HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS AS AN UNDER-DIAGNOSED CAUSE OF FLAP FAILURE IN HEPARIN-NAIVE PATIENTS: A CASE REPORT AND SYSTEMATIC REVIEW OF THE LITERATURE

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Background: Heparin-induced thrombocytopenia and thrombosis (HITT) is an immune complex mediated and potentially devastating cause of flap loss in microvascular surgery. HITT may be an under-reported cause of early-flap failure due to subclinical manifestations at the time of flap loss. A case report of a patient presenting with HITT-related flap failure and the results of a systematic literature review of the clinical presentation of HITT in microsurgery are presented here. *Case Report:* A patient suffering from a chronic wound on the right medial malleolus was treated with an ALT flap, which was compromised by thrombosis. Multiple attempts to rescue the flap including thrombolysis, popliteal AV loop, and a second free flap were all unsuccessful. Six days following the initial procedure, a diagnosis of HITT was made following a positive HITT-antibody test as the cause of flap failure. *Methods:* PubMed, MEDLINE, and EMBASE searches yielded 113 results, of which 6 met our criteria for manuscripts describing HITT in microsurgical procedures. *Results:* Evaluation of the peer-reviewed literature describing HITT in microsurgery suggests that HITT-related flap failure occurs rapidly, more frequently in heparin-naïve patients, and in advance of systemic thrombosis and thrombocytopenia. *Conclusions:* Due to the rapid and unpredictable onset of HITT during microsurgery, we recommend maintaining an index of suspicion for HITT in flaps with otherwise unexplained early thrombosis. We also encourage hematology consultation, discontinuing heparin use and initiating alternate thromboprophylaxis in order to inhibit the potential for subsequent life-threatening systemic complications as well as improving the potential for delayed reconstructive success.
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Free flap failure is a common post-operative complication in reconstructive plastic surgery, with a reported incidence of 1–5%.[1] Although many factors contribute to flap failure, it frequently occurs as a consequence of venous and/or arterial thrombosis, which has been reported in 3.3–9.9% of free-flaps.[2–7] Of the various known pathogenetic processes leading to thrombosis, heparin-induced thrombocytopenia and thombosis syndrome (HITTs) has recently been demonstrated to have a significant impact on flap survival if not detected and managed early.[8–11]

Heparin-induced thrombocytopenia and thrombosis (HITT) manifests in two forms. HITT type I is associated with direct heparin-induced platelet activation, causing a transient thrombocytopenia that usually normalizes within 1–2 days after heparin administration, and is only occasionally linked to thrombotic events. HITT type I affects up to 10% of patients, but due to spontaneous resolution, requires only observation rather than active intervention.[12] HITT type II, on the other hand, has much more serious sequelae, and has been reported to affect ~600,000 individuals per year in the United States.[13] HITT type II is an immune mediated systemic condition characterized by immune complex-mediated platelet activation with subsequent thrombocytopenia.[14] HITT type II is a less common condition than HITT type I, normally presenting 4–10 days following heparin treatment and frequently in conjunction with thrombosis, which can have devastating outcomes in microsurgery. Although thrombocytopenia in HITT typically occurs 4–10 days after exposure to heparin, it can occur earlier in patients who have previously received heparin treatment. Late-onset HITT has also been reported, with thrombocytopenia presenting itself up to 100 days following treatment with heparin.[15] Paradoxically, thrombotic events in HITT arise in concert with thrombocytopenia due to antibody mediated platelet activation and aggregation.[16,17] Vascular occlusion and organ damage may occur anywhere, but thrombosis associated with HITT has a predilection for areas of pre-existing endothelial injury, such as newly affixed flaps.[17]

Despite well-documented signs of HITT, a recent report further suggested the possibility of the existence of a locally limited form of HITTs in microsurgery.[8] This so-called "local-form" is characterized by flap loss occurring very early in the post-operative course and without the usually associated drop in platelet count.[8] We present here a similar, potentially "locally-limited," case of HITT with early flap failure with delayed

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thrombocytopenia, and a systematic review of published reports describing HITT in microsurgery. In the present manuscript, our goals are to assess the clinical presentation of HITT during microsurgery and to identify factors which may inform/influence future practice regarding case management.

CASE REPORT

The patient was a 50-year-old nonsmoking male with no known history of comorbid disease or previous heparin exposure. The patient sustained a work trauma-related right bimalleolar fracture and was treated with open reduction and internal fixation (ORIF) of the fracture. Chronic osteomyelitis and hardware infection with isolated *enterococcus* on culture complicated the post-operative course, and the patient was treated with broad-spectrum antibiotics and local wound care for 2 months. An anterolateral thigh flap (ALT flap) was planned for soft tissue coverage of his 9 cm x 8 cm chronic right medial malleolus wound.

The patient's pre-operative laboratory parameters (including coagulation profile, CBC, ESR, CRP) were within normal limits. During the initial flap procedure, the ALT flap based on the descending branch of the lateral circumflex vessel was anastomosed to the anterior tibial artery and its accompanying vein. Moderate venous congestion was noted intra-operatively, however additional quality veins were not found at the donor site, and as a result, the venous anastomosis was revised and hand sewn. After re-anastomosis, flow was observed both with Doppler and clinical strip test confirmation. Despite repeated confirmation of flow, the flap still clinically appeared mildly congested. Because of this sequence of events and our clinical observations, we initiated a heparin drip, heparin soaks, antibiotics, and treatment with medicinal leeches. Hourly monitoring of the flap was continued, and despite evidence of flow in the venous system, there remained clinical suspicion of mild-to-moderate congestion. On post-operative day 2, the flap demonstrated an acute decrease in colour, temperature, and Doppler signal, and was then promptly returned to the OR for exploration and re-anastomosis. Upon re-exploration, multiple venous and arterial thrombi were discovered. Direct administration of 6 mg tissue plasminogen activator (tPa) in a closed-loop circuit was administered and vascular flow was restored to the flap.

Three days following surgical re-exploration, the flap once again displayed arterial compromise and an arteriogram was performed. Imaging revealed acute thrombosis and occlusion of the right anterior tibial artery. Given the patient's normal platelet count (176 x 10^9/L) and the local distribution of thrombi within the flap, the likelihood of HITT was overlooked, and the patient continued to receive heparin treatment. On post-operative day 4, it was decided to attempt another free flap to close the wound. This time a right radial forearm free flap (RFFF) was attached to a right popliteal arterio-venous (AV) loop using a left saphenous vein graft; no delay of the AV loop was performed. Enoxaparin (40 mg SC daily) was used for VTE prophylaxis. The RFFF persisted with good perfusion for 4 days, and then acute compromise was noted on post-operative day 5. The patient was once again returned to the OR for attempted thrombolysis with a Fogarty catheter, closed-loop administration of tPa (10 mg IV), and multiple attempts at reanastomosis. Thrombi continued to reform intra-operatively and it was not possible to reestablish vascular flow to the flap. The flap was then debrided intra-operatively and the wound was closed with a VAC™ device.

Hematology was consulted to look for possible subclinical coagulopathy and a positive result for heparin-PF4 antibodies was discovered by enzyme-linked immunoassay (ELISA) 2 days following placement of the RFFF (6 days after the initial surgery). A diagnosis of HITT was established despite the absence of thrombocytopenia or systemic thrombotic manifestations during the patient's reconstructive course. With HITT strongly suspected as the etiology of the flap failure, enoxaparin anticoagulation was promptly substituted for fondaparinux, a synthetic heparin-like polysaccharide targeting only the coagulation factor Xa and without affinity for PF4.[18] This eliminated the formation of heparin/PF4+antibody complexes. In the days following this substitution, platelet counts promptly increased to 483–529 x 10^9, further supporting the diagnosis. Retrospectively, the patient's pretest clinical scoring system "4-T score" was calculated to be 4, which only represented an intermediate risk for HITTs[19] (Table 1).

Despite continued fondaparinux treatment and bridging to warfarin anticoagulation, the patient was discovered to have a left-sided above-the-knee deep vein thrombosis (DVT). Given hematology's opposition against further operative interventions and the continued venous thromboembolism risk post-HITT, the patient agreed to undergo a trans-tibial amputation. Further management included placement of an inferior vena cava (IVF) filter, and rehabilitation. The patient's post-amputation wound healed well with no further complications.

MATERIALS AND METHODS

We conducted a systematic search of PUBMED, MEDLINE, and EMBASE databases for the period between 1996 to December 06, 2012. Our search strategy focused on two main concepts: "Heparin-induced

Table 1. 4T-Score: Pretest Scoring System for HIT

4 T's	0 point	1 point	2 point
Thrombocytopenia	<30% platelet count fall or <10 $\times$ 10^9/L platelet nadir.	A 30–50% fall in platelet count or platelet nadir 10–20 $\times$ 10^9/L.	>50% fall in platelet count or nadir 2–100 10^9/L.
Timing of platelet count fall	Early drop (<4 days) in platelet count in never exposed.	Onset after 10 days, or some platelet count data missing.	Clear onset between 5-10 days after initiation of heparin, or platelet fall $\leq$1 day.
Thrombosis $\pm$ other sequela	None	Progressive or recurrent thrombosis.	New thrombosis (confirmed), skin necrosis present, systemic reaction to heparin bolus.
Other causes of thrombocytopenia	Definite	Possible	No alternative explanation.

Adapted from G. K, L.O., et al. (2006).

thrombocytopenia and thrombosis", and "microsurgery". From the first concept, we searched subject headings including "drug induced thrombocytopenia", "heparin induced thrombocytopenia", "HITT" as well as MESH terms including "thrombocytopenia/chemically induced" and "heparin/adverse effects". From the second concept, we searched subject headings and MESH terms which included: "graft rejection", "plastic surgery", "skin transplant", "flap failure", "tissue flap", "surgical flap", "graft rejection", "surgical flaps", "microsurgery". Selected studies were limited to humans and English publications. We screened all relevant publications. Bibliographies of relevant reports were cross-checked for other suitable studies. The journals and conference proceedings that were specifically hand searched for the review included a total of 12 publications. Two authors completed study inclusion and data extraction independently (DJ and JV). Studies were excluded from the review if HITT occurred in the absence of microsurgery.

RESULTS

A total of 113 articles were screened and assessed for eligibility by two of the authors (19 EMBASE, 26 OVID, 68 PUBMED). Of these captured results, a total of 6 articles were selected for inclusion because of their relevance to HITT in microsurgery. The included articles have been summarized in Table 2. There was a total of 477 patients included in the 6 articles. Of these articles, 5 discussed individual cases of HITT in a total of 8 flaps. We divided the papers into three groups: prior heparin exposure, heparin-naïve, and prior heparin status not discussed. The characteristics of HITT affected flaps included: malperfusion, decreased arterial Doppler signal, venous congestion, arterial thrombosis, and frank necrosis. The timing of flap failure was variable, ranging from post-operative day 1 (6 hours) to post-operative day 5. The treatment involved discontinuation of heparin, followed by various options, including: a direct thrombin inhibitor (lepirudin, argatroban), danaparoid sodium, and medicinal leeches. Selected treatment was based on clinician preference.

In the literature, we identified five manuscripts describing Busch et al. described two cases of HITT in microsurgery in a report published in 2009.[8] In the first case, they observed HITT 12 hours post-operatively in a patient with previous heparin exposure which was unsuccessfully treated with revision by 12 microvascular anastomoses; this case was confirmed with a positive HITT antibody test. Their second case involved a patient with unknown previous heparin status who was referred to their care for flap failure due to HITT which occurred at an unknown period of time post-operatively. They identified this patient as HITT positive by HITT antibody assay, and discontinued heparin, started lepirudin, and successfully closed the defect 10 days later with an anterolateral thigh flap. Tremblay et al published a manuscript in 2008 describing HITT in two heparin-naïve patients.[11] In their first case, a heparin-naïve patient presented with venous congestion secondary to HITT 26 hours post-operatively. They treated with leeches and various types of anti-coagulation and although the flap remained viable for $\sim$1 month, it ultimately failed. HITT was confirmed by positive antibody test. In the second case, a heparin-naïve patient presented with HITT 2 days post-operatively, which was successfully treated with danaparoid sodium anticoagulation and leech therapy. HITT was confirmed by antibody test. McCleave described a case of HITT in microsurgery in 2010 in a heparin-naïve patient 5 days post-operatively, which was unsuccessfully treated with re-exploration.[9] The HITT antibody assay was negative, but the platelet aggregation assay was positive. Medina et al. described two flaps in one patient with unknown prior heparin exposure in 2010, which were both affected by HITT.[20] The initial flap was affected by HITT 4 days post-operatively and was treated by placement of a second flap. Congestion was noted in the second flap immediately post-operatively, and was successfully treated with leeches and argatroban. The authors did not specifically state

Table 2. Description of Studies Included in Systematic Review

Study and year	Number of patients	HITT flap characteristics	Time until flap failure	Treatment of HITT	Confirmation of HITT by antibody test
Past heparin exposure					
Chen et al. (2008)[16]	470; Group (A): 260 flaps received heparin; Group (B): 245 flaps no heparin	Flaps affected by HITT not discussed.	Group (A): 1 total flap loss, 6 partial flap loss; Group (B): 2 total flap loss, 5 partial flap loss. *Timing of flap loss not reported.	No significant difference in success rates between microvascular free tissue transfer with/or without intra-operative heparin. No existing protocol yet established for flap loss.	N/A
Busch et al. (2009)[8]	2; *Case 1* – Unknown* *Case 2* – Heparin exposed	Malperfusion, arterial thrombosis	Case 1: 12 hours post-op. Case 2: referred from another hospital.	Heparin discontinued; direct thrombin inhibitor (lepirudin).	Case 1: Yes Case 2: Yes
Heparin naïve					
Tremblay et al. (2008)[11]	2	Venous congestion	Case 1: 26 hours post-op. Case 2: Day 2 post-op.	Case 1: Medicinal leeches (post-op day 5); Heparin discontinued (post-op day 12); Argatroban. Case 2: Heparin discontinued (post-op day 8); Danaparoid sodium (Orgaran) intiated, leech therapy.	Case 1: Yes Case 2: Yes
McCleave (2010)[9]	1	Venous congestion, thrombosis, arterial thrombosis	Post-op day 5.	Immediate: Heparin stopped; lepirudin commenced (0.15 mg/kg/hour). Long term: warfarin	Antibody test negative, platelet aggregation assay positive.
Unknown Heparin Exposure					
Medina et al (2010)[20]	1 patient (2 flaps)	Necrotic, venous congested	Post-op day 4 (1st flap); post-op day 1 (2nd flap).	Heparin discontinued; medicinal leeches; argatroban.	No. HITT confirmed by hypercoaguable workup.
Schleich et al. (2008)[10]	1	Decreased arterial Doppler signal	6 hours post-op day 1.	Immediate: discontinuation of heparin; immediate intravenous therapy with argatroban. Long term: warfarin.	Yes

whether a HITT antibody test was positive, but note diagnosis of HITT via a hypercoaguable workup. The final report that we found to describe cases of HITT in microsurgery was reported by Schleich et al. in 2008 in a patient with uknown prior heparin exposure.[10] In their case, congestion was observed 6 hours post-operatively, and successfully treated by discontinuing heparin and switching to anticoagulation with argatroban. They later confirmed their diagnosis of HITT with a positive antibody test.

DISCUSSION

Heparin-induced thrombocytopenia and thrombosis is a well-documented risk of heparin anticoagulation. However, in microsurgery, as demonstrated by the case presented here and by previously published reports describing HITT in skin flaps, HITT can present with a more insidious onset. While there are only 8 previously published manuscripts describing HITT in microvascular surgery, the cases reviewed here show that in microvascular free flaps, HITT has a tendency to present earlier than the typical 5–14 day post-operative timeframe, before measureable thrombocytopenia, and importantly, in patients without previous exposure to heparin.

Two of the earliest reported cases of flap failure associated with HITT were described by Tremblay et al. in 2008.[11] Tremblay describes two patients who began to demonstrate signs of flap venous congestion within hours post-operatively after having received unfractionated heparin (UFH) during flap surgery, with both cases also demonstrating marked drops in platelet count starting as early as postoperative day 1.[11] Schleich et al. reported a similar case in 2008, whereby a patient receiving systemic heparinization for a latissimus dorsi free flap began to show signs of venous congestion in the flap tissue only 6 hours post-operatively, with concomitant serial drops in the platelet count.[10] Similarly, in the case of HITT that we present, our patient developed rapid intraoperative venous congestion and the initial flap failed within 24 hours. Our experience and the limited number of case studies describing HITT in microsurgery support a trend that HITT-related flap failure presents rapidly.

In 2009, Busch et al. described two more cases of total flap loss caused by HITT whereby early onset and recurrent arterial thromboses occurred in the absence of significant platelet drops.[8,20] It was speculated that these conditions represented a locally limited form of the syndrome, in which the immune process occurs at the anastomotic site where heparin is injected locally.[8] The case presented in this report illustrates a very similar HITT-associated flap failure occurring early and without overt thrombocytopenia in a patient with no known past heparin exposure. However, although the patient's clinical course initially depicted locally limited thrombosis, he subsequently developed a DVT. Therefore, we postulate that the seemingly "locally limited form" of HITTs may in fact be a manifestation of a systemic production of antibodies which initially have a predilection for forming thromboses in areas of vascular damage, such as a flap anastomoses. Adding to this is the "iceberg theory", which states that only a fraction of individuals possessing the anti-heparin/PF4 antibodies present with clinical symptoms of HITT, and the remaining individuals, representing the underwater portion of the iceberg, harboring the anti-heparin/PF4 antibodies will neither develop the clinical symptoms of HITT nor thrombosis.[21,22] It follows that the observed venous congestion in the absence of thrombocytopenia could be related to a lower threshold in flaps for presentation with HITT. These cases suggest that in flap failure, unlike other conditions associated with heparin anticoagulation, HITT may occur before presentation of thrombocytopenia.

Flap failure associated with HITT has also been described in patients without previous heparin exposure. In a case reported by McCleave, venous congestion in a free rectus muscle flap only occurred after post-operative day 5, but the patient had no previous heparin exposure.[9] Similarly, in the case we report here, the patient had no prior heparin treatment, yet developed HITT within 1 day following administration of heparin. It was suggested by McCleave that the previously reported cases demonstrating earlier onset of HITT were likely the result of recent prior sensitization to heparin, but it could simply be due to a lower threshold for the onset of HITT in patients receiving microvascular surgery. Although there is only minimal data available in the literature, the fact that over a quarter of the cases of HITT in flap surgery published (including this study) are documented in heparin-naïve patients, warrants further investigation into this relationship as it compares to other surgical patients receiving heparin anticoagulation.

The devastating outcomes associated with HITT have resulted in the development of a series of clinical correlations and guidelines to both identify high-risk patients as well as to rapidly diagnose HITT.[23] The most common clinical presentation of HITT is described by the 4T's: Thrombocytopenia, Thrombosis, Timing, and oTher causes (Table 1).[19] The "4T Score" represents a clinical scoring system, used to estimate a pretest probability of the likelihood of HITT. The clinical score is based on several characteristics including Thrombocytopenia, Timing of platelet count fall, Thrombosis and absence of oTher explanations as the cause of HITT. Evidence a low score ($\leq$3) demonstrates unlikely HITT ($<$5%), an intermediate score (4-5) has a clinical profile of HITT, but alternate explanations may still be relevant, and finally a high score ($\geq$6) representing a likely case of HITT ($>$80%).

Other clinical signs of HITT in patients receiving heparin intravenously include acute reactions such as fever, chills, flushing, hypertension, tachycardia, dyspnea, and diarrhea, as well as local skin reactions at the heparin injection site.[24] It should be noted, however, that the clinical signs of HITT in a flap are identical to that of a flap that has suffered thrombosis due to a technical anastomotic issue. The downstream effect of HITT is to create anastomotic thrombotic complications. Therefore, clinical or other monitoring techniques (for example, transcutaneous O2, venous coupler Doppler, temperature probe) will all show the same effect regardless of the etiology of the flap failure, further complicating identification of the cause of flap failure.

Collectively, our assessment of the case and literature regarding heparin-induced thrombocytopenia and thrombosis in microsurgery suggests that HITT often presents more rapidly, before thrombocytopenia, and in patients without previous heparin exposure in flap surgery. We acknowledge that this observational framework is based on a very small sample size and warrants further investigation into HITT in microsurgery to confirm the validity of these preliminary discussions. However, the diagnosis of HITT in these cases occurs with low pretest probability based on the 4T system. The 4T system is still very relevant in flap surgery. However, given that the failed flaps reviewed here often occurred in a setting of low pretest probabilities, the flap microenvironment may increase the likelihood of HITT and thus necessitate a higher index of suspicion in flap failure. Possible explanations for more rapid onset of HITT in microsurgery could be the associated endovascular manipulation, or perhaps a lower threshold in flaps for activation of the heparin/PF4-antibody complexes that mediate HITT.

The complications associated with HITT further address the need for the development of consensus guidelines for anticoagulation during microsurgery. Anticoagulation exacerbates the risk of hemorrhage intra- and postoperatively, and the conferred benefits of anticoagulation described to date are debatable. A study investigating the role of heparin post-operatively in replantation patients showed that post-operative administration of heparin did not alter outcomes, and that the most important predictor of microsurgical success was the type of injury sustained by the patient and the technical expertise of the surgeon[25]. Other studies also report that intraoperative and postoperative administration of anticoagulation did not affect thrombotic complications, and that the incidence of flap failure is probably independent of anticoagulation[16,26]. The use of anticoagulation in patients affected by certain genetic conditions, such as sickle cell disease, have also been linked to precipitation of complications providing further caution for population-dependent anticoagulation considerations[27]. However, the theoretical benefits of heparin use were confirmed by Khouri et al, who demonstrated a reduction of post-operative complications with application of subcutaneous heparin, although no reductions in thrombotic complications were observed with vessel irrigation with heparin or post-operative intravenous heparin treatment[2]. A case series evaluating compromised flaps in trauma patients proposed a treatment algorithm for salvaging compromised free flaps, and recommends heparin irrigation of the flap as an option upon identification of thrombosis as the cause of flap failure[28]. The debate among the timing, delivery, and associated benefits of heparin treatment during microsurgery, in addition to further complications such as HITT, underscore the need for development of evidence-based guidelines for the use of anticoagulation during microsurgical procedures.

In conclusion, due to the rapid onset of HITT before the traditional clinical indicators in the flap failure reported here, it follows that HITT could be responsible for even more undocumented failed flaps than have been described in the literature. We recommend a higher index of suspicion of HITT in flaps presenting with early venous congestion, especially when other technical and medical etiologies have been ruled out. We advocate for serious consideration of HITT, hematology consultation, and switching thromboprophylaxis to an anticoagulant that functions independent of PF4 in response to persistent thrombosis-related flap compromise without any other identifying causes. We believe that with proper identification of HITT, consequent appropriate medical management can lead to superior systemic and reconstructive patient outcomes.

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