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Original Article

Are venous thromboembolism risk assessment tools reliable in the stratification of microvascular risk following lower extremity reconstruction?

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ABSTRACT

Introduction: The incidence of flap failure is significantly higher in the lower extremity compared to free tissue transfer in the head, neck and breast. The most common cause of flap failure is venous thrombosis. The aim of this study was to assess the reliability of venous thromboembolism (VTE) risk assessment tools in this high-risk cohort and to assess the ability of such tools to identify patients at risk of developing microvascular venous thrombosis and venous thromboembolism following lower extremity free flap reconstruction.

Methods: A single centre retrospective cohort study was conducted between August 2012-August 2019. Adult patients who had undergone free tissue transfer following open lower extremity fractures were eligible for inclusion. All patients were retrospectively risk assessed using the Department of Health (DoH), Modified Caprini and Padua VTE risk assessment tools.

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Results: Fifty-eight patients were included; all were at high risk of DVT according to the DoH (mean score ± SD, 3.7 ± 0.93), Caprini (10.2 ± 1.64) and Padua (5.4 ± 0.86) risk assessment tools. All patients received appropriate thromboprophylaxis; the incidence of symptomatic hospital acquired VTE was 3.5%. Micro-anastomotic venous thrombosis occurred in 4 patients resulting in one amputation. Partial flap necrosis occurred in 7 patients. There were no significant differences in scaled Caprini (median score, 10 vs 9, $z = 1.289$, $p = 0.09$), DoH (3 vs 3, $z = 0.344$, $p = 0.36$), and Padua (5 vs 5.5, z= -0.944, $p = 0.17$) scores between those with and without microvascular venous thrombosis.

Conclusion: This data suggests that current VTE risk assessment tools do not predict risk of microvascular venous thrombosis following lower extremity reconstruction. Further prospective studies are required to optimise risk prediction models and thromboprophylaxis use in this cohort.

Introduction

The risk of venous thromboembolism (VTE) in patients with open extremity fractures is highly variable owing to independent procedure and patient specific risk factors.[1] In the context of polytrauma, VTE risk is associated to a prothrombotic state characterised by decreased levels of functional protein C and abnormal prothrombin levels.[2] Major trauma (injury severity score ≥9) is associated with a 58% incidence of in hospital lower extremity deep venous thrombosis (DVT).[3]

In patients with major lower limb trauma, as many as 23.5% of tibial fractures present as open injuries requiring free flap reconstruction,[4] with a reported failure rate of 6%.[5] Flap failure predominantly occurs within the first 48 h, due to microanastomotic venous thrombosis (35%), microanastomotic arterial thrombosis (28%), haematoma (26%) and recipient vessel disruption (11%).[6]

Thromboprophylaxis is key in the patient with polytrauma and major orthopaedic injuries and must be delivered taking into account the VTE risk and the potential risk of bleeding from acquired injuries. This represents a challenge where limited data and guidance is available, leading to practice being largely driven on a case by case basis.[7,8]

Chemical prophylaxis in this population can be contraindicated in the presence of concomitant traumatic brain injury, solid organ injury, thrombocytopenia, active haemorrhage and pelvic and/or retroperitoneal haematoma. In those undergoing lower limb reconstructions, this may further predispose to flap haematoma, which has a reported incidence of 4.7% and a subsequent flap failure rate of 22.7% secondary to local pedicle compression and inflammatory changes.[9]

Various risk assessment tools have been developed to guide clinical decision making and rationalise thromboprophylaxis delivery. The Caprini[10] and Padua[11] risk assessment tools were all initially developed in medical cohorts, although the Caprini score has been validated in patients undergoing reconstructive surgery[12] and those in surgical intensive care,[13] including patients who had undergone lower limb reconstruction following major orthopaedic trauma. Despite this, the Caprini score is not referenced in the 2012 American College of Chest Physicians recommendations for VTE prophylaxis in orthopaedic procedures.[14] To the authors knowledge, no study to date has investigated the ability of VTE risk assessment tools to predict the risk of microvascular venous thrombosis following lower extremity reconstruction.

Established risk factors for microanastomotic thrombosis include diabetes mellitus, smoking, traumatic vessel injury, acquired and hereditary coagulopathies.[15] Similar risk factors for developing VTE

have been described; major trauma and lower extremity injuries constitute a strong risk, respiratory failure and previous VTE constitute a moderate risk and prolonged bed rest, extended immobility, increasing age[16] and smoking[17] constitute weak risk for developing VTE.

The aim of this study was to assess the ability of VTE risk assessment tools to predict the risk of developing microvascular venous thrombosis following lower extremity free flap reconstruction, and whether these may be suitable to assess this cohort of patients.

Methods

A retrospective cohort study at a single Major Trauma Centre was conducted. All adult patients admitted between August 2012 and August 2019 with open lower extremity fractures requiring free tissue transfer were eligible for study inclusion. Electronic health records and clinic letters were used to collect data on the following: patient demographics, clinical factors related to thrombosis, injury location, mechanism of injury, Gustilo-Anderson Grade, definitive skeletal fixation modality, flap type, number of venous anastomoses, return to theatre within 72 h, documented post-operative thromboprophylaxis, documented post-operative VTE (defined as symptomatic deep venous thrombosis or pulmonary embolism occurring within 90 days of hospital admission), documented flap necrosis (clinical evidence of skin necrosis requiring intervention) and documented flap failure (complete flap necrosis requiring flap removal).

Study participants

Adult patients with an open lower extremity fracture with associated soft tissue damage requiring free tissue transfer were included. Patients under the age of 18 at the time of injury were excluded. Any adults presenting with traumatic limb amputation were also excluded.

Risk assessment tools

The Modified Caprini risk assessment tool (RAT)[10] (Appendix 1) has been validated for use in surgical patients.[12,13] It categorises patients as highest, high, moderate and low risk for VTE with scores of $\geq$5, 3–4, 2 and 0–1 respectively. Early ambulation is recommended for low risk, mechanical or pharmacological prophylaxis is recommended for moderate risk and pharmacological prophylaxis is recommended for high and highest risk patients. The DoH RAT[18] (Appendix 2) is intended for use in both surgical and medical inpatients. A single risk factor should prompt chemical thromboprophylaxis in the absence of bleeding risk factors. The Padua Risk Assessment Model[11] (Appendix 3) is validated for medical inpatients and considers a score of $\geq$ 4 as high risk. Chemical prophylaxis is recommended for high risk patients with adequate renal function and without evidence of thrombocytopaenia or major bleeding. In this review, all three RATs were applied to each patient with a lower extremity traumatic injury.

Statistical analysis

Descriptive statistics were used to provide average values for both raw and scaled scores across all three risk assessment tools. Raw scores denote the number of actual factors presents according to each RAT and scaled scores were calculated using assigned weights for each factor. The Mann–Whitney U test was used to determine if statistically significant differences in scaled scores existed between patients with and without microvascular venous thrombosis. All statistical analyses were carried out using SPSS (version 24.0; SPSS Inc, Chicago, IL) and $p < 0.05$ was considered significant.

Results

A total of 58 patients were included in this study, 84% were male with a mean age of 39.1 ($\pm$ 16.8) years; demographic and injury specific details are outlined in Table 1. The mean body mass index (BMI) of our cohort was 26.4 $\pm$ 4.3. No patients were on anticoagulation or taking hormone

Table 1
Demographic and injury specific data.

Gender	Frequency
Male	49
Female	9
Injury location	
Left knee	0
Left lower limb	20
Left ankle	4
Left foot	5
Right knee	1
Right lower limb	21
Right ankle	2
Right foot	5
Mechanism	
RTA	44
Fall	9
Chronic wound	2
Crush injury	1
Penetrating trauma	1
Bomb blast	1
Gustillo-Andersen Grade	
3b	56
3c	2
Co-morbidities	
Hypertension	3
Diabetes mellitus	4
Previous malignancy	3
Thrombocytopaenia	1
Tuberculosis	1
Asthma	2
Epilepsy	1
Multiple sclerosis	1
Hemochromatosis	1
Alcohol excess	2
Inguinal hernia	1
Depression	2

replacement therapy; the prevalence of previous VTE was 0%. One patient in our cohort was thrombocytopaenic on admission (platelet count <150,000) secondary to chronic alcohol excess. All patients were operated upon by one of four consultant plastic surgeons at a single institution. The use of Flowtron boots on the contralateral limb is routine practice at our institution during the reconstruction of unilateral open extremity fractures using flaps from the ipsilateral limb.

In our cohort, 67.2% of patients received soft tissue coverage with an Anterolateral Thigh (ALT) flap and all patients received chemical thromboprophylaxis, see Table 2. All procedures lasted longer than 90 min and patients were confined to bed rest for 72 h following lower extremity reconstruction.

All patients were deemed high risk of developing DVT according to the DoH, Caprini and Padua risk assessment tools, see Fig. 1. The incidence of symptomatic venous thromboembolism developed within 90 days in our cohort was 3.5% ($n = 2$). Both patients sustained open tibial fractures; one developed a lower extremity DVT 55 days following surgery and the other developed a left axillary vein DVT 25 days following surgery. Neither had previous documented VTE events.

Return to theatre following lower limb reconstruction was required in 18 patients, see Table 3. Partial flap necrosis occurred in 7 patients, all of whom were successfully treated with debridement, flap advancement and skin grafting. Micro-anastomotic venous thrombosis occurred in four patients (6.9%). In three cases the limb was salvaged with flap excision and further subsequent free flap reconstruction ($n = 2$) or application of a split thickness skin graft ($n = 1$). One patient with microvascular thrombosis underwent through knee amputation due to concurrent recurrence of squamous cell carci-

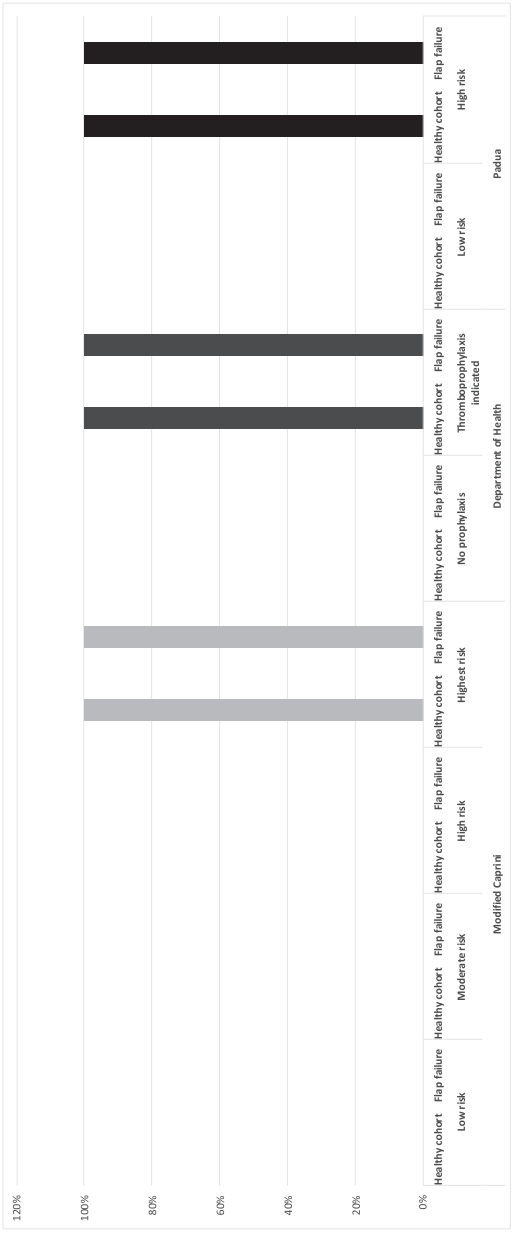

Fig.1. Comparative bar chart demonstrating the proportion of patients in both healthy and flap failure cohorts categorised as low, moderate, high and highest risk (as per Modified Caprini), no prophylaxis and thromboprophylaxis indicated (as per Department of Health) and low and high risk (as per Padua).

Table 2
Operative management and thromboprophylaxis of included patients.

Definitive skeletal fixation modality	Frequency (entire cohort; $n = 58$)	Frequency (flap failure cohort; $n = 4$)
External fixation	31	3
Intramedullary nail	13	–
Taylor spatial frame	5	–
Open reduction internal fixation	7	1
Kirschner wire	2	–
Flap type		
ALT	39	3
LD	4	–
RFF	9	–
MSAP	4	–
Gracillis	1	–
DIEP	1	1
Number of venous anastomoses		
1	17	2
2	28	2
3	3	–
Documented post-operative thromboprophylaxis		
Aspirin alone	11	2
Enoxaparin alone	9	1
Tinzaparin alone	3	–
Aspirin + Enoxaparin	28	1
Aspirin + Tinzaparin	6	–
Enoxaparin + DOAC	1	–

ALT, anterolateral thigh; DIEP, deep inferior epigastric perforator; DOAC, direct oral anticoagulant; LD, latissimus dorsi; MSAP, medial sural artery perforator; RFF, radial forearm flap.

noma. Flap haematoma occurred in 5 patients, all of whom were successfully treated with haematoma evacuation.

There were no significant differences in scaled Caprini (median score, 10 vs 9, $z = 1.289$, $p = 0.09$), DoH (3 vs 3, $z = 0.344$, $p = 0.36$), and Padua (5 vs 5.5, $z = -0.944$, $p = 0.17$) scores between those with and without microvascular venous thrombosis.

Discussion

This study demonstrates that current venous thromboembolism risk assessment tools are not able to stratify the risk of microvascular venous thrombosis in patients with lower extremity trauma who have undergone free flap reconstruction. All participants in our cohort were deemed high risk of developing DVT and all received chemical thromboprophylaxis with a 3.5% incidence of 90-day VTE despite a 12% incidence of partial flap necrosis and a 6.8% incidence of free flap failure. All VTE RAT scores demonstrated moderate agreement, suggesting congruency between factors considered by each tool in this patient group.

Venous thrombosis at the microanastomotic site predominantly occurs after 24 h. Preoperative factors such as diabetes mellitus, smoking, traumatic vessel injury, acquired and hereditary coagulopathies are known to increase the risk of anastomotic thrombosis.[15] Traditionally, microsurgical technique has been heralded as the single most important factor for the success of microvascular anastomoses.[19] However other procedure specific factors such as the use of vein grafts[20] and the presence of chronic wounds[21] at recipient sites are known to be associated with microvascular thrombosis and flap failure. Vein grafts were not used in our cohort; one patient had a chronic wound secondary to squamous cell carcinoma and subsequently underwent through knee amputation due to recurrence and microvascular venous thrombosis.

Currently, 96% of reconstructive surgeons use anticoagulation in free flap procedures, however limited data from human subjects exists to support a single peri–operative protocol for anticoagulation in microsurgery.[22] In a prospective study of 493 free flaps, Khouri et al. demonstrated that prophylac-

Table 3
Demographic, operative and outcome data related to all patients who returned to theatre within 72 h of original free flap reconstruction.

Age/gender	Mechanism	Medical co-morbidities	BMI	Bony fixation	Soft tissue reconstruction	Number of venous anastomoses	Post-operative VTE prophylaxis	Documented complications	Outcome
53/M	RTA	–	27	EF	RFF	2	Aspirin 75 mg Enoxaparin 20mg	Flap haematoma and wound dehiscence	Flap salvage with haematoma evacuation
42/M	RTA	–	28	IM nail	ALT	1	Aspirin 75 mg Enoxaparin 20mg	Flap haematoma (x2)	Flap salvage with haematoma evacuation
31/M	RTA	–	27	EF	ALT	2	Aspirin 150 mg EOD (Later started on Warfarin)	Microanastomotic venous thrombosis Flap haematoma (x5)	Flap salvage with haematoma evacuation
38/M	Fall	–	31	EF	ALT	1	**Flap 1**: Aspirin 150 mg EOD **Flap 2**: 5000 units heparin intra-operatively. Aspirin 150 mg EOD.	Mircoanastomotic venous thrombosis, flap failure.	Flap removal, second free flap
59/M	Chronic wound secondary to SCC	SCC	26	EF	DIEP	2	Enoxaparin 20mg	Recurrence of SCC. Mircoanastomotic venous thrombosis	Through knee amputation
19/M	RTA	–	24	EF	ALT	3	Aspirin 150 mg EOD	Partial flap necrosis. Flap haematoma.	Flap salvage with haematoma evacuation and flap advancement
28/M	RTA	–	23	EF	ALT	2	Aspirin 150 mg EOD	Partial flap necrosis	Flap salvage with debridement and SSG
48/F	Fall	–	27	IM	ALT	2	Enoxaparin 20mg	Partial flap necrosis and failure (local flap)	ALT free flap
59/M	Fall	HTN T2DM	30	ORIF	ALT	1	Aspirin 75 mg Enoxaparin 20mg	Microanastomotic venous thrombosis	Limb salvage with flap removal and SSG to bare area
33/M	Penetrating trauma	–	30	EF	ALT	2	5000 units heparin intra-operatively. Aspirin 75 mg and Enoxaparin 20 mg post-operatively.	Significant bone loss, fracture non-union	Below knee amputation

(*continued on next page*)

Table 3 (*continued*)

Age/gender	Mechanism	Medical co-morbidities	BMI	Bony fixation	Soft tissue reconstruction	Number of venous anastomoses	Post-operative VTE prophylaxis	Documented complications	Outcome
45/M	Crush injury	–	22	ORIF	ALT	2	Aspirin 75 mg Tinzaparin 4500 units	Questionable lower limb vascularity following ORIF. Two stage ALT.	Flap salvage
37/M	RTA	–	19	IM	MSAP	2	Enoxaparin 20mg	Partial flap necrosis	Flap salvage with debridement, advancement and SSG
36/M	Fall	Asthma	28	ORIF	ALT	2	5000 units heparin intra-operatively. Enoxaparin 20 mg post-operatively.	Partial flap necrosis	Flap salvage with debridement, advancement and SSG
26/M	RTA	–	26	EF	RFF	2	Aspirin 75 mg	Partial flap necrosis	Flap salvage with debridement and advancement
61/M	RTA	–	28	IM	ALT	1	Aspirin 75 mg Enoxaparin 20mg	Flap haematoma	Flap salvage with haematoma evacuation
21/M	RTA	–	23	IM	LD	1	Aspirin 75 mg Enoxaparin 20mg	Partial flap necrosis	Flap salvage with debridement, advancement and SSG
43/M	Fall	–	27	ORIF	MSAP	2	Aspirin 75 mg Enoxaparin 20mg	Partial flap necrosis	Flap salvage with debridement, advancement and SSG
69/M	Fall	Previous prostate cancer, inguinal hernia	29	EF	ALT	1	Aspirin 75 mg	Fracture non-union with infected metalwork	Below knee amputation

ALT, anterolateral thigh flap; DIEP, deep inferior epigastric perforator flap; EOD, every other day; EF, external fixation; HTN, hypertension; IM, intramedullary nail; LD, latissimus dorsi flap; MSAP, medial sural artery perforator flap; ORIF, open reduction internal fixation; RFF, radial forearm flap; RTA, road traffic accident; SCC, squamous cell carcinoma; SSG, split thickness skin graft; T2DM, Type 2 diabetes mellitus.

tic dose subcutaneous heparin significantly reduced the odds of venous thrombosis by 27%.[23] Patients who received pre-operative systemic therapy with heparin, aspirin or dextran demonstrated a 2.2% incidence of flap failure compared to 4.6% in those without pre-operative therapy. Data related to the dose and duration of the pre-operative therapy were not provided. In our cohort, patients who experienced microvascular venous thrombosis received a combination of Aspirin 150 mg every other day, Enoxaparin 20 mg, Aspirin 75 mg and Enoxaparin 20 mg following free flap reconstruction. The present data do not support superiority of a single post-operative VTE prophylactic regimen.

Heparin has proven efficacy at preventing microvascular thrombosis however haematoma and bleeding are significant complications that preclude routine systemic use. Pugh et al., reported a 66% incidence of haematoma formation when heparin was used alone in or in combination following lower extremity reconstruction.[24] A retrospective cohort study of 505 patients did not demonstrate a significant difference in the incidence of microvascular thrombosis or haematoma formation between cohorts treated with and without intravenous boli of 3000 units heparin before flap pedicle ligation. Both cohorts received post-operative treatment with aspirin and low molecular weight heparin.[25] The incidence of haematoma in our cohort was 8.6%, all of whom were successfully treated with evacuation. The reported incidence of flap failure following haematoma is 22.7%. Flap failure following haematoma occurs due to local pedicle compression and subsequent thrombosis in conjunction with local inflammatory changes occurring within the flap. Platelet degradation, thrombin formation and generation of reactive oxygen species (ROS) occur in response to haematoma formation and lead to both complement and neutrophil activation. Intimal damage, hypercoagulability and blood flow stasis lead to tissue ischaemia with degradation of haem, further perpetuating a pro-inflammatory cascade. Free flaps are devoid of sympathetic nervous supply and lymphatic drainage, which renders them uniquely susceptible to haematoma induced inflammatory tissue injury.[26]

To the authors knowledge, this is the first study which seeks to apply VTE RATs in a cohort of patients at risk of microvascular thrombosis following free flap reconstruction. However, our results must be considered in view of the study limitations. The present study was retrospective and thus relied on accurate documentation of risk factors and outcomes in electronic medical records. The actual incidence of patient specific risk factors may not have been captured although the retrospective nature of the study did permit recruitment of a cohort comparable to what has been published in the literature.

Future work to determine which factors influence the risk of thrombosis following lower extremity reconstruction is necessary to improve rationalisation of anti-coagulant and antithrombotic therapy. Indeed, the development of a prognostic model for microvascular venous thrombosis in lower extremity reconstruction will represent a step towards stratified intervention for such patients. This could be achieved through multivariable regression analysis on large, prospectively collected data sets such as the UK Flap Registry.[27] Surgeon specific factors such as number of prior microsurgical reconstructive procedures should be considered alongside patient specific and peri–operative factors known to increase risk of microanastomotic venous thrombosis. Following external validation, the impact of a prognostic model on clinical practice and outcomes would then be determined.

In conclusion, current VTE risk assessment tools do not stratify patients at risk of developing microvascular venous thrombosis following lower limb reconstruction. Further prospective cohort studies are required to determine factors which influence microvascular thrombosis from which risk prediction models can be built.

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Ethical approval

N/A

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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