



Free flap thrombosis in patients with hypercoagulability: A systematic review

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Original Article

Background Even with satisfactory anastomosis technique and adequate experience of the surgeon, flap loss due to thrombosis can still occur due to the patient's underlying condition. Patients with hypercoagulability due to etiologies such as malignancy, hereditary conditions, and acquired thrombophilia are among those who could benefit from free flap procedures. This review aimed to evaluate the risk of free flap thrombosis in patients with hypercoagulability and to identify the most effective thromboprophylaxis regimen.

Methods This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. The PubMed, Embase, and Cochrane Library databases were explored. Types of free flaps, types of hypercoagulable states, thrombosis prevention protocols, thrombosis complication rates, and flap vitality outcomes were reviewed. Samples from the included studies were pooled to calculate the relative risk of free flap thrombosis complications in patients with hypercoagulability compared to those without hypercoagulability.

Results In total, 885 articles underwent title, abstract, and full-text screening. Six articles met the inclusion criteria. The etiologies of hypercoagulability varied. The overall incidence of thrombosis and flap loss in hypercoagulable patients was 13% and 10.3%, respectively. The thrombosis risk was two times higher in hypercoagulable patients ($P = 0.074$) than in controls. Thromboprophylaxis regimens were variable. Heparin was the most commonly used regimen.

Conclusions Hypercoagulability did not significantly increase the risk of free flap thrombosis. The most effective thromboprophylaxis regimen could not be determined due to variation in the regimens. Further well-designed studies should be conducted to confirm this finding.

Keywords Free tissue flaps / Thrombophilia / Thrombosis

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INTRODUCTION

Since Buncke and Schulz [1] successfully performed rabbit ear replantation with vascular anastomoses of less than 1 mm in 1966, microsurgery has developed rapidly. The success rate of free tissue transfer utilizing microsurgical techniques reached

95.9% in the late 1990s, and microsurgery has since been established as a dependable reconstructive technique [2].

The anastomosis technique and the surgeon's experience are considered to be the two most important factors contributing to the success of free flap procedures. However, even with satisfactory anastomosis technique and adequate experience of the sur-

geon, flap loss can still occur. Therefore, the failure of free flap procedures is deemed to be multifactorial [3,4]. Other factors associated with flap loss are coagulopathy, infection, vasopressors, hypotension, and the type of the flap [4].

Coagulopathy refers to a group of disorders considered to be a potential cause of flap loss that act synergistically with other well-identified factors [4]. Several reports have suggested that patients with a hypercoagulable state due to conditions such as malignancy, hereditary factors, and acquired thrombophilia might not be good candidates for free tissue transfer procedures [5-7]. However, the advance of microsurgical procedures in recent years has led to the rise of free tissue transfer procedures in malignancy-related reconstruction. Hence, it is essential to investigate the relationship between hypercoagulability and the incidence of thrombosis and flap loss in order to ensure effective patient selection and to design suitable thrombosis prevention protocols for free tissue transfer procedures. Previous review articles explored free flap surgery in hypercoagulable patients, but they have been limited to reports presenting a small number of cases without a control group [5,8,9]. This study systematically reviewed the risk of thrombosis in patients with hypercoagulability who underwent a free flap procedure and received a thromboprophylaxis regimen. More importantly, this study emphasized the quality of the evidence and the review process to provide a more reliable summary and recommendations.

METHODS

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [10]. We investigated studies that involved free tissue transfer procedures performed in patients with any type of hypercoagulable state. Studies were excluded if they did not clearly present thrombosis as a complication or specify the cause of thrombosis. We also excluded case reports, comments, and letters to the editor.

A systematic literature search of the PubMed, Embase, and Cochrane Library databases was performed on April 1, 2018. The search terms used were “free flap,” “microsurgery,” “hypercoagulable state,” “hypercoagulability,” “thrombophilia,” “anticoagulant,” “anticoagulation,” “antithrombotic,” and “thromboprophylaxis.” The search included related terms in the Medline Medical Subject Heading Library. The literature search was limited to human studies.

For this review, we defined a hypercoagulable state as any hereditary or acquired disorder that rendered the patient susceptible to thromboembolism-related complications. This definition included any previous history of thromboembolism, hereditary

mutations of coagulation factors, malignancy, and autoimmune disease confirmed by laboratory evidence [5,9]. Thrombosis that occurred at the anastomosis site was considered to be a complication.

Title and abstract screening were performed to identify relevant studies. The full text of selected studies was read. Study selection was based on the inclusion criteria and exclusion criteria, according to consensus between the authors. The following data were extracted from the studies: types of free flaps performed, types of hypercoagulable states, thrombosis prevention protocols, thrombosis complication rates, and final flap outcomes. Samples were pooled when appropriate and allocated into two groups: hypercoagulable patients and non-hypercoagulable patients. The thrombosis and flap loss rate in each group were used to calculate the relative risk of thrombosis complications in patients with hypercoagulability. Studies conducted by the same group of authors were screened for data duplication.

We evaluated the quality of the studies included in this review using the Quality Assessment Tool for Case Series Studies provided by National Institute of Health, Department of Health and Human Services of the US Government [11]. The statistical analysis was performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The chi-square test was used to examine the association between hypercoagulability and the occurrence of thrombosis and flap loss.

RESULTS

Database exploration yielded 885 articles in the PubMed, Embase, and Cochrane database. Title and abstract screening yielded 16 relevant articles. The full text of those studies was subsequently read to assess whether they matched our inclusion and exclusion criteria. Two studies were excluded because they included pedicled flaps [7,12]. One study was excluded because it explored the hemostasis profile in failed cases only [4]. Another study was excluded because some of the thrombophilia diagnoses were based only on thrombosis events related to the free flap procedure without a previous history of thromboembolic events or laboratory confirmation [13]. Four case reports, a letter to the editor, and a literature review were excluded [5,6,8,9,14,15]. Six series of patients that matched the inclusion and exclusion criteria were included in this review (Fig. 1). The quality of the studies included in this review was assessed according to the Quality Assessment Tool for Case Series Studies checklist as shown in Table 1 [16-21].

Wang et al. [16] studied free tissue transfer in patients with various hypercoagulable conditions in whom several free flap modalities were used. A second study conducted by Wang et al.

Fig. 1. Flow diagram of the systematic literature search

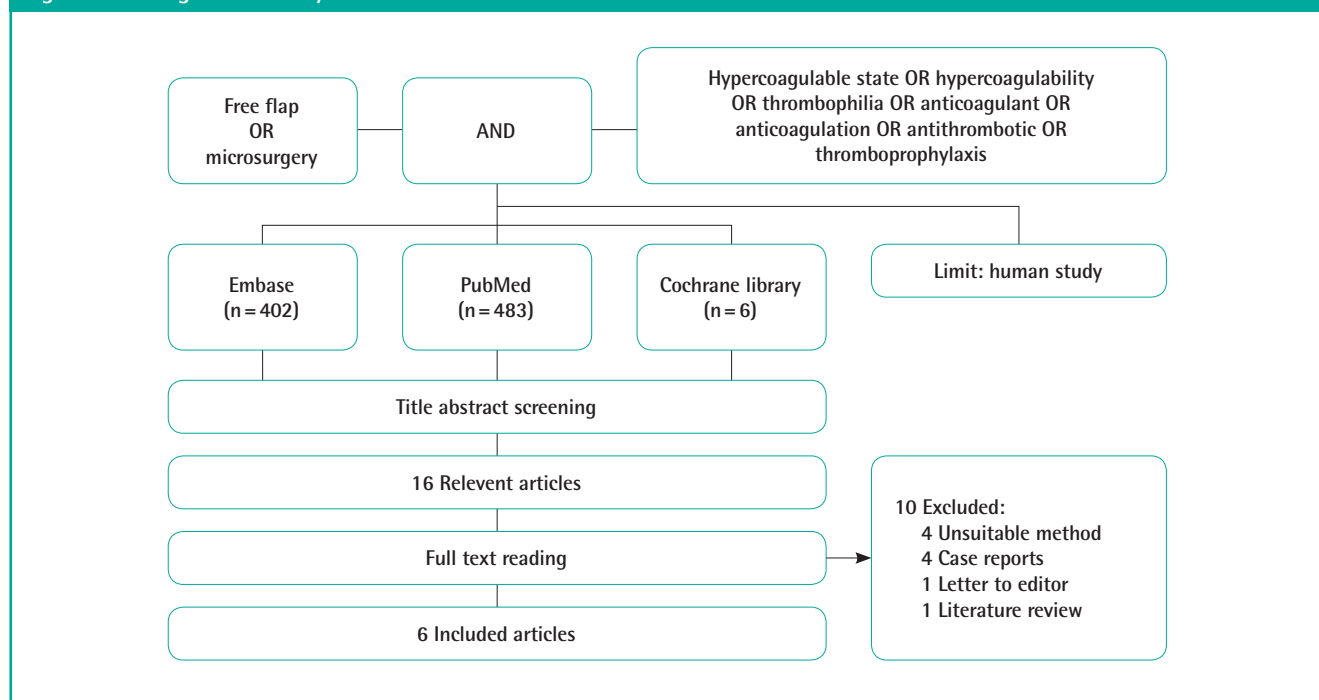


Table 1. Quality assessment of the included studies [12]

Criteria	Wang et al. (n=58) [16]	Wang et al. (n=32) [17]	Arnljots et al. (n=103) [18]	Olsson et al. (n=7) [19]	Nelson et al. (n=32) [20]	DeFazio et al. (n=43) [21]
1. Clearly stated study's question or objective	+	+	+	+	+	+
2. Clearly and fully described study population	+	+	+	+	+	+
3. Consecutive cases	+	+	+	Not stated	+	+
4. Comparable subjects	No comparison	No comparison	Unclear	Unclear	Retrospective cohort comparison	+
5. Clearly described intervention	+	+	+	+	+	+
6. Clearly defined, valid, reliable, and consistently implemented outcome measurement	+	+	+	+	+	+
7. Adequate length of follow up	+	+	+	+	+	+
8. Well described statistical method	+	No statistical analysis	No statistical analysis	+	+	+
9. Well described results	+	+	-	+	+	+

[17] (the same group of researchers) explored free flap procedures performed in hypercoagulable patients with collagen vascular disorders. We examined the cases presented in these two studies and found no subject duplication. Both studies involved the same group of surgeons performing free tissue transfer procedures. Arnljots et al. [18] explored the relationship between hypercoagulability with activated protein C resistance and the occurrence of free flap loss. Olsson et al. [19] investigated hypercoagulability in patients with malignancy who underwent free flap procedures. Nelson et al. [20] studied anticoagulation protocols used in free flap procedures in hypercoagulable patients. They included a group of subjects that were previously analyzed by Wang et al. [16,20]. These subjects were not in-

cluded in the pooled data to prevent duplication. DeFazio et al. [21] conducted a study of free tissue transfer procedures for lower extremity reconstruction. Some of their subjects had a hypercoagulable condition. These studies and their findings are outlined in Table 2.

Based on the pooled data, the incidence of thrombosis in hypercoagulable patients was 13%, while the incidence of flap loss was 10.3%. In the non-hypercoagulable group, the incidence of thrombosis and flap loss was 6.3% and 4.5%, respectively. There was no statistically significant difference in the thrombosis rate ($P=0.074$) or flap loss rate ($P=0.084$).

All subjects in each study received a thromboprophylaxis regimen regardless of their hypercoagulability status. Various proto-

Table 2. Summary of the included studies

Study	Patients Total no.	Free flaps, No. (%)		Types of free flap	Types of hypercoagulability	Thrombosis, No. (%)		Flap loss, No. (%)	
		Non-hypercoagulable	Hypercoagulable			Non-hypercoagulable	Hypercoagulable	Non-hypercoagulable	Hypercoagulable
Wang et al. [16]	41	0	58 (100)	TRAM, DIEP, IGAP, SIEA, Hyperhomocysteinemia, essential thrombocytosis, antiphospholipid antibody, history of DVT or PE, CVA or MI, multiple miscarriages, prothrombin gene mutation, protein C deficiency, Factor V Leiden mutation, SLE	0	12/58 (20.7)	0	8 (13.8)	
Wang et al. [17]	25	0	32 (100)	TRAM, DIEP, RF, IGAP	0	0/32 (0)	0	0/32 (0)	
Arnljots et al. [18]	100	91 (88.4)	12 (11.6)	TRAM, LD, RA, Gracilis, Scapula, RF, Scarpa's fascia	4/91 (4.4)	1/12 (8.3)	Total 1 (1.2), partial 3 (3.2)	Total 1 (8.3)	
Olsson et al. [19]	7	3 (42.9)	4 (57.1)	RF	Malignancy related: elevated fibrinogen, elevated D-dimer, elevated TAT	0/3 (0)	2/4 (50)	0/3 (0)	
Nelson et al. [20] ^a	11	0	15 (100)	TRAM, DIEP, ALT, SIEA, free style thigh	History of thromboembolic event, SLE, Factor V Leiden mutation, anticardiolipin	0	0/15 (0)	0	
DeFazio et al. [21]	41	18 (41.9)	25 (58.1)	ALT, gracilis, VL, RF, TRAM, parascapular, MSAP	Hyperhomocysteinemia, elevated PAI, antiphospholipid antibody, SLE, protein S, protein C deficiency, antithrombin III deficiency, elevated factor-VIII	3/18 (16.7)	4/25 (16)	1/18 (5.6)	

TRAM, transverse rectus abdominis muscle; DIEP, deep inferior epigastric perforator; IGAP, inferior gluteal artery perforator; SIEA, superficial inferior epigastric artery; LD, latissimus dorsi; ALT, anterolateral thigh; FFF, free fibular flap; VL, vastus lateralis; DVT, deep vein thrombosis; PE, pulmonary embolism; CVA, cerebrovascular accident; MI, myocardial infarction; SLE, systemic lupus erythematosus; RF, radial forearm; RA, rectus abdominis; TAT, thrombin-antithrombin III complex; MSAP, medial sural artery perforator flap; total, total loss of the flap; partial, partial loss of the flap (more than 20% of the flap volume).
^aSubjects previously reported by Wang et al. [16] were excluded to prevent duplication of data.

cols were employed in these studies. Heparin was the most common agent used. Wang et al., [16,17] in both of their studies, utilized four main thromboprophylaxis protocols according to each surgeon's routine practice. All of the protocols involved administration of either low-molecular-weight or unfractionated heparin, with or without the addition of aspirin. Some patients who underwent evaluations by hematologists used additional measures, such as clopidogrel, warfarin, and temporary cessation of estrogen receptor antagonist treatment [16,17]. No preoperative thromboprophylaxis was given unless advised by the hematologist. Arnljots et al. [18] and Olsson et al. [19] employed preoperative and postoperative thromboprophylaxis using heparin and dextran. Arnljots et al. [18] added dextran and intravenous heparin intraoperatively. Nelson et al. [20] proposed a novel thromboprophylaxis regimen protocol based on a preoperative thrombophilia workup. They mainly used heparin intraoperatively and postoperatively. DeFazio et al. [21] linked the thromboprophylaxis regimen to the occurrence of a thromboembolic event and the decision to perform a salvage procedure. The dose and duration of the thromboprophylaxis regimen varied, as summarized below in Table 3.

DISCUSSION

As free tissue transfer comes to be more commonly performed in daily practice, it is expected that microsurgeons will encounter a broader spectrum of patients, including those with thrombophilia. It is widely accepted that the anastomosis technique, the surgeon's experience, and the type of free flap are the most influential factors in free tissue transfer procedures. Nevertheless, thrombophilia or hypercoagulability might pose a considerable problem [4]. In this review, we found six studies that were relevant for determining whether hypercoagulability is related to a higher incidence of free flap thrombosis. We also attempted to evaluate the effectiveness of various thromboprophylaxis regimens. All the studies included were case series, classified as level IV evidence. Some of the recognizable weaknesses of the studies were their retrospective nature, lack of a baseline comparison analysis between groups, historical cohort comparison, and small sample size (Table 1).

The analysis of the pooled data showed that the incidence of thrombosis and flap loss were higher in the hypercoagulable group. The available evidence suggested that there was an overall 2 times higher risk of thrombosis and 2.3 times higher risk of flap loss in patients with hypercoagulability. However, these results were not statistically significant. Therefore, hypercoagulability was not considered a contraindication for free flap procedures.

Table 3. Summary of thromboprophylaxis regimen across the studies

Study	Preoperative thromboprophylaxis	Intraoperative thromboprophylaxis	Postoperative thromboprophylaxis
Wang et al. [16,17]	None None None None	None None None IV heparin 300 U/hr before vessel clamping	SQ heparin 5,000 U/8 hr SQ heparin 5,000 U/8 hr, aspirin 325 mg for 2 wk (started after discharge) SQ heparin 500 U/8 hr, aspirin 325 mg for 2 wk (started from POD 1 until 2 wk) Heparin drip 300 U/hr, aspirin 81 mg (started from POD 1 until 2 wk)
Arnljots et al. [18]	SQ enoxaparin 2,000–4,000 U (evening before surgery)	1,000 mL Dextran, IV heparin bolus 80–100 U (during vascular reperfusion)	500 mL Dextran (POD 2 and 4), SQ enoxaparin 2,000–4,000 U (POD 5 until fully ambulant)
Olsson et al. [19]	SQ Dalteparin 2,500–5,000 U (evening before surgery) or 2,500 U (morning)	None	SQ Dalteparin 2,500–5,000 U until POD 5–7
Nelson et al. [20]	None	SQ heparin 5,000 U at induction, IV heparin bolus 2,000 U prior to anastomosis, heparin drip 500 U/hr at time of anastomosis	Heparin drip 500 U/hr (titrated to therapeutic level), warfarin or enoxaparin (until 1 mon)
DeFazio et al. [21]	None	IV heparin bolus 5,000 U prior to pedicle division	Depends on thrombotic complication and salvage procedure: SQ heparin 5,000 U/8 hr, aspirin 325 mg for 2 wk, IV heparin bolus 150 U/kg, heparin drip 500 U/hr, SQ enoxaparin for 2 wk (after discharge)

SQ, subcutaneous; POD, postoperative day; IV, intravenous.

Caution should be taken in interpreting this finding. The thrombosis rate in the hypercoagulable group might have been lower than expected due to the masking effect of the thromboprophylaxis regimen in both the hypercoagulable and non-hypercoagulable groups. While the benefit of anticoagulants in patients without hypercoagulability is still questioned, some evidence has confirmed its role in hypercoagulable patients [8,9,20]. This might have led to a lower thrombosis and flap loss rate in the hypercoagulable group, with a consequent impact on the statistical analysis. Since this possibility cannot be excluded, hypercoagulable patients should be identified and treated properly.

The types of hypercoagulability itself might influence the risk of thrombosis, as there were varying rates of thrombosis across the studies. Based on the existing literature, different types of thrombophilia have different risk profiles for thrombosis [22]. For instance, protein S and protein C deficiency had a higher relative risk of venous thromboembolism compared to Factor V Leiden thrombophilia [22]. However, no previous study has explored these risk variations in microvascular anastomosis. Thrombosis was encountered as a complication in the study of Wang et al. [16], whereas there were no such cases among the collagen vascular disorder patients analyzed by Wang et al. [17] despite the fact that these two studies had an identical thromboprophylaxis strategy, the same operating surgeons, and similar types of free flaps. In contrast, Olsson et al. [19] documented a 50% thrombosis rate in patients with malignancy-related hypercoagulability. Alternatively, this discrepancy could have been due to the small sample size.

Numerous studies have questioned the benefit of routine anti-

coagulation agent administration in free flap procedures. Some studies have even suggested that the use of high-dose heparin may have detrimental effects [23]. However, anticoagulation use in free tissue transfer candidates with a hypercoagulable state has been recommended [8,9].

All the studies included in this review used anticoagulation agents in highly variable doses, durations, and combinations. Wang et al. [16] and Wang et al. [17] employed four main protocols, using primarily postoperative heparin and aspirin administration, with the addition of intraoperative heparin administration in one protocol. Wang et al. [16] performed a statistical analysis revealing that there was no superior protocol among those studied in terms of preventing thrombosis complications. The same thromboprophylaxis regimens resulted in no thrombosis complications in the study of Wang et al. [17], suggesting that hypercoagulability type might influence the result. Wang et al. [16] reported that involvement of a hematologist in the selection of thromboprophylaxis regimen had a positive correlation with good flap outcomes ($P = 0.064$). Nelson et al. proposed a new thromboprophylaxis protocol and compared it with one of the protocols previously described by Wang et al. [16]. They showed that using a different thromboprophylaxis regimen might affect the thrombosis rate in hypercoagulable patients [20]. While that result seemed promising, further research is needed to overcome the limitations of that study, which include a retrospective comparison and small sample size. DeFazio et al. [21] applied an algorithmic approach to determine the thromboprophylaxis regimen based on the occurrence of thrombotic complications and the decision to perform a salvage procedure.

By using this protocol, they managed to obtain a comparable incidence of thrombosis between hypercoagulable and non-hypercoagulable patients. However, the flap loss rate was still unsatisfactory.

Arnljots et al. [18] used a combination of heparin and dextran as preoperative, intraoperative, and postoperative anticoagulants. This study was the only one of the six studies we reviewed that utilized dextran. The most recent studies have indicated that dextran use was related to higher rates of thrombosis and free flap loss [24]. Olsson et al. [19] administered heparin preoperatively and postoperatively.

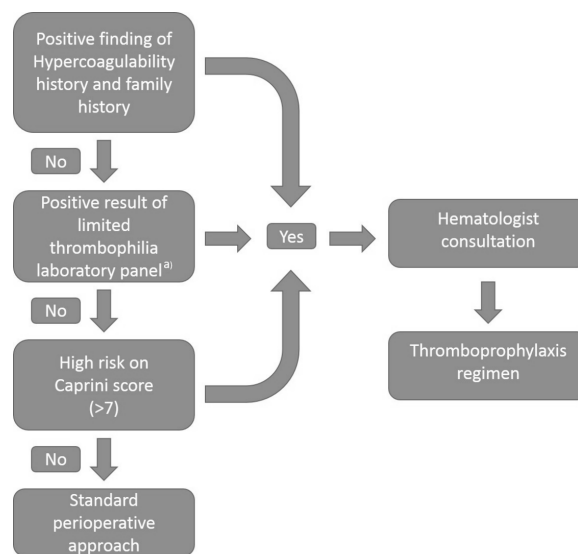
The timing of thromboprophylaxis regimen administration was also a noteworthy variable. Most of the studies used postoperative thromboprophylaxis. Nelson et al. [20] emphasized the importance of using an intraoperative anticoagulant to prevent the formation of the nidus of thrombosis. Preoperative thromboprophylaxis was not a popular option among the studies. The use of preoperative and intraoperative thromboprophylaxis had to be well managed to prevent blood loss and bleeding-related complications.

Since a hypercoagulable state was frequently found during surgery or after flap failure had occurred [7-9,15], free flap candidates must undergo proper preoperative preparation. A thorough history should be taken to discover any previous history of a hypercoagulable state, venous thromboembolism event, or related family history [8,9]. When there is no suspicion of hypercoagulability, it is debatable whether a panel of laboratory examinations should be performed. Some studies have pointed out that hereditary thrombophilia is rare. In addition, laboratory tests are costly and negative results do not necessarily exclude hereditary thrombophilia or other biological risks related to thrombosis [8,9]. However, a cost-effectiveness analysis found that a limited panel of laboratory tests (activated protein C resistance, lupus anticoagulant, hyperhomocysteinemia, protein S deficiency, and factor VIII excess) was actually more cost-efficient than blind administration of thromboprophylaxis for all patients [25]. Thus, we support the use of limited panel tests in such patients. Calculation of the Caprini score might also help in determining the risk of thromboembolism as a complication even though its efficacy to predict thrombosis in microsurgery procedures has not been evaluated [8].

Given negative results of both history and laboratory tests, the choice of using a thromboprophylaxis regimen can be made based on the surgeon's personal experience and preferences. If there is a positive finding in the patient's history, laboratory panel test, or a high-risk classification based on the Caprini score, then a consultation with a hematologist is recommended to determine the most appropriate thromboprophylaxis regimen.

Fig. 2. Detection and management of hypercoagulability in microsurgery

Proposed algorithm for the assessment of free tissue transfer procedure candidates. ^{a)}Activated protein C resistance, lupus anticoagulant, hyperhomocysteinemia, protein S deficiency, and factor VIII excess.



Various studies have suggested that collaboration with a hematologist in the management of these cases might be beneficial [8,9,16]. We combined previously reported algorithms and proposed an approach to assess the risk and to manage hypercoagulability in free flap candidates (Fig. 2).

We are aware of the limitations of this review, particularly the fact that all of the studies assessed had a limited level of evidence. Due to the retrospective nature of some studies, we also understand the risks of bias as a limiting factor. In addition, the exclusion of mechanical or technical factors as the etiology of thrombosis complications during re-exploration was an operator-dependent decision, which might have affected the incidence calculations. Lastly, the broad variety of the types of hypercoagulable states and variation in thromboprophylaxis regimens might hinder a clear evaluation of the risk of thrombosis and the role of anticoagulant agents.

A hypercoagulable state did not appear to increase the risk of thrombosis and flap loss in free flap procedures significantly. Stronger evidence is needed to confirm this finding. Therefore, a hypercoagulable state is not a contraindication for free flap procedures, but a thromboprophylaxis regimen should be administered. The most effective thromboprophylaxis regimen could not be determined based on the currently available studies. Well-designed prospective randomized controlled trials of comparable thromboprophylaxis regimens need to be per-

formed in the future to assess the risk of thrombosis more accurately in patients with various types of hypercoagulability.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The study was performed in accordance with the principles of the Declaration of Helsinki.

Author contribution

Conceptualization: Biben JA, Atmodiwirjo P. Data curation: Biben JA, Atmodiwirjo P. Formal analysis: Biben JA, Atmodiwirjo P. Methodology: Biben JA, Atmodiwirjo P. Project administration: Biben JA. Visualization: Biben JA, Atmodiwirjo P. Writing - original draft: Biben JA, Atmodiwirjo P. Writing - review & editing: Biben JA, Atmodiwirjo P. Approval of final manuscript: all authors.

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