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Perioperative Thromboprophylaxis in Digital Replantation: A Systematic Review

Dimitris Reissis, MBBS, BSc, MRCS*
Luke Geoghegan, MBBS, BSc†
Raghda Sarsam, MBBS, MRCS‡
Quillan Young Sing, MBBS, MRCS‡
Dariush Nikkhah, BM, MSc, FRCS(Plast)*

Background: There is no international consensus on the use of perioperative thromboprophylaxis in digital replantation. Suboptimal perioperative management may lead to replant failure, which compromises extremity function, worsens psychosocial outcomes for patients, and incurs significant cost. This systematic review evaluates and compares the efficacy and safety of perioperative antithrombotic protocols used in digital replantation.

Methods: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)–compliant prospectively registered (PROSPERO, CRD42018108695) systematic review was conducted. Cochrane Central Register of Controlled Trials, Medline, EMBASE, and Scopus were searched up until December 2019. Articles were assessed for eligibility in duplicate by 2 independent reviewers. All comparative studies that examined the use of perioperative thromboprophylaxis in digital replantation were eligible for inclusion.

Results: Collectively, 1,025 studies were identified of which 7 met full inclusion criteria reporting data from 635 patients (908 digital replants, 86% men, average age 37.3 years). Laceration was the most commonly reported mechanism of injury (68%), with 33% of replantation occurring in Tamai zone III. Fourteen distinct perioperative protocols were identified. One study reported significantly higher digital survival with continuous heparin infusion versus bolus heparin. Five studies demonstrated a significantly higher incidence of complications among patients treated with systemic heparin.

Conclusions: The clinical efficacy and safety of perioperative antithrombotic therapy following digital replantation remains equivocal. The perceived benefits of improved digital survival must be tempered against the adverse systemic side effects of antithrombotic and anticoagulant therapies until further prospectively collected data sets become available. *(Plast Reconstr Surg Glob Open 2020;8:e2806; doi: 10.1097/GOX.0000000000002806; Published online 21 May 2020.)*

INTRODUCTION

Traumatic digital injuries account for 1% of all emergency department presentations.[1] Digital injuries are a frequent cause of morbidity; the implications of loss of extremity function extend beyond the affected individual given the disproportionate representation of young, otherwise healthy, men in the patient demographic.[2]

Graft integrity following digital replantation is dependent upon microvascular patency, with luminal occlusion from venous and arterial thrombi resulting in congestion and ischemic necrosis if not adequately treated. Technical success of a digital replantation depends on many factors. Nonmodifiable factors include mechanism of injury, level of amputation, patient age, smoking status, and pre-existing vascular disease.[3] Modifiable factors include surgical technique and perioperative management.[4]

The leading cause of replantation failure is microvascular venous thrombosis.[5] Venous thrombi form in areas of vascular stasis primarily due to activation of the coagulation cascade, with 80% occurring during the

*From the *Department of Plastic and Reconstructive Surgery, Royal Free NHS Foundation Trust, London, United Kingdom; †Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London, London, United Kingdom; and ‡Department of Plastic and Reconstructive Surgery, Broomfield Hospital, Chelmsford, United Kingdom.*

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first 48 hours following digital replantation.[6] Arterial thrombi occur following disruption of endothelial integrity, with both platelet and coagulation cascade activation implicated in arterial thrombogenesis. The relative occurrence of arterial thrombi is less than that of venous thrombi; however, 90% of arterial thrombi form within the first postoperative day.[7]

Prophylactic antithrombotic agents are widely used to mitigate the risk of early vascular complications, with the use of aspirin, intravenous heparin, dextran, phosphodiesterase inhibitors, low molecular weight heparin (LMWH), and local heparin administration previously reported.[8–10] However, universal consensus regarding the type of antithrombotic agent used, optimum dosage, and duration of prophylactic therapy is lacking. Current antithrombotic guidelines are equivocal, with largely anecdotal evidence and individual preference informing the development of antithrombotic protocols. Conflicting evidence regarding the efficacy and safety of antithrombotic agents exists, particularly upon consideration of intervention-related complications such as hemorrhage, hematoma, and thrombocytopenia. The aim of this systematic review is to evaluate the safety and efficacy of perioperative anticoagulation protocols as defined by the presence of complications and rate of digital survival following replantation.

METHODS

Methods were developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement; the protocol was registered in the prospective register of systematic reviews (PROSPERO, reference number CRD42018108695).

Eligibility Criteria

Randomized controlled trials, nonrandomized controlled trials, cohort studies, case–control studies, and case series investigating the comparative effect of perioperative thromboprophylaxis on outcomes of digital replantation were included, irrespective of sample size. We limited our analysis to comparative studies only. Expert opinion, review articles, single case reports, studies that did not report survival rates, noncomparative studies, and studies investigating antithrombotic therapies for salvage purposes were excluded.

Participants

All studies examining the use of perioperative thromboprophylaxis in single and multiple digital replantation of the thumb and/or index-little digits, in both adults and children, were included. Studies examining replantation proximal to the metacarpophalangeal joint, distal fingertip amputation, or composite grafts, where no microvascular anastomosis was performed, were excluded.

Interventions and Comparators

Studies investigating all types of perioperative thromboprophylaxis, including local and systemic administration and all dose regimens, were included. Comparative studies were defined as those that compared digital survival between distinct antithrombotic protocols (either directly or using historic controls) or studies that compared digital survival using a control cohort.

Outcomes

The primary outcome measure was replant survival, as an indication of microvascular patency and technical success of digital replantation. Secondary outcome measures included intervention-related complications such as bleeding and the need of blood transfusion.

Search Strategy

A sensitive search strategy was developed using index and free-text terms in conjunction with a search strategist; full search strategies are given in Supplemental Digital Content 1 (**see figure, Supplemental Digital Content 1,** which displays search strategy for EMBASE and Pubmed, **http://links.lww.com/PRSGO/B370**). They were applied to the Cochrane Central Register of Controlled Trials (CENTRAL), Medline and In Process (1946 to December 2019), EMBASE (1974 to December 2019), and Scopus (1996 to December 2019). The search was limited to human subjects. No date or language restrictions were applied. A secondary search of the reference lists of relevant articles was also performed.

Study Selection

After pooling, the bibliographic EndNote database, version X7 (Thomas Reuters, New York City, N.Y.) was used to compile potentially eligible articles and filter any duplicates. Two reviewers (D.R., L.G.) independently reviewed all titles and abstracts of potentially eligible studies using a standard inclusion criteria pro forma. Full-text articles were then assessed to elucidate study eligibility. Disagreement was resolved through consensus discussion and referral to a third reviewer.

Data Extraction and Analysis

Two reviewers (D.R., L.G) independently extracted data from included studies and assessed the fidelity of collected data. A standard data extraction form was used to collect data regarding the study characteristics, including design, number of patients, anatomical level of amputation, mechanism of injury, thromboprophylactic protocol used, digital replant survival rate, and postoperative complications (local and systemic). The methodological quality of included studies was assessed. Randomized controlled trials were assessed using the Cochrane Risk of Bias tool,[11] and nonrandomized comparative studies were assessed using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool[12]

RESULTS

Search Results

One thousand twenty-five records were identified through database searching: 398 from Medline, 137 from the Cochrane library, 195 from EMBASE, and 295 from Scopus. An additional 48 studies were identified through review of other sources. Upon removal of duplicate studies 393 records remained; 126 full-text articles were assessed for study eligibility, with 7 meeting full inclusion criteria (Fig. 1).

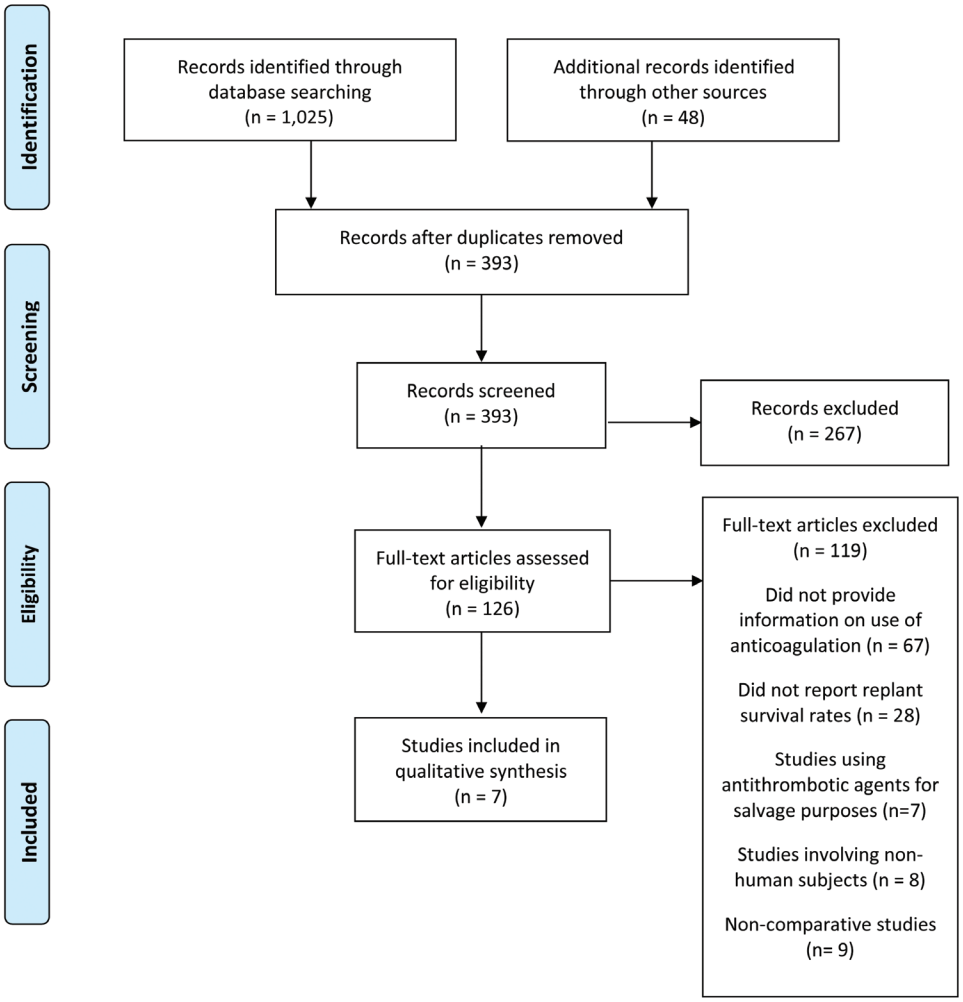

Fig. 1. PRISMA flow diagram detailing a stepwise approach for study selection.

Study Characteristics

Of the included studies, 3 were randomized controlled trials and 4 were retrospective cohort studies based on an established definition.[13] Three out of the 4 retrospective cohort studies used differing anticoagulation protocols in parallel,[14–16] and one retrospective cohort study used differing anticoagulation protocols sequentially across 2 distinct time periods.[9]

Quality of Included Studies

All included retrospective cohort studies were assessed as fair or poor quality, and included randomized controlled trials had either some concerns or a high risk of bias. Included studies had a mean sample size of 105 (range 46–319) and provided a varying amount of data related to potential confounding factors such as zone of replantation and co-morbidities.

Demographic Details

A total of 635 patients with 908 digital replantations were included in the present review; 86% were men with an average age of 37.3 years. Collectively, 5% of the cohort suffered from hypertension and 19% were smokers. Reported mechanisms of injury necessitating replantation included laceration (68%), avulsion (19%), and crush injuries (13%). Three out of the 7 studies accurately reported replantation level with reference to Tamai zones. The commonest level of replantation was in zone III (33%).

Interventions

Fourteen distinct pre- and postoperative antithrombotic protocols were used across all studies comprising antiplatelet agents (aspirin and dextran), anticoagulants (LMWH and unfractionated heparin), and vasodilators (papaverine and prostaglandin E2); see Table 1. One study reported the use of vein grafts in arterial (n = 11) and venous (n = 2) microanastomotic repair.[18]

Outcomes

All included studies reported digital survival as a primary outcome measure, with a mean success rate of 86.5% ± 9.3. One study reported statistically significant differences in digital survival rate following postoperative treatment with either continuous infusion or bolus heparin. Lee et al[9] demonstrated that patients treated with 12,500

Table 1. Comparative Studies Investigating Local and Systemic Thromboprophylactic Regimen

Source	Study Design	No. Patients (Digits)	Anticoagulation Protocol	Duration of Anticoagulation	Digital Survival (%)	Complications	Mean Follow-up Duration
Ngaage et al[14]	Retrospective cohort	— (66)	Preoperative rectal aspirin (n = 16)	—	94%	27% complications	
			No antithrombotic therapy (n = 50)		90%	49% complications Significant difference in the incidence of unspecified soft tissue complications between cohorts	12.6 months
Zhu et al[16]	Retrospective cohort	319 (477)	No antithrombotic therapy (n = 88)		89%	Postoperative hemorrhage (cohort not specified)	1 month
			Dextran (500 mL IV OD) and LMWH (4,000 units SC OD)	7 d	91%		
			Dextran (500 mL IV OD) and PGE1 (120 μg IV OD)	7 d	89%		
			All patients received papaverine 30 mg IM TDS postoperatively for 7 days				
Nikolis et al[15]	Retrospective cohort	— (71)	Aspirin 325 mg PO (n = 10)	>3 d	95.4% overall (no significant difference between cohorts reported)	Overall complication rate, 20.5% Venous congestion, 13.1% Thrombosis, 4% Hematoma, 2.3% Partial necrosis, 1.1% Complication rate significantly higher in the cohort receiving heparin infusion ($P = 0.001$)	—
			Aspirin 325 mg PO + Heparin 5,000 units SC BD (n = 36)				
			Aspirin 325 mg PO + IV Heparin infusion (aPTT 70–90 s) (n = 36)				
Lee et al[9]	Retrospective cohort	61 (61)	Loading dose 12,500 units heparin followed by continuous infusion 12,500 units at rate 20 mL/h (aPTT 51–70 s) (n = 34)	—	91.2%	Blood transfusions required in 29% of continuous cohort versus 7.4% of bolus cohort ($P = 0.032$) No major bleeding complications in either group ($P = 0.108$)	14 days
			IV bolus heparin 12,500 units OD/BD (depending on blood flow/bleeding) (n = 27)		59.3% ($P < 0.05$)	No significant decrease in patients' platelet levels in either group	
			Both cohorts received Aspirin 300 mg PO OD and PGE1 10 mg IV OD			Leeches used in both infusion (n = 5) and bolus (n = 8) cohorts for venous congestion	
Chen et al[8]	RCT	46 (55)	LMWH 5,000 units SC pre-op, 2,500–5,000 units SC BD (n = 26)	7 d	92.3%	Arterial insufficiency: 7.7% LMWH, 7.1% UFH Venous compromise, 11.5%; LMWH, 14.3% UFH	—
			UFH 2,500 units IV pre-op, 1,250 units + 500 mL dextran-40 BD (n = 28)	7–10 d	89.2%	Increased bleeding (ecchymosis, wound, gingival, hematuria, epistaxis, and gastrointestinal) in UFH cohort Increased biochemical coagulopathy in UFH cohort	
AQ5 Li et al[17]	RCT	60 (69)	LMWH 0.4 mL SC BD (unknown dose)	7–10 d	94.3%	aPTT prolongation was significantly longer in the UFH cohort ($P < 0.05$)	—
			UFH 10,000 units SC BD	7–10 d	94.15%	Platelet count dropped significantly compared to preoperative levels in the UFH cohort ($P < 0.05$)	
			Both cohorts also received Papaverine 60 mg IM QDS, Dextran 500 mL BD, Dipyridamole 25 mg PO TDS and Aspirin 50 mg PO QDS for 7–10 days				
Nishijima et al[18]	RCT	88 (101)	No heparin		84%	Infection (3% vs 6% vs 3%)	1 month
			Heparin 10,000 units IV infusion	7 d	89%	Venous congestion (3% vs 25% vs 18%, $P = 0.035$). Venous congestion significantly higher in patients who received heparin versus controls ($P = 0.02$)	
			Heparin 17,500 units IV infusion (aPTT 1.5–2.5 baseline)	7 d	79%	Ischemia (6% vs 6% vs 6%)	

All changes were not statistically significant unless otherwise stated.

BD, twice daily; IV, intravenous; OD, once daily; PGE1, prostaglandin E1; PO, oral; QDS, four times a day; RCT, randomized control trial; SC, subcutaneous; TDS, three times a day; UFH, unfractionated heparin.

units heparin followed by continuous heparin infusion with a target activated partial thromboplastin time (aPTT) between 51 and 70 seconds had a digital survival rate of 91.2% in contrast to patients treated with 12,500 units intravenous bolus therapy directed by the presence of bleeding within the replanted digit. The digital survival rate in the latter cohort was significantly lower at 59.3%.

Three studies reported a significantly higher incidence in postoperative complications in patients who received heparin infusions.[9,15,18] Nikolis et al[15] reported significantly higher rate of composite complications (including venous congestion, thrombosis, hematoma, and partial necrosis) in patients receiving continuous heparin infusions with a target aPTT between 70 and 90 seconds. Lee et al[9] report that patients who received a continuous heparin infusion (target aPTT 51–70 seconds) had a significantly higher incidence of blood transfusion compared with patients who received 12,500 units intravenous bolus heparin. Nishijima et al[18] reported a significantly higher incidence of venous congestion in patients who received postoperative heparin (either 10,000 units or 17,500 units) versus controls.

One paper reported the use of functional measures following digital replantation. Ngaage et al[14] reported a significant difference in monofilament testing (4.41 versus 3.09; $P = 0.046$), crude grip strength (39.3 versus 73.0 lbs; $P = 0.043$), and relative grip strength compared to the uninjured hand (47.3% versus 62.6%; $P = 0.042$) in patients treated without antithrombotic therapy and aspirin, respectively. These results may be confounded by the significantly longer follow-up period in the aspirin cohort as compared to the control cohort (17.7 versus 12.4 months; $P = 0.33$).

DISCUSSION

Replantation has been shown to yield more quality adjusted life years than revision amputation in the treatment of digital amputation injuries. Digital replantation incurs a significantly greater cost than revision amputation with broad incremental cost-effectiveness ratios depending on the injury scenario.[19] Infection, prolonged wound healing, impaired extremity function are complications of replant failure, often requiring further surgical procedures and a prolonged inpatient stay.[20] It is imperative that sound perioperative management is used to minimize the risk of replant failure to optimize individual hand function and subsequent cost per quality adjusted life year gained.

We examined the comparative evidence for different perioperative antithrombotic protocols following digital replantation and identified 14 distinct protocols across the 7 studies that met the inclusion criteria. This may represent the distinct lack of equipoise surrounding perioperative antithrombotic protocols.

Heparin was the most commonly used antithrombotic agent and was used in 11 out of 14 identified perioperative protocols. Perioperative protocols that utilized heparin can be broadly categorized into bolus subcutaneous use, low-dose infusion, and high-dose heparin infusion used alone or in combination with other antiplatelet and vasodilatory agents. One retrospective cohort study demonstrated that patients treated with controlled continuous heparin infusion (aPTT target 51–70 seconds) had a significantly higher digital replantation success rate compared with patients treated with intermittent bolus heparin (91.2% versus 59.3%; $P = 0.032$).[9] All other included studies failed to demonstrate statistically significant differences in digital replant survival rates between perioperative antithrombotic protocols. Lee et al's[9] comparative study defined replant failure as any digit that demonstrated necrosis, shrinkage, lack of bleeding on pinprick testing, and discoloration at the time of discharge. This composite, subjective outcome measure may be limited by detection and confirmation bias, ultimately limiting the internal validity and utility of the study findings.

The theoretical benefits of thromboprophylactic agents are well acknowledged in the current literature. However, Zhu et al[16] demonstrated no significant difference in digital survival among patients who received LMWH 4000 units compared with untreated controls (91% versus 89%, respectively; $P > 0.05$). Similarly, Nishijima et al[18] found no significant difference in digital survival among patients treated with 10,000 units intravenous heparin, 17,500 units intravenous heparin, and untreated controls (79% versus 89% versus 84%, respectively; $P > 0.05$). These findings are further supported by Veravuthipakorn and Veravuthipakorn,[21] who report a 91% digital survival rate without the routine use of perioperative thromboprophylaxis.

When compared with untreated controls, Nishijima et al[18] demonstrated a significantly higher rate of venous congestion in patients treated with systemic heparin (3% versus 21%; $P = 0.02$). Nikolis et al[15] demonstrated a significantly higher composite complication rate (comprising venous congestion, thrombosis, hematoma, and partial necrosis) in patients receiving systemic heparin infusions. Lee et al[9] reported that a significantly higher proportion of patients treated with continuous systemic heparin required blood transfusions compared with those treated with bolus therapy (29% versus 7.4%; $P = 0.03$), although there were no significant differences in major bleeding complications between cohorts. Li et al[17] reported a significant decrease in serum platelet level following systemic therapy with unfractionated heparin that was not observed in patients treated with subcutaneous LMWH.

The currently available data do not demonstrate superiority of a single perioperative protocol in optimizing digital replantation success. Systemic intravenous heparin therapy may increase individual risk of thrombocytopenia and bleeding complications without a discernible benefit in graft survival rates following replantation. However, significant variation exists between studies regarding the type of antithrombotic therapy, combination therapy, route of administration, dose regimen, and timing of administration. Differential reporting of nonmodifiable risk factors for replantation success including mechanism of injury, level of replantation, and co-morbidities limits comparative analysis of study findings. High success rates of digital replantation without use of any perioperative antithrombotic agents may suggest that overriding microsurgical and patient-specific factors contribute significantly to replant survival.

Our results must be considered in view of the study limitations. Although a robust methodology was used, it is possible that relevant publications were overlooked. The quality of data generated is dependent upon the quality of reviewed studies; heterogenous reporting of potential confounding factors and outcome measures limits comparative analysis. Reported management strategies identified in the present review may not reflect current clinical practice.

The limitations of our current understanding of perioperative thromboprophylaxis in digital replantation may stem from an oversimplified attempt to apply a one-size-fits-all approach to replantation. Indeed, the development of a prognostic model for microvascular venous thrombosis in digital replantation will represent a step toward stratified intervention for patients. Further prospective cohort studies are required to determine the individual weighted effect of modifiable and nonmodifiable risk factors on digital replantation survival. This could be achieved through multivariate statistical analysis on large, prospectively collected data sets such as the UK hand registry.

In conclusion, few comparative studies have investigated the role of perioperative antithrombotic therapy in digital replantation. The clinical efficacy and safety of perioperative antithrombotic therapy remain equivocal, and current perioperative strategies must temper the perceived benefits of improved digital survival with adverse systemic side effects of antithrombotic therapies until further prospectively collected data sets become available.

Dariush Nikkhah, BM, MSc, FRCS(Plast)
Department of Plastic and Reconstructive Surgery
Royal Free NHS Foundation Trust
London NW3 2QG
United Kingdom
E-mail: dariushnikkhah@hotmail.com

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