 h
0.1–0.35	0	No change to dose and no repeat laboratory draws
0.36–0.50	60	Decrease by 1 unit/kg/h and redraw laboratories in 6 h
>0.50	60	Decrease by 2 units/kg/h and redraw laboratories in 6 h

Abbreviation: aFXa, anti-factor Xa.
Note: Anti-factor Xa (aFXa) drawn at least 6 hours after initiation and 6 hours after a rate change. Discontinue protocol when aFXa levels are within goal range.
X = 500 units/h ÷ patient weight (kg).

or below goal range (<0.1 and >0.35 IU/mL) aFXa levels crossed over to the interventional arm of the study and received real-time dose adjustments and repeat laboratory draws. The heparin infusion was managed according to the protocol in ►**Table 1** until adequate aFXa levels were achieved, until the heparin infusion was discontinued by the attending physician, or if the patient or the attending surgeon requested study withdrawal.

We prospectively identified patients, and collected patient demographics and comorbid conditions using a chart review and face-to-face patient interviews after enrollment. Baseline VTE risk was quantified using a 2005 Caprini score.[14]

The primary outcome of interest was the percentage of patients with an aFXa within target range on 500 units/h heparin infusion. Secondary outcomes included the number of heparin rate adjustments required to reach target range, percentage of patients achieving an aFXa within target range with dose adjustment, weight-based heparin dose required to reach target aFXa, and 90-day VTE or bleeding events.

VTE was defined as an imaging confirmed deep vein thrombosis or pulmonary embolism (PE) within 90 days of surgery. Bleeding events were defined as any bleeding event which caused heparin cessation, or necessitated unplanned transfusion, percutaneous drainage procedures, or return to the operating room. All patients were contacted by the study staff at 90 days after surgery to identify VTE or bleeding events which were diagnosed or managed at other institutions.

Analysis Plan

The planned analysis examined characteristics of patients whose aFXa level was or was not in target range while on heparin 500 units/h. As none of 20 patients had an in-range level, this analysis was not possible. A descriptive analysis was performed on patients who achieved in-range aFXa in response to dose adjustment, to improve understanding of the impact of real-time dose adjustment and how heparin metabolism could be predicted by patient weight. Descriptive statistics were generated on 90-day VTE and bleeding.

Results

Twenty-two eligible patients were identified and approached from November 1, 2016, to September 1, 2017. Twenty patients consented to participate. Usable data were available for all patients enrolled. Patients were representative of those who typically undergo microsurgical procedures and required a diverse range of surgical procedures (►**Table 2**). No patients were receiving antiplatelet agents preoperatively, but all patients received aspirin 325 mg daily in the perioperative period. One patient was lost to follow-up on postoperative day 76.

The target aFXa range for adequate VTE prophylaxis in patients who receive unfractionated heparin infusions is 0.1 to 0.35 IU/mL. When receiving unfractionated heparin at 500 units/h, none of 20 patients (0%) had a detectable aFXa level. These patients received a median initial dose of 6.5 units/kg/h (range: 4.4–10 units/kg/h).

All patients received real-time heparin dose adjustment based on the protocol in ►**Table 1**. Twelve patients ultimately achieved in-range aFXa, at a median dose of 11.8 units/kg/h (range: 8.9–18 units/kg/h). Among patients who achieved in-range aFXa, the median number of dose adjustments required was 5 (range: 4–11) and the median time to achieve in-range aFXa was 2.54 days (range: 1.07–3.5). Real-time heparin dose adjustment allowed a significantly increased proportion of patients to achieve in-range aFXa levels (60 vs. 0%, $p = 0.0001$).

Four of the 12 patients who achieved in-range aFXa levels received a heparin bolus of 3,000 units prior to initiation of the heparin infusion. Among patients who received a bolus, median time to achieve in-range aFXa was 2.44 days, while those who did not receive a bolus had a median time to in-range aFXa of 2.54 days ($p = 0.81$). Those who received a bolus underwent a median of 6.5 rate adjustments, while those who did not receive a bolus underwent a median of 5 rate adjustments ($p = 0.51$).

Eight patients never obtained an aFXa within goal range. Two patients refused additional laboratory draws, two patients' heparin infusions were stopped in anticipation of discharge from the hospital, and rate adjustments were stopped per attending preference in four instances (►**Table 3**).

No patients experienced reoperative hematoma or unexpected cessation of heparin infusion; however, one patient had rate adjustment helds due to moderate bleeding at the donor site on postoperative day 2. This patient did not achieve in-range aFXa levels and developed bilateral PE on postoperative day 59. Two replantation patients had unsalvageable venous congestion while receiving unfractionated heparin and required amputations.

Discussion

This clinical trial monitored aFXa levels in microsurgery patients who received fixed-dose heparin infusions and performed real-time heparin infusion dose adjustment to ensure patients received adequate VTE prophylaxis. Our study clearly demonstrates that fixed-dose heparin infusion at 500 units/h provides inadequate VTE prophylaxis for the overwhelming majority of patients (none of 20 patients in this study). The study also indicates that a conservative dose adjustment algorithm with 1 unit/kg/h increases allows a greater proportion of patients (60%) to achieve in-range levels in an average of 2.44 days. This is similarly concerning, as delay in prophylaxis is associated with later VTE events.[15]

Anticoagulants and antiplatelet agents are used in microvascular surgery to prevent microvascular thrombosis and subsequent flap or replant failure.[5] When utilizing fixed-dose heparin infusions to promote microvascular patency, surgeons do not typically provide additional chemical prophylaxis against VTE.[16–18] This study directly challenges the current dogma surrounding the level of anticoagulation provided by low-dose heparin infusions, including its adequacy for VTE prevention. None of 20 patients enrolled had a detectable level of anticoagulation while receiving heparin infusion at 500 units/h. This indicates that fixed-dose

Table 2 Baseline demographics

Patient	Age (y), gender	Weight (kg)	Caprini score	Initial heparin rate (units/kg/h)	Procedure
1	59, F	67.7	8	7.4	Bilateral abdominal free flap breast reconstruction
2	47, F	97	15	5.2	Abdominal-based free flap to right lower leg
3	63, M	57.2	9	8.7	Free flap to distal tibia wound
4	45, F	91.6	7	5.5	Bilateral abdominal free flap breast reconstruction
5	64, F	72.7	9	6.9	Right hemiabdominal free flap VRAM reconstruction
6	31, M	70.6	4	7.1	Fibula free flap to mandible
7	18, F	64.9	10	7.7	Replantation left hand
8	18, F	50	4	10	Free flap to left foot wound
9	51, M	113.9	4	4.4	Repair of digital artery and dorsal vein of thumb
10	20, F	82.1	4	6.1	Vein graft of digital arteries
11	42, M	71.7	3	7	Small finger right hand revascularization
12	58, F	84.4	9	5.9	Left abdominal free flap breast reconstruction
13	27, F	60.2	5	8.3	Repair of dorsal vein ring finger and radial digit artery finger
14	43, F	84.7	9	5.9	Bilateral abdominal free flap breast reconstruction
15	25, M	60.9	2	8.2	Left middle finger radial artery graft, ulnar artery graft, and radial artery repair
16	34, M	106.7	3	4.7	Left thumb replantation
17	54, F	100	7	5	Right abdominal free flap breast reconstruction
18	38, F	67.7	4	7.4	Bilateral DIEP
19	52, F	84.7	6	5.9	Bilateral abdominal free flap breast reconstruction
20	46, F	82.1	4	6.1	Right abdominal free flap breast reconstruction
Median	44	77.4	5.5	6.5	
Range	18–64	50–113.9	2–15	4.4–10	

Abbreviations: DIEP, deep inferior epigastric perforators; VRAM, vertical rectus abdominis myocutaneous.

heparin infusion, while clinically impactful for microvascular patency, is generally insufficient for VTE prophylaxis.

Nelson et al compared subcutaneous unfractionated heparin with heparin infusions titrated to therapeutic levels in 23 hypercoagulable patients undergoing microsurgery. Patients in the novel protocol group received 2,000 units IV heparin prior to anastomosis followed by 500 units/h heparin infusion at the time of anastomosis. Those in the pre-protocol group received 5,000 units subcutaneous heparin every 8 hours. In the 11 patients who received the novel protocol, no perioperative thrombotic events occurred, while thrombotic events occurred in 3 of the 12 patients in the pre-protocol group. While bleeding complication rates were significantly higher in the heparin infusion group, there were no flap losses. This study differs slightly from ours in that the heparin infusions were titrated to therapeutic levels, it shows that the utilization of a heparin infusion rather than subcutaneous heparin is safe and effective in this patient population.[19]

The goal aFXa range for VTE prophylaxis of 0.1 to 0.35 IU/mL is widely accepted and was utilized by Cheng et al in their study exploring standard subcutaneous dosing of unfractionated heparin for VTE prophylaxis in surgical intensive care unit patients. In their study, 50 patients were randomized to receive subcutaneous unfractionated heparin 5,000 units three times daily or unfractionated IV heparin titrated to an activated partial thromboplastin time of 40 to 45 seconds. All patients received aFXa monitoring. Patients receiving subcutaneous dosing had no detectable aFXa level for 5 days postoperatively, while those receiving IV dosing had increased levels comparatively on postoperative days 3 through 5. Additionally, Sonoclot analysis, a measure of whole blood coagulation, of the two groups was performed. Patients receiving subcutaneous dosing demonstrated a hypercoagulable profile, while patients receiving IV dosing had a normal coagulation profile. This shows that undetectable aFXa levels in surgical patients receiving unfractionated heparin during the acute postoperative period may be associated with a hypercoagulable state and theoretically an increased risk of VTE.[13] Inadequate aFXa levels in surgical patients who receive enoxaparin prophylaxis have similarly been associated with symptomatic VTE in plastic surgery and trauma surgery patients and with all-cause VTE in the trauma and orthopaedic populations.[20–23]

The heparin doses required to achieve goal prophylactic aFXa levels (8.9–18 units/kg/h) were similar to the starting infusion rate for the acute coronary syndrome protocol at our

Table 3 Primary and secondary outcomes (all patients)

Patient	Weight (kg)	Initial heparin rate (units/kg/h)	Number of rate adjustments	Time to adequate aFXa (d)	Last aFXa	Final heparin rate (units/kg/h)
2	97	5.2	5	2.33	0.12	10.2
4	91.6	5.5	5	2.5	0.11	10.5
5	72.7	6.9	9	3.23	0.31	14.4
7	64.9	7.7	6	2.78	0.18	13.7
8	50	10	8	3.5	0.14	18
9	113.9	4.4	5	1.07	0.12	9.4
10	82.1	6.1	7	3.12	0.1	13.1
12	84.4	5.9	3	1.65	0.11	8.9
13	60.2	8.3	2	1.63	0.19	10.3
14	84.7	5.9	5	2.58	0.19	10.9
15	60.9	8.2	5	2.13	0.18	13.3
16	106.7	4.7	8	2.72	0.1	12.7
1	67.7	7.4	2		<0.1	9.4
3	57.2	8.7	2		<0.1	8.7
6	70.6	7.1	5		<0.1	12.1
11	71.7	7	3		<0.1	10
17	100	5	4		<0.1	9
18	67.7	7.4	1		<0.1	8.4
19	84.7	5.9	1		<0.1	6.9
20	82.1	6.1	4		<0.1	10.1
Median	77.4	6.5	5	2.54	0.1	10.25
Range	50–113.9	4.4–10	1–9	1.63–3.5	<0.1–0.31	6.9–18

Abbreviation: aFXa, antifactor Xa.

institution (12 units/kg/h). This may be due to the hypermetabolic nature of patients in the postoperative period.[10] On average, patients in this study required 2.44 days to achieve in-range levels. This functionally results in a delay to provision of adequate VTE chemical prophylaxis. Delay to chemical prophylaxis initiation has been associated with increased risk for postoperative VTE among surgical patients.[15,24]

Our study suggests that an initial weight-based heparin dose may allow a larger proportion of patients to have in-range aFXa, or at least would decrease the number of dose adjustments required to achieve goal aFXa levels and time to adequate VTE chemical prophylaxis. Patients who achieved in-range aFXa levels did so on a heparin dose of 8.9 to 18 units/kg/h. Based on this work, an initial heparin dose of 10 to 12 units/kg/h might best optimize risk for bleeding and VTE (►**Table 4**). Another option would be to institute a more aggressive dose adjustment protocol; however, we would favor a higher weight-based dose on initiation as rate adjustment in

Table 4 Proposed weight-based protocol

aFXa (unfractionated) (units/mL)	Stop infusion (min)	Rate change
Initial dose	0	10 units/kg/h
<0.1	0	Increase by 1 unit/kg/h and redraw laboratories in 6 h
0.1–0.35	0	No change to dose and no repeat laboratory draws
0.36–0.50	60	Decrease by 1 unit/kg/h and redraw laboratories in 6 h
>0.50	60	Decrease by 2 units/kg/h and redraw laboratories in 6 h

Abbreviation: aFXa, anti-factor Xa.

Note: Heparin will be initiated by the operating surgeon, with or without a 3,000-unit intravenous bolus, at a rate of 500 units/h. Postoperative day 1, after evaluation by the operating surgeon, heparin dose will be increased to 10 units/kg/h. aFXa to be drawn at least 6 hours after initiation and 6 hours after a rate change. Discontinue protocol when aFXa levels are within goal range.

increments of 1 unit/kg/h is standard among nearly all heparin protocols and has been shown to be safe. Future studies should validate this claim, and would need to incorporate real-time aFXa monitoring and dose adjustment.

We were unable to perform any meaningful statistical analysis as our primary outcome (in-range aFXa levels in response to 500 units/h of unfractionated heparin) was achieved by none of the patients. However, while the true proportion of patients who receive adequate VTE prophylaxis on 500 units/h of heparin is unknown, we can definitively say that it is low. Real-time titration of heparin infusions using a standardized protocol appears to be safe as only one patient experienced one of the prespecified safety outcomes for clinically relevant bleeding (5%). Similar studies report a bleeding rate of 5 to 6%.[16,17] With a paucity of outcome events, we must note that our observed rate of 5% may under- or overestimate the true rate of bleeding. A larger enrollment could examine this question more closely.

Conclusions

Fixed-dose heparin infusions at a rate of 500 units/h are not sufficient to achieve an adequate level of anticoagulation for the prevention of VTE in the overwhelming majority of microsurgical patients. Real-time heparin titration, guided by aFXa levels and a written protocol, allows a significantly increased proportion of patients to achieve an in-range level. Future studies should examine the impact of weight-based unfractionated heparin infusions initiated at 10 to 12 units/kg/h on adequacy of aFXa levels, risk for bleeding, and prevention of VTE.

Conflict of Interest
None.

Acknowledgments
This study was funded by a grant awarded to the investigators by the Plastic Surgery Department at the University of Utah. Dr. Pannucci receives salary support from the American Association of Plastic Surgeons/Plastic Surgery Foundation Academic Scholar Program.

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