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GLOBAL OPEN

ORIGINAL ARTICLE
Reconstructive

Free Flap Surgery Outcome Related to Antithrombotic Treatment Regime: An Analysis of 1000 Cases

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Background: Autologous free tissue transfer is today an integral part of reconstructive plastic surgery, but still lacks generally accepted guidelines regarding antithrombotic agents. We hypothesized that the overuse of antithrombotic agents could be a risk factor for free flap complications and therefore studied a treatment protocol adjustment.

Methods: Consecutive free flaps between 2005 and 2020 at a single center were analyzed for complications in relation to the use of pre- and intraoperative treatment with three different antithrombotic agents. The use of preoperative low molecular weight heparin (LMWH), intraoperative heparin, and dextran were analyzed in relation to outcome variables, thromboembolic events, or reexploration for hematoma.

Results: Nine hundred thirty-one patients underwent 1000 microvascular free flaps for breast (n = 487), head and neck (n = 365), and extremity (n = 148) reconstruction. Within the first postoperative week, 44 cases had a thromboembolic event and 58 cases underwent hematoma-related reexploration. In the multivariate analysis, thromboembolic events were associated with extremity reconstruction (P = 0.02) and smoking (P = 0.02). Hematoma-related reexploration was more common with triple antithrombotic therapy compared with all other treatment regimes (P < 0.05). The number of antithrombotic agents used perioperatively was linearly decreased, from three to none, over the elapsed time period (P < 0.001).

Conclusions: Hematoma was the most common reason for reexploration and was further associated with the use of multiple antithrombotic agents. Cessation of triple treatment was associated with less hematomas and further reduction of antithrombotic agents did not result in any increase of thromboembolic events. Evidence-based guidelines are warranted for antithrombotic regimes in standard free flap surgery. *(Plast Reconstr Surg Glob Open 2021;9:e3961; doi: 10.1097/GOX.0000000000003961; Published online 6 December 2021.)*

INTRODUCTION

Reconstruction with autologous free flaps has increased during the past two decades and is today an integral part of reconstructive plastic surgery. Success rates of free flap procedures have also increased accordingly to levels between 95% and 99%.[1–3] Flap thrombosis is the most commonly reported complication and also one of the most common reasons for flap failure.[4] To reduce the risk of flap thrombosis, several different antithrombotic medications and regimes have been used, such as dextran, heparin, low molecular weight heparin (LMWH), and acetylsalicylic acid (ASA), alone or in combination. While most agents have proved to be efficient to reduce thrombosis in animal studies, the results in human studies have not been convincing. Favorable effects of antithrombotic regimes to reduce the risk of free flap thrombosis have not been clearly described, but instead an increased risk of

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hematoma complications has been suggested.[3,5–8] A hematoma at the recipient site could lead to pedicle compression or kinking, with the risk of a vascular compromise with subsequent flap failure if not revised adequately.[5]

During the latter half of the 2000s, a high incidence of bleeding complications was noted at our department. This, in combination with the emerging evidence that the antithrombotic medications failed to improve flap survival clinically, led to an adjustment of the routinely used antithrombotic regime at our department.[8] We hypothesized that the decreased usage of antithrombotic medications has led to fewer complications in terms of fewer hematomas, without increasing the risk of thrombosis.

MATERIAL AND METHOD

A retrospective cohort study was conducted, including all consecutive free flap cases at Karolinska University Hospital over a period of 15 years, July 2005–July 2020. The study was approved by the Regional Ethics Committee Stockholm, Dnr 2006/834-31 Amd 2016/1578-32. Data regarding patient characteristics, including age, sex, smoking habits, comorbidities, and type of reconstruction, were retrieved from hospital medical records, as were medications used in the perioperative period. Postoperative complications, including surgical reexploration for hematoma and free flap thrombosis together with systemic venous thromboembolic events (VTE), were registered within the first postoperative week.

The use of antithrombotic agents was between 2005 and 2011 according to a treatment protocol; LMWH (enoxaparin 40 mg or dalteparin 2500/5000 IU) subcutaneous (s.c.) the night before surgery; 2500 IU heparin intravenous (i.v.) intraoperatively; and 500 ml dextran 70 for 10 hours (50 ml/hour) i.v. intraoperatively and during the first and third postoperative days. During the following years, there was a gradual reduction of antithrombotic agents routinely administrated, which was evaluated. Throughout the study period, patients routinely received postoperative LMWH for 10 days or until ambulation to prevent systemic venous thrombosis.

The primary endpoint was to identify complications related to either bleeding or thromboembolic events within the first postoperative week. A patient was coded as having a thrombotic complication if an established arterial or venous thrombosis or a venously compromised flap was found during the reexploration without a concurrent hematoma or if the patient suffered from systemic VTE [ie, deep vein thrombosis (DVT) or pulmonary embolism]. Furthermore, revisions of nonviable flaps were grouped as a thromboembolic event because complete failure inevitably is associated with vascular compromise. Hematoma complication was defined as a patient taken back to surgery due to a bleeding of the donor or recipient site. If a hematoma was found at reexploration with a concurrent thrombosis, and if it was impossible to determine whether the hematoma or the thrombosis was the initial problem, it was defined as a bleeding complication.

Takeaways

Question: Does antithrombotic medication have a beneficial effect on free flap surgery?

Findings: A step-wise reduction of antithrombotic agents used during free flap surgery and the postoperative course led to fewer hematoma-related reexploration within a week, without increasing the risk for flap thrombosis or systemic thromboembolism.

Meaning: Our results, in combination with available literature, show that there is no evidence that additional antithrombotic agents would lead to a better microsurgical outcome.

The results are presented as a mean and SD for continuous variables, and as percentages for categorical variables. A linear regression was used to analyze if the number of medications used decreased over time. To assess whether the antithrombotic therapies were associated with thrombosis or hematoma, a binary logistic regression was performed. Previously identified risk factors for flap complications (age, smoking, body mass index (BMI), cardiovascular disease, previous radiotherapy, reconstructive region) and the different antithrombotic regimes were all included in the multivariate analyses, regardless of significance in the univariate analyses. Gender was excluded from the multivariate analyses since breast reconstruction was included as a variable in the analysis and this group only contained females. The binary regression analyses were repeated to enable comparison between the different therapies. A two-tailed P value of less than 0.05 was considered significant. All statistical analyses were performed with SPSS 26.0 software for OS X.

RESULTS

One thousand free flap surgeries were performed in 931 patients between August 2005 and July 2020. Of these, 487 were breast reconstructions, 365 head and neck reconstructions, and 148 extremity reconstructions. A multivariate analysis was therefore conducted with respect to the different conditions associated with these three reconstruction sites. There was a marked increase in number of free flaps performed per year at the study center, from 35 flaps in 2006 to 127 flaps in 2019. (**See figure 1, Supplemental Digital Content 1,** which displays yearly distribution of antithrombotic therapies and number of free flaps. http://links.lww.com/PRSGO/B854.)

The mean age of the total cohort was 53.5 years and 66.1 % were women. Triple antithrombotic therapy with dextran, preoperative LMWH and intraoperative heparin was administered in 212 patients, 238 patients received LMWH preoperatively and heparin intraoperatively, 151 patients had LMWH preoperatively, 213 had heparin intraoperatively, and 186 patients received no other treatment than postoperative LMWH as a standard VTE prophylaxis, which was given to all patients. Descriptive statistics for the different therapy groups are shown in Table 1.

Table 1. Descriptive Statistics

	Dextran + LMWH Preoperative + Heparin Intraoperative, n = 212	LMWH Preoperative + Heparin Intraoperative, n = 238	LMWH Preoperative, n = 151	Heparin Intraoperative, n = 213	No Treatment, n = 186
Age	54 (14)	57 (15)	58 (16)	49 (12)	50 (13)
Sex, female	57.1	55.0	35.8	91.1	86.6
Current smoking	14.4	15.5	15.2	3.8	2.2
BMI, kg/m²	25 (4)	25 (4)	26 (5)	25 (3)	26 (3)
Cardiovascular disease*	28.8	35.3	36.4	12.7	14.5
Previous RT	61.1	47.9	28.2	66.7	59.9
Reconstructive region					
Breast	39.6	30.3	5.3	80.8	81.2
Head and neck	47.6	51.7	78.1	6.6	4.8
Extremity	12.7	18.1	16.6	12.7	14.0

*Acute myocardial infarction, stroke, peripheral vascular disease, hypertension, or diabetes mellitus.
Data are presented as mean and SD for continues variables and percentage for categorical variables. All patients received postoperative LMWH for a week or until ambulation to prevent systemic venous thrombosis.
n, number of cases; RT, radiotherapy.

Total flap loss occurred in 25 cases (2.5%) of the total cohort, and 102 (10.2%) had a thromboembolic or hematoma complication within a week after the initial flap surgery. Complications within the first postoperative week are presented in detail in Table 2.

Temporal Aspects of Antithrombotic Treatment

During the years 2005-2011, a majority of the patients received triple therapy with preoperative LMWH, dextran and intraoperative heparin. In 2011, the routine use of dextran was ceased (SDC1, http://links.lww.com/PRSGO/B854). The usage of preoperative LMWH from 2013 and onwards has been restricted to patients with a known increased risk of VTE and patients with head and neck cancer. The usage of intraoperative heparin gradually decreased with a marked reduction during 2018 when it was formally omitted from the standard treatment protocol. The results from the linear regression model show a significant decrease in usage of antithrombotic agents over time ($P < 0.001$). Supplemental Digital Content 2 shows the mean numbers of medications used and the percent of complications for each study year. **(See figure 2, Supplemental Digital Content 2,** which displays temporal aspects of antithrombotic treatment and complications. **http://links.lww.com/PRSGO/B855**.)

Table 2. Complications within the First Postoperative Week

	No. Cases
Thromboembolic Events	**44**
Venous thrombosis or venous congestion	25
Arterial thrombosis	8
Total flap failure	5
Pulmonary embolism	6
Deep venous thrombosis	0
Bleeding complications	58
Recipient site hematoma without vascular comprise	24
Recipient site hematoma and venous stasis	19
Recipient site hematoma and partial venous thrombosis	4
Recipient site hematoma and venous thrombosis	2
Recipient site hematoma and arterial thrombosis	1
Recipient site hematoma and arterial and venous thrombosis	3
Donor site hematoma	5

Thromboembolic Events

Within the first postoperative week, a total of 44 cases had a thromboembolic event without concurrent hematoma: 25 cases with flap venous thrombosis or venous congestion needing reexploration, eight cases with flap arterial thrombosis, five cases of revision for total flap failure, six cases of pulmonary embolism, and zero cases of DVT (Table 2). In the univariate analysis, the significant factors were female gender (OR 0.45 [95% CI 0.25–0.83] $P = 0.01$), current smoking (OR 2.38 [95% CI 1.11–5.11] $P = 0.03$), BMI (OR 1.08 [95% CI 1.01–1.16] $P = 0.03$), and extremity reconstruction compared with breast reconstruction (OR 3.03 [95% CI 1.41–6.52] $P = 0.005$). The combination of preoperative LMWH and heparin intraoperatively had a significantly increased risk for thrombosis compared with triple therapy with the addition of dextran (OR 2.98 [CI 95% 1.07–0.29] $P = 0.04$). In the multivariate analysis, current smoking (OR 2.64 [95% CI 1.14–6.14] $P = 0.02$) and extremity reconstruction compared with breast reconstruction (OR 3.62 [95% CI 1.25–10.49] $P = 0.02$) were the only significant factors (Table 3).

Bleeding Complications

Fifty-eight cases underwent hematoma-related re-exploration: 24 cases with recipient site hematoma without vascular comprise, 19 cases with recipient site hematoma and venous stasis, four cases with recipient site hematoma and partial venous thrombosis, two cases with recipient site hematoma and venous thrombosis, one with recipient site hematoma and arterial thrombosis, three cases with recipient site hematoma and arterial and venous thrombosis (all of which have had at least one previous reexploration with hematoma evacuation), and five cases of donor site hematoma (Table 2). The univariate analysis showed that all treatment regimens had a significant decreased risk for hematomas compared with triple therapy with the combination of dextran, preoperative LMWH, and intraoperative heparin: LMWH preoperative + heparin intraoperative (OR 0.50 CI 95% [0.26–0.98] $P = 0.04$), LMWH preoperative (OR 0.15 [CI 95% 0.05–0.51] $P = 0.002$), heparin intraoperative (OR 0.29 [CI 95% 0.13–0.66] $P = 0.003$), and LMWH postoperative (OR 0.29 [CI 95% 0.12–0.69] $P = 0.005$). The same factors were significant

Table 3. Multivariate Logistic Regression for Thrombosis

		OR [95% CI]	P
Age		1.03 [1.00–1.05]	0.06
Current smoking		2.65 [1.14–6.14]	0.02
BMI		1.07 [1.00–1.15]	0.06
Cardiovascular disease*		0.50 [0.11–2.23]	0.37
Previous RT		1.78 [0.79–4.03]	0.17
Reconstructive region			
Breast		Ref	
Head neck		0.93 [0.33–2.64]	0.89
Extremity		3.62 [1.25–10.49]	0.02
Treatment regimes			
Dextran + LMWH preoperative + heparin intraoperative	LMWH preoperative + heparin intraoperative	2.71 [0.87–8.48]	0.09
	LMWH preoperative	2.05 [0.57–7.36]	0.27
	Heparin intraoperative	1.30 [0.34–5.06]	0.70
	No treatment	1.86 [0.51–6.85]	0.35
LMWH preoperative + heparin intraoperative	LMWH preoperative	0.75 [0.30–1.90]	0.55
	Heparin intraoperative	0.48 [0.16–1.40]	0.18
	No treatment	0.69 [0.26–1.82]	0.45
LMWH preoperative	Heparin intraoperative	0.64 [0.18–2.27]	0.49
	LMWH postoperative	0.91 [0.28–2.96]	0.87
Heparin intraoperative	No treatment	1.43 [0.47–4.31]	0.53

All patients received postoperative LMWH for a week or until ambulation to prevent systemic venous thrombosis.
*Acute myocardial infarction, stroke, peripheral vascular disease, hypertension, or diabetes mellitus.
RT, radiotherapy.

DISCUSSION

The current study shows a reduction in antithrombotic medications used over time for free flap thrombosis prophylaxis, without an increased risk for flap failure or systemic thrombosis. The reduction was, however, associated with a decreased risk of reexploration due to hematomas.

During the last two decades there has been a general trend towards a reduced usage of antithrombotic medications in the postoperative setting of microsurgical free flaps. However, there is still no gold standard for antithrombotic prophylaxis in free flap surgery and different regimes of pre-, intra-, and postoperative antithrombotic medications

in the multivariate analysis and no other variables contributed significantly to the results (Table 4).

have rather been based on local protocols and surgeons' own experience and preferences.[9] It is safe to say that not one antithrombotic therapy regime fits all patients. However, our longitudinal study is, to our knowledge, the first one to evaluate microsurgical outcome after a stepwise reduction of antithrombotic agents. The results support previously published studies showing a lack of efficiency of several antithrombotic regimes in reducing the risk for a pedicle thrombosis, and rather highlights the risk by overtreament.[3,6–8] We did not study the effect of ASA because it used to be prescribed only after discharge from the hospital. Therefore, it should not have affected the outcome since only complications during the first postoperative week are described in the current study. ASA is no longer routinely used at the study center.

In the current study, smoking, with a detrimental effect on vascular function,[10] was associated with thromboembolic

Table 4. Multivariate Logistic Regression for Hematoma

		OR [95 % CI]	P
Age		1.01 [0.99–1.04]	0.31
Current smoking		1.88 [0.82–4.31]	0.13
BMI		0.98 [0.91–1.06]	0.59
Cardiovascular disease*		0.75 [0.25–2.27]	0.61
Previous RT		1.02 [0.53–1.97]	0.95
Reconstructive region			
Breast		Ref	
Head and neck		0.66 [0.29–1.49]	0.32
Extremity		0.77 [0.27–2.22]	0.63
Treatment regimes			
Dextran + LMWH preoperative + heparin intraoperative	LMWH preoperative + heparin intraoperative	0.45 [0.22–0.93]	0.03
	LMWH preoperative	0.16 [0.04–0.56]	0.004
	Heparin intraoperative	0.27 [0.11–0.67]	0.004
	No treatment	0.27 [0.11–0.70]	0.007
LMWH preoperative + heparin intraoperative	LMWH preoperative	0.35 [0.10–1.27]	0.11
	Heparin intraoperative	0.60 [0.23–1.59]	0.30
	No treatment	0.61 [0.22–1.65]	0.33
LMWH preoperative	Heparin intraoperative	1.71 [0.40–7.41]	0.47
	No treatment	1.72 [0.39–7.59]	0.47
Heparin intraoperative	No treatment	1.01 [0.36–2.84]	0.99

All patients received postoperative LMWH for a week or until ambulation to prevent systemic venous thrombosis.
*Acute myocardial infarction, stroke, peripheral vascular disease, hypertension, or diabetes mellitus
RT, radiotherapy.

events, whereas only a trend was observed for increasing age and BMI. Free flap extremity reconstruction was also associated with thromboembolic complications. Extremity reconstructions are most often performed after lower leg trauma, where there is often concurrent vessel damage at the recipient site, which could make the anastomosing more challenging.[11] With reference to vascular surgery, it is generally accepted that vascular anastomosis in "low-flow" areas on the lower leg are more prone to vascular complications, compared with "high-flow" areas, such as the neck and upper thorax.[12]

Not surprisingly, when three antithrombotic acting agents were used at the same time, it resulted in an increased risk of hematomas compared with when fewer agents were used. However, it is not possible with the current data to separate the contributing effect of several medications used at the same time and the effect of dextran, since dextran always was used in combination with preoperative LMWH and intraoperative heparin. Previous studies have not shown an increased risk of bleeding when dextran has been compared with other antithrombotic agents or no antithrombotic treatment.[6,7]

Dextran was omitted from the standard treatment at our department in 2011 since there was evolving evidence showing no beneficial effect with dextran used in head and neck free flaps, but rather an increased risk for systemic complications.[13] Over the last decade, most centers have abandoned the use of dextran because several studies have confirmed that it does not decrease the risk for thrombosis and flap failure[7,14–16]

The next antithrombotic medication that was excluded from our protocol for free flap surgery was preoperative LMWH, even though it was still used in high risk patients as well as most of the head and neck free flaps and the lower leg reconstructions throughout the study period. We could not find this change to be associated with an increased risk of thrombosis or decreased risk of hematoma. However, all patients did receive postoperative LMWH as prophylaxis for systemic VTE. The LMWH prophylaxis starts on the first postoperative evening, at earliest 6 hours after the surgery is finished. Zhou et al recently showed an increased risk of bleeding in the group of head and neck patients randomized to postoperative LMWH compared with those receiving dextran and ASA or no antithrombotic agent.[7] On the other hand, even when triple VTE prophylaxis with LMWH, sequential compressive devices, and early ambulation was used in microsurgical breast reconstruction, 3.4% of the patients had a subclinically detected DVT.[17] Emphasizing the importance of chemoprophylaxis to prevent systemic VTE, the American Association of Plastic Surgeons recommend that chemoprophylaxis should be considered in patients with a Caprini score greater than eight.[18]

Lastly, the routine use of heparin intraoperatively was stopped at our department, although it was not associated with thrombosis or hematoma-associated reexplorations. However, it is still administered in a few selected cases with atherosclerotic vessels or evident intima loosening, such as severe radiation induced vasculopathy. Some animal studies have shown favorable results when systemic heparin has been used in microsurgery, but this has not been confirmed in humans.[8,19–21]

Bleeding-related complications accounted for the majority (58/102) of reexplorations that were performed within the first postoperative week, in contrast to some previous studies where thrombosis was more common.[3,4,6,14,22] An overuse of anticoagulants at our unit could therefore potentially explain those complications, of which half (29/58) were bleedings only. One reason for the high proportion of bleeding complication could be that we counted all hematomas with a concurrent venous stasis or a thrombosis as bleeding-complications, while other studies might have reported it as thrombotic complications. Very few previous studies report how they classify the combination of a pedicle thrombosis with a concurrent hematoma. Instead, complications are just defined as thrombosis or hematoma. For future studies it would be of interest to specify this matter. Noteworthy, only six patients (~10%) in the hematoma-complication group had a concurrent manifest arterial and/or venous thrombosis in the current study. Of these, 50% had at least one previous reexploration for hematoma at the recipient site before a thrombosis evolved. This leaves only three reexplorations to be discussed whether the bleeding or the thrombosis came first. With a hematoma at the recipient site, there is a risk of both direct compression/kinking of the pedicle, but also a secondary infection caused by the hematoma. Ahmed et al reported that over 20% of the hematomas created a pedicle compromise and over half of these had a pedicle thrombosis at revision.[5] Corbitt et al showed that infection was the most common reason for total flap loss in head and neck-surgery, though they did not specify the reason for infection.[23] Furthermore, we also included hematomas of the donor site that needed a revision surgery in our analysis, which contributed to a larger hematoma complication-group.

Limitations need to be acknowledged. First of all, the analysis combines three different types of free flaps: breast, head and neck, and extremity. To compensate for this diverse patient cohort, multivariate analysis was conducted. Noteworthy, the reduction of antithrombotic medication has been general for all free flaps at our department. Given the retrospective design, there is a risk of selection bias in that intraoperatively problematic flaps received more antithrombotic treatments since it is up to each surgeon to decide what type of antithrombotic treatments to use. However, in our center the practice is that a treatment protocol for a specific procedure is established within the group of surgeons and these protocols are most often followed, reducing the risk for selection bias. This is supported by a uniform stepwise reduction of agents presented in this study. Importantly, there is a risk that the increased experience of the surgeons biases the results, and we could not analyze if increased experience had a significant effect on the decreased risk for hematomas and other complications. The increased number of free flaps at the study center could indicate more experienced surgeons over time. On the other hand, the number of surgeons performing microvascular free flap procedures have during the same period increased and, unfortunately, several microvascular surgeons have resigned during the study period. Furthermore, the tradition in our

department has been that an experienced microsurgeon is always present at the procedures. However, a specific complication may also relate to a less-experienced surgeon since the majority of our cases are performed in a two-team approach. Noteworthy, a study by Kou et al could not find an association between years of surgical experience and flap complication as long as the operator had acquired board certification in plastic and reconstructive surgery.[24] Finally, we only compared the effect of perioperative variations and did not have a true "no antithrombotic" group to compare with the different antithrombotic regimes, since all our patients received postoperative LMWH.

CONCLUSIONS

Hematoma was the most common reason for re-exploration and was further associated with the overuse of antithrombotic agents. The gradual reduction of antithrombotic agents did not result in an increase in thromboembolic events in the current study. According to our results, in combination with available literature, there is no evidence that additional antithrombotic agents, except for treatment with postoperative LMWH for DVT prophylaxis, would lead to a better microsurgical outcome. At the same time, there is evidence that antithrombotic treatment leads to an increased risk for hematomas. With today's shorter operations and faster mobilization, future prospective multicenter studies ought to be performed to safely establish evidence-based guidelines regarding antithrombotic therapy in autologous free tissue transplantation.

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