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Perioperative anticoagulation in free microvascular flaps – a comparison of different prophylactic regimes in oncologic reconstructive surgery

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ABSTRACT. – OBJECTIVE: **Free tissue transfer has an established place in oncologic head and neck surgery. However, the necessity and specific regimen of perioperative thromboprophylaxis remain controversial. Here, the risk of postoperative hemorrhage contrasts with vascular pedicle thrombosis and graft loss. This work compares three different heparin protocols (A-C) with regard to postoperative complications.**

PATIENTS AND METHODS: **A retrospective analysis of our free flap transplants between 2004 and 2023 was conducted. Inclusion criteria were thromboprophylaxis with (A) 500 IU/h unfractionated heparin (UFH), (B) low-molecular-weight heparin (LMWH) once daily, and (C) LMWH once daily with additional immediate preoperative administration. Primary endpoints were the incidence of postoperative bleeding and hematoma and the appearance of flap thrombosis.**

RESULTS: **We evaluated 355 cases, 87 in group A, 179 in group B, and in group C 89 patients. Overall, postoperative bleeding occurred in 8.7% of patients, and 83% underwent hemostasis under intubation anesthesia, with no significant difference between groups ($p = 0.784$). Hematoma formation requiring revision was found in 3.7% of patients ($p = 0.660$). We identified postoperative hematoma as a significant influencing factor for venous pedicle thrombosis (OR 3.602; $p = 0.001$). Venous and arterial flap thrombosis in the graft vessel showed no difference between the groups ($p = 0.745$ and $p = 0.128$).**

CONCLUSIONS: **The three anticoagulation regimens appear to be equivalent therapy for the prevention of thrombosis without significant differences in postoperative bleeding. The use of LMWH with additional preoperative administration can, therefore, be administered in free flap reconstruction.**

Key Words:
Free flap, Anticoagulation, Microvascular reconstruction, Flap thrombosis, Hematoma, Bleeding, Heparin.

Introduction

After ablative surgery of cancer in the head and neck region, microvascular reconstruction using free flaps is an established and widely used procedure. In addition to the most commonly used radial forearm flap, the anterolateral thigh flap has now also become firmly accepted in the reconstruction of the head and neck region[1]. Both enable consistent success rates of 90-99%, although thrombosis of the graft vessels is still a serious complication[2-4]. In most cases, venous congestion is the reason for inferior blood supply to the flap[2,5]. It is not uncommon for venous inadequate perfusion to be secondary to a postoperative hemorrhagic event, which occurs in up to 10% postoperatively[6-9]. Although early recognition and immediate revision of a thrombosed anastomosis may lead to flap salvage, prevention of this event should remain the primary goal[10]. Perioperative anticoagulation is a commonly used method to decrease the tendency to thrombosis and improve blood flow to the free flaps[11]. However, in addition to the reduced risk of vascular pedicle thrombosis, an increased incidence of postoperative hemorrhagic events has also been reported[12]. The ideal anticoagulant should, therefore, effectively prevent vascular pedicle thrombosis while not increasing the risk of postoperative bleeding or hematoma formation[2,3]. Many antithrombotic agents are available and there is no consensus on the most effective postoperative treatment regimen. Currently, use, timing, and duration are mainly based on clinical experience and practice[13]. With regard to heparin in particular, there is a great deal of disagreement regarding dosage and molecular form [unfractionated

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heparin (UFH) *vs.* low-molecular-weight heparin (LMWH)] with regard to the risk of a bleeding event[10,12,14]. Due to the potent anticoagulant effect of unfractionated heparin, the concern of hematoma formation is always a subject of current debate[15-17]. In contrast, low-molecular-weight heparin is thought to have limited hemorrhagic potential because of its lack of thrombin inhibitory activity[2,18,19]. Therefore, no uniform thromboprophylaxis protocol for the prevention of flap failure after tumor resection with free reconstruction has been established so far[20,21].

Patients and Methods

Study Design

We performed this retrospective study in a tertiary hospital and an academic cancer center. Approval was obtained from the local Ethics Committee and conducted according to the Declaration of Helsinki.

Admission Criteria

We included all patients with oncological surgery and microvascular flap transplantation who received perioperative antithrombotic therapy with either (A) low-dose UFH (500 IU/hour), (B) LMWH started postoperatively (20/40 mg daily) or (C) LMWH applied perioperatively (20/40 mg daily) with an additional administration on the morning of the surgery in our department between January 2004 and April 2023. Patients who did not receive the low-dose UFH or LMWH protocol, for example, because of cardiac risk factors or UFH/LMWH at therapeutic doses, were excluded from the study. The analysis did not include patients in whom LMWH administration on the morning of surgery could not be reliably tracked.

Patient Outcome Characteristics

Patient information, including epidemiologic, oncologic, and surgery-specific parameters, was retrospectively recorded and analyzed. In addition, patient-specific medical records were recorded to determine health status. Furthermore, the medical records were reviewed for postoperative complications such as partial or complete flap failure, thrombosis of the flap pedicle, and minor or major events of postoperative bleeding, hematoma formation, and salivary fistula. We also included thromboembolic events such as deep vein thrombosis and pulmonary embolism.

Features of Thromboprophylaxis

We divided all patients into three groups based on the type of perioperative antithrombotic prophylaxis. Patients who received low-dose UFH after surgery are referred to as "Group A". Patients who received risk-adapted subcutaneously applied low-molecular-weight heparin after surgery are referred to as "Group B". Patients who also received an equal dose of enoxaparin immediately preoperatively in addition to the postoperative subcutaneous application are referred to as "Group C". The surgeon decided whether to use UFH or LMWH, depending on individual experience. Before April 2020, anticoagulation with LMWH was started postoperatively according to in-house guidelines. Since April 2020, an additional risk-adjusted dose has been administered on the morning of surgery. Therefore, patient selection was not randomized. Intravenous administration of low-dose UFH was performed using a standard protocol of 500 IU per hour *via* a perfusion system. Intentionally, dosing was not administered after affecting the activated partial thromboplastin time (APTT). All patients with LMWH received a standard protocol using subcutaneously applied enoxaparin (Clexane, Sanofi Aventis, Frankfurt, Germany). According to the Antithrombotic and Thrombolytic Therapy Conference[22], we assessed individual thrombosis risk using exposure and dispositional risk factors. Patients with a body weight of less than 50 kg received 20 mg of enoxaparin once daily; from a body weight of 50 kg, 40 mg of enoxaparin was applied once daily. Antithrombotic therapy was continued in all groups until the fifth postoperative day. We aimed for patient mobilization on the first postoperative day. In addition, we did not use other anticoagulants that affected clotting time. As an indicator of coagulation, APTT and prothrombin time were measured according to the Quick value [prothrombin time (PT)] on the first to third day [postoperative day 1-3 (POD1-3)], third to fifth day (POD3-5), and eighth to the 12th day after surgery (POD8-12) in each group. For each group, coagulation parameters were compared at different time points to determine any change in coagulation or overdose of heparin. It must be deliberately mentioned that LMWH does not affect APTT or PT.

Properties of the Microvascular Anastomosis

We performed all surgeries with a team of several surgeons from our ENT department, in which all members were qualified to perform each surgical step. Therefore, each surgeon could take

turns performing the tumor resection and neck dissection while the other performed the defect reconstruction. For time-saving reasons, the flap was elevated in parallel once the extent of the resection defect was determined. The surgeon with the most experience was responsible for performing the microvascular anastomosis. The arterial anastomosis was performed under a microscope using a single suture technique with 8.0 or 9.0 sutures. We performed venous anastomosis either with a coupler (Synovis, Micro Companies Alliance, Birmingham, AL, USA) in an end-to-end technique or with single sutures in an end-to-end or end-to-side technique to the jugular veins. Intraluminal heparin application was used in both groups during surgery when a microvascular anastomosis was performed. All patients were monitored in the intermediate care unit during the first 48 hours after surgery, with the head maintained in an upright position of 30 degrees to avoid neck compression. Flap monitoring was performed by an experienced and trained ENT surgeon at two-hour intervals for the first five days. The flaps were monitored by clinical assessment of color and consistency and by Doppler ultrasound examination of the pedicle. The position of the pedicle was marked intraoperatively by the ENT surgeon, who sutured the anastomosis. We defined flap failure as the interruption of arterial flow by observation of pale skin or venous congestion by observation of bluish-livid flap color, which always led to immediate surgical revision.

Outcome Parameters

Primary endpoints were the overall incidence of postoperative bleeding and hematoma and the number of flap losses. Minor complications were addressed by adequate conservative therapy, whereas major complications required surgical revision. For flap loss, we distinguished complete flap loss as a complete necrosis of the graft from partial flap failure for a partial necrosis of the graft without limitation of functionality and continuity. We further documented the occurrence of postoperative thrombosis of the arterial and venous pedicle and the incidence of postoperative salivary fistula. Secondary endpoints were the incidence of postoperative systemic complications.

Statistical Analysis

Patient characteristics, time values, and radiation dose are presented in mean and standard deviation (SD). The oncologic parameters and treatment modality frequency are presented in absolute and relative values. The Chi-square test compared nominal parameters between the three groups to show their homogeneity. We used the *t*-test and the ANOVA-test (one-factor analysis of variance) to reach the metric parameters between the groups. Survival rates were calculated using the Kaplan-Meier method and compared by the log-rank test. Overall survival was calculated from the surgery date to the date of death from an unspecified cause or the date the patient was last documented as living. We performed binary logistic regression analysis to determine the influence of confounding variables on the occurrence of postoperative hemorrhagic events. A p-value lower than $p \leq 0.05$ was considered statistically significant. For statistical analyses, we used SPSS Statistics (Statistics for Windows, version 25.0, IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

We included 355 patients in this study who underwent free flap reconstructions. Groups A, B, and C included 87, 179, and 89 patients. Group A had 72 men and 15 women (mean age 57.9 ± 11.2 years). Group B comprised 138 males and 41 females (mean age 59.7 ± 10.5 years). Group C included 67 men and 22 women (mean age 62 ± 9.9 years). The patient groups did not differ significantly concerning sex ($p = 0.445$) and age ($p = 0.339$). Smoking history ($p = 0.125$), alcohol consumption ($p = 0.356$), and pre-existing medical conditions were also homogeneously distributed between the groups. We observed more heart failure patients in group A ($p = 0.006$). The mean length of hospital stay was 21.3 ± 9.3, 20.1 ± 16.3 days, and 24.8 ± 13.1 for the prophylaxis groups, respectively ($p = 0.635$). The average stay in the intermediate care unit was 5.0 ± 2.6 days, 2.7 ± 1.9 days, and 4.8 ± 4.1 days for groups A, B and C, respectively (Table I, $p = 0.189$).

All patients underwent free flap reconstruction and unilateral or bilateral neck dissection after oncologic tumor resection. All groups had a uniform distribution of T stage ($p = 0.199$) and location of the primary tumor ($p = 0.076$). In most cases (91%), free flap reconstruction was used to restore the upper digestive tract. The remaining cases involved the reconstruction of external defects. In groups A and C, a radial forearm flap (RFF) was performed in 85% and 88% of patients and an anterior lateral femoral flap (ALTF) in 11% and 12%

of patients. In group B, the ratio of ALTF (32%) to RFF (66%) was significantly higher compared to the other groups, respectively ($p = 0.000$). We have a salvage situation in 14.9%, 18.9%, and 10.1% of groups A to C ($p = 0.166$) (Table I).

Regarding the coagulation values, significant differences between APTT preoperatively and postoperatively were found between the groups using the ANOVA test [preoperative F (2, 323) = 9.022, $p = 0.001$; POD1-3 F (2, 91) = 5.262, $p = 0.006$; POD3-5 F (2, 70) = 3.216, $p = 0.043$; POD8-12 F (2, 62) = 3.129, $p = 0.048$, Table II]. Further analysis between groups by post hoc test showed significant differences between group A and group C at every collected point of time (preoperative: 3.221; 95% CI 1.79 - 5.264; $p = 0.001$; POD1-3: 8.105; 95% CI 3.002 - 13.207; $p = 0.002$; POD3-5: 8.911; 95% CI 1.289 - 16.532; $p = 0.022$; POD8-12: 4.944; 95% CI 0.299 - 9.588; $p = 0.035$). In contrast, no difference was shown in the comparison of PT between the groups.

Postoperative Outcome

Postoperative bleeding occurred in 24 cases (8.7%), of which 21 (5.6%) were major and 3 (3.1%) were minor. In group A, 4 (4.6%) major and 3 (3.4%) minor bleeding events occurred. In group B, 12 (6.7%) major and 8 (4.5%) minor bleeding was documented. In group C, 5 (5.6%) major bleeding occurred, whereas no minor bleeding occurred (major bleeding $p = 0.784$ and minor bleeding $p = 0.134$; Table III). Logistic regression analysis showed no significant superiority of any of the anticoagulation regimens concerning the occurrence of major bleeding (odds ratio 0.935; 95% CI 0.645-1.344; $p = 0.722$) or minor bleeding (odds ratio 0.432; 95% CI 0.168-1.108; $p = 0.081$).

Postoperative hematomas were detected in 57 (16.1%) cases, including 13 (3.7%) major and 44 (12.4%) minor hematomas. In group A, 4 (4.6%) major and 12 (13.8%) minor hematomas occurred. In group B, 7 (3.9%) major and 22 (12.3%) minor hematomas were documented. In group C, 2 (2.2%) major and 10 (11.2%) minor hematomas occurred (major hematomas $p = 0.660$ and minor hematomas $p = 0.871$; Table III). Logistic regression analysis showed no significant superiority of any of the anticoagulation regimens concerning the occurrence of major hematoma (odds ratio 0.842; 95% CI 0.512-1.384; $p = 0.498$) and minor hematoma (odds ratio 0.968; 95% CI 0.746-1.256; $p = 0.806$).

The presence of postoperative hematoma seems to have a significant influence on the occurrence of venous pedicle thrombosis (OR 3.602; 95% CI 1.766 - 7.343; $p = 0.001$), whereas arterial thrombosis showed no association ($p = 1.000$).

Regression analysis of potential confounders showed no significant association of a hemorrhagic event with preoperative anticoagulant medication ($p = 0.627$), heart failure ($p = 0.181$), nicotine abuse ($p = 0.852$), or alcohol consumption ($p = 0.560$). In contrast, previous radiotherapy significantly impacted the occurrence of a bleeding event (odds ratio 2.383; 95% CI 1.272-4.465; $p = 0.007$).

A comparison of postoperative PT and APTT showed no significant differences with or without a postoperative bleeding event (Table IV). We also did not detect significantly increased coagulation values in postoperative hematomas (Table V).

Thrombosis of the vascular pedicle was observed on average 48.5 ± 74.1 hours after surgery, leading to immediate surgical revision. We observed venous pedicle involvement in 5 (5.7%), 15 (8.4%), and 7 (7.9%) of the prophylaxis groups, respectively ($p = 0.745$). Besides, in two cases of each group A (2.3%) and group B (1.1%) and one case of group C (1.1%), the arterial pedicle was additionally occluded. We observed an isolated arterial thrombosis in other 3 (3.5%) patients of group A, 2 (1.1%) of group B, and 1 (1.1%) of group C ($p = 0.128$). Overall, we confirmed a flap thrombosis rate of 8 (9.2%), 17 (9.5%), and 8 (8.9%) in the groups, respectively ($p = 0.990$; Table III).

Overall, flap survival was 93.5% (330/355), 96.6% (84/87), 93.3% (167/179), and 91% (81/89) for groups A to C ($p = 0.338$). Three total flap losses (3.4%) and five partial flap losses (5.7%) occurred in group A, a total of 12 (6.7%) and four partial flap losses (2.2%) occurred in group B, and eight total flap losses (8.9%) and no partial loss occurred in group C ($p = 0.323$ and $p = 0.048$; Table III).

Large salivary fistulas were found in 4 (4.6%) (A), 12 (6.7%) (B), and 9 (10.1%) (C) cases ($p = 0.349$). In addition, no case of heparin-induced thrombocytopenia occurred. One case of long artery embolism was documented in group A (1.1%) and two cases in group C (2.2%), while this complication was not detected in group B ($p = 0.120$). The overall revision rate, including neck examination alone without anastomosis revision, was 16 (18.4%), 36 (20.1%), and 16 (17.9%) for the prophylaxis groups, respectively ($p = 0.807$; Table III).

Table I. Patient characteristics for all patients and groups of patients are divided based on perioperative thrombosis prophylaxis..

	Group A (n = 87)	Group B (n = 179)	Group C (n = 89)	All patients (n = 355)	Statistical comparison of groups A *vs.* B *vs.* C *p*-value
Gender (n, %)					0.445
Male	72 (82.8%)	138 (77.1%)	67 (75.3%)	277 (78%)	
Female	15 (17.2%)	41 (22.9%)	22 (24.7%)	78 (22%)	
Age (mean years ± SD)	57.9 ± 11.2	59.7 ± 10.5	62 ± 9.9	59.9 ± 10.6	0.339
Location of primary (n, %)					0.076
Oral cavity	16 (18.4%)	27 (15.1%)	14 (15.7%)	57 (16.1%)	
Oropharynx	41 (47.1%)	95 (53.1%)	46 (51.7%)	182 (51.3%)	
Hypopharynx	16 (18.4%)	24 (13.4%)	19 (21.3%)	59 (16.6%)	
Larynx	3 (3.4%)	14 (7.8%)	9 (10.1%)	26 (7.3%)	
Other	11 (12.6%)	19 (10.6%)	1 (1.1%)	31 (8.7%)	
Tumor stage (n, %)	(n = 82)	(n = 174)	(n = 89)	(n = 345)	0.199
T1	11 (13.4%)	16 (9.2%)	17 (19.1%)	44 (12.8%)	
T2	23 (28.1%)	68 (39%)	33 (37.1%)	124 (35.9%)	
T3	28 (34.1%)	49 (28.2%)	21 (23.6%)	98 (28.4%)	
T4	20 (24.4%)	41 (23.6%)	18 (20.2%)	79 (22.9%)	
Preoperative radiotherapy (n, %)	13 (14.9%)	34 (18.9%)	9 (10.1%)	20 (7.5%)	0.166
Radiation dose in Gy (mean ± SD)	69.9 ± 20.7	62.4 ± 13.6	69 ± 2.6	66.3 ± 12.1	0.296
Flap type (n, %)					***0.000**
Radial forearm flap	74 (85.1%)	119 (66.5%)	78 (87.6%)	271 (76.3%)	
Anterior lateral thigh flap	10 (11.5%)	57 (31.8%)	11 (12.4%)	78 (21.9%)	
Other	3 (3.4%)	3 (1.7%)	0 (0%)	6 (1.7%)	
Venous anastomoses (n, %)	(n = 85)	(n = 177)	(n = 86)	(n = 348)	***0.000**
1	37 (43.5%)	129 (72.9%)	32 (37.2%)	198 (56.9%)	
2	48 (56.5%)	40 (22.6%)	53 (61.6%)	141 (50.5%)	
3	0 (0%)	8 (4.5%)	1 (1.2%)	9 (2.6%)	
Use of coupler (n, %)	72 (82.8%)	146 (81.6%)	69 (80.2%)	287 (82.5%)	0.321
Operation time (mean min ± SD)	716 ± 217	674 ± 174	647 ± 134	678 ± 178	***0.035**
Hospitalization (mean days ± SD)	21.3 ± 9.3	20.1 ± 16.3	24.8 ± 13.1	22.6 ± 13.8	0.635
Time on ICU (mean days ± SD)	5 ± 2.6	4.3 ± 1.9	4.8 ± 4.1	4.2 ± 3.5	0.189
Alcohol	34 (35.8%)	73 (40.8%)	29 (32.6%)	134 (37.7%)	0.356
Smoking	70 (80.1%)	143 (79.9%)	62 (69.6%)	275 (78.6%)	0.125
Pack years (mean ± SD)	37 ± 20	36 ± 18	30 ± 18	35 ± 19	0.152
Preoperative anticoagulation (n, %)	17 (19.5%)	28 (15.6%)	17 (19.1%)	62 (17.5%)	0.249
Heart failure (n, %)					***0.006**
NYHA I	1 (1.1%)	3 (1.7%)	0 (0%)	4 (1.5%)	
NYHA II	9 (10.3%)	9 (5%)	1 (1.1%)	19 (5.4%)	
NYHA III	6 (6.9%)	2 (1.1%)	1 (1.1%)	9 (2.5%)	
PAOD (n, %)					0.954
Fontaine 1	3 (3.5%)	3 (1.7%)	2 (2.2%)	8 (2.3%)	
Fontaine 2	0 (0%)	1 (0.6%)	0 (0%)	1 (0.3%)	
Fontaine 3	1 (1.1%)	1 (0.6%)	0 (0%)	2 (0.6%)	
Coronary heart disease (n, %)	10 (11.5%)	14 (7.8%)	9 (10.1%)	33 (9.3%)	0.566
Apoplex, c. a. (n, %)	6 (6.9%)	11 (6.1%)	1 (1.1%)	18 (5.1%)	0.1
Pulmonary diseases (n, %)	11 (12.6%)	18 (10.1%)	15 (16.9%)	44 (12.4%)	0.281
Diabetes mellitus (n, %)	11 (12.6%)	22 (12.3%)	14 (15.7%)	46 (13.2%)	0.732
Hypertonia (n, %)	37 (42.5%)	77 (43%)	45 (50.6%)	159 (45%)	0.479

Gy, grey; ICU, intermediate care unit; NYHA, New York Heart Association; PAOD, peripheral artery occlusive disease; *vs.*, versus. *$p < 0.05$.

The occurrence of postoperative complications and revision surgery did not significantly affect overall survival in this study cohort (77.6% for revision *vs.* 73.7% for no revision; follow-up of 79.9 ± 29.3 months; $p = 0.768$).

Discussion

This study compares low-dose UFH and LMWH in different regimens in free microvascular reconstruction after head and neck cancer. Based

Table II. Coagulation parameters for all patients and groups of patients divided based on perioperative thrombosis prophylaxis.

	Group A (n = 87)	Group B (n = 179)	Group C (n = 89)	All patients (n = 355)	F (DFn, DFd)	*p*-value
aPTT (mean ± SD)						
Preoperative	32.1 ± 7.3	31.1 ± 4.4	28.9 ± 2.8	30.8 ± 5.1	F (2, 323) = 9.022	***0.001**
A *vs.* B						0.497
A *vs.* C						***0.001**
B *vs.* C						***0.001**
POD1-3	42.4 ± 12.6	38.6 ± 10.3	34.3 ± 4.3	39.5 ± 11	F (2, 91) = 5.262	***0.006**
A *vs.* B						0.058
A *vs.* C						***0.002**
B *vs.* C						0.099
POD3-5	42.4 ± 26.2	35.9 ± 5.8	33.5 ± 6.9	37.8 ± 17.1	F (2, 70) = 3.216	***0.043**
A *vs.* B						0.053
A *vs.* C						***0.022**
B *vs.* C						0.533
POD8-12	37.2 ± 9.6	36.2 ± 9.2	32.3 ± 4.9	35.3 ± 8.5	F (2, 62) = 3.129	***0.048**
A *vs.* B						0.881
A *vs.* C						***0.035**
B *vs.* C						0.071
PT (mean ± SD)						
Preoperative	93.8 ± 8.3	94.4 ± 9.5	96.6 ± 5.5	94.8 ± 8.4	F (2, 325) = 2.606	0.075
POD1-3	76.3 ± 11.5	78.5 ± 13.3	76.7 ± 10.3	77.2 ± 12	F (2, 135) = 0.482	0.619
POD3-5	85.5 ± 12.8	86 ± 12.4	87 ± 10.7	86.1 ± 12.1	F (2, 125) = 0.137	0.872
POD8-12	83.1 ± 18.9	80 ± 20.2	87.5 ± 10.7	83.2 ± 17.6	F (2, 103) = 1.614	0.204

APTT, activated partial thromboplastin time; PT, prothrombin time; POD, postoperative day; F (DFn, DFd), F-value (degree of freedom for the numerator, degree of freedom for the denominator). *$p < 0.05$.

on the current data, we can assume comparable adequacy of UFH and LMWH at different doses. Even though coagulation values showed statistically significant differences between groups pre- and postoperatively, both bleeding events ($p = 0.784$ and $p = 0.127$) and hematoma formations ($p = 0.660$ and $p = 0.874$) were without relevant differences between groups (Table II). The overall thrombosis rate also did not differ between the different thromboprophylaxis groups ($p = 0.990$). However, postoperative hematoma was found to be a significant influencing factor for venous pedicle thrombosis (OR 3.602; $p = 0.001$). With an overall flap survival rate of 94.5%, the presented results are in agreement with those of the current literature[6,20]. No significant differences in flap survival ($p = 0.323$) and overall revisions ($p = 0.807$) can be found in the three groups (Table III).

Although the guidelines[22] for thrombosis prophylaxis recommends perioperative anticoagulation in case of a long duration of surgery as well as an underlying malignant disease, the specific use for the prevention of flap thrombosis is repeatedly part of current investigations and discussions[11]. An evidence-based recommendation regarding type, duration, and dosage has not yet been established but depends much more on the individual experience of the surgeon[2,23-25].

Our study cannot highlight an increased bleeding tendency with additional preoperative LMWH administration compared with postoperative thromboprophylaxis alone. This finding is in agreement with a retrospective evaluation by Eley et al[3], in which different doses of postoperatively applied dalteparin were investigated with regard to hemorrhagic events. They found no increase in hemorrhagic events after increasing the dose from 5,000 IU once daily to 5,000 IU twice daily[3]. Similarly, in Blackburn et al[12], doubling the preoperative dalteparin application from 2,500 IU to 5,000 IU did not result in increased bleeding events requiring revision. Flap survival was 91%, with a significant difference between the high-dose group (83%) and the low-dose group (93%)[12]. In both studies[3,12], the effect of a postoperative hemorrhagic event on flap loss due to secondary congestion with graft thrombosis was not investigated.

However, this very influence was highlighted in a large retrospective cohort analysis of 1,884 free head and neck reconstructions by Ahmad et al[7]. Eighty-eight (4.7%) major hematomas were identified, leading to pedicle thrombosis in twelve cases (0.6%) and clinical inferior blood flow in

Table III. Patients' outcomes for all patients and groups of patients divided based on perioperative thrombosis prophylaxis.

	Group A (n = 87)	Group B (n = 179)	Group C (n = 89)	All patients (n = 355)	Statistical comparison of groups A *vs.* B *vs.* C *p*-value
Total flap loss (n, %)	3 (3.4%)	12 (6.7%)	8 (8.9%)	23 (6.5%)	0.323
Partial flap loss (n, %)	5 (5.7%)	4 (2.2%)	0 (0%)	9 (2.5%)	***0.048**
Postoperative bleeding (n, %)					
Minor	3 (3.4%)	8 (4.5%)	0 (0%)	3 (3.1%)	0.127
Major	4 (4.6%)	12 (6.7%)	5 (5.6%)	21 (5.6%)	0.784
Heamtoma formation (n, %)					
Minor	12 (13.8%)	22 (12.3%)	10 (11.2%)	44 (12.4%)	0.874
Major	4 (4.6%)	7 (3.9%)	2 (2.2%)	13 (3.7%)	0.660
Flap thrombosis (n, %)					
Total rate	8 (9.2%)	17 (9.5%)	8 (8.9%)	33 (9.3%)	0.990
Arterial	3 (3.5%)	2 (1.1%)	1 (1.1%)	6 (1.7%)	0.128
Venous	5 (5.7%)	15 (8.4%)	7 (7.9%)	27 (7.6%)	0.745
Salivary fistula (n, %)					
Minor	9 (10.3%)	22 (12.3%)	7 (7.9%)	38 (10.7%)	0.53
Major	4 (4.6%)	12 (6.7%)	9 (10.1%)	25 (7%)	0.349
Overall revision rate (n, %)	16 (18.4%)	36 (20.1%)	16 (17.9%)	68 (19.2%)	0.807
Deep vein thrombosis (n, %)	-	-	-	-	
Pulmonary artery embolism (n, %)	1 (1.1%)	0 (0%)	2 (2.2%)	3 (0.8%)	0.12
Heparin-induced thrombocytopenia	-	-	-	-	
5-year-OS	66.7%	70.1%	88.8%	74.3%	0.128
Follow-up (mean month ± SD)	91.1 ± 54.9	101.8 ± 57	24.9 ± 10.6	79.9 ± 58.6	***0.001**

OS, overall survival; *vs.*, versus; *$p < 0.05$.

Table IV. Coagulation parameters depending on postoperative bleeding.

	Bleeding (major and minor)	MW ± SD	*p*-value
APTT			
POD1-3	Yes	40.8 ± 8.1	0.591
	No	39.3 ± 11.4	
POD3-5	Yes	37.8 ± 7.9	0.995
	No	37.8 ± 18.3	
POD8-12	Yes	36.5 ± 8.1	0.608
	No	35.2 ± 8.5	
PT			
POD1-3	Yes	75.1 ± 10.5	0.425
	No	77.6 ± 12.2	
POD3-5	Yes	86.8 ± 12.2	0.791
	No	85.9 ± 12.1	
POD8-12	Yes	77.3 ± 19.2	0.216
	No	83.9 ± 17.3	

APTT, activated partial thromboplastin time; PT, prothrombin time; POD, postoperative day; MW, molecular weight.

Table V. Coagulation parameters depending on postoperative hematoma formation.

	Hematoma formation (major and minor)	MW ± SD	*p*-value
APTT			
POD1-3	Yes	41.1 ± 11.2	0.368
	No	39 ± 10.9	
POD3-5	Yes	38.3 ± 6.7	0.875
	No	37.7 ± 18.8	
POD8-12	Yes	36.9 ± 10.1	0.283
	No	34.8 ± 7.9	
PT			
POD1-3	Yes	75.2 ± 11.8	0.314
	No	77.8 ± 12.1	
POD3-5	Yes	83.3 ± 11	0.195
	No	86.8 ± 12.3	
POD8-12	Yes	81.2 ± 17.4	0.533
	No	83.8 ± 17.7	

APTT, activated partial thromboplastin time; PT, prothrombin time; POD, postoperative day; MW, molecular weight.

eight cases (0.4%)[7]. This study confirms our findings in that there is a significant association between postoperative hematoma and the risk of venous flap thrombosis. Also, in a study of anticoagulants for prophylaxis of pedicle thrombosis, Kroll et al[26] found an increasing rate of hematoma formation from 5.3% without anticoagulation to 6.7% with low-dose heparin to 20% with high-dose heparin[26]. Thus, an arbitrary increase in perioperative anticoagulation could pose a threat to transplant success.

We can confirm that APTT and PT had no significant association with the occurrence of postoperative bleeding events and hematoma formations in our cohort (Table IV and Table V). Interestingly, when comparing the groups, there was a constant significant difference between the APTT of the UFH group and the LMWH group with additional immediate preoperative administration (Table II). It should be mentioned that LMWH has no effect on APTT[16]. Numajiri et al[15] showed in a study an increasing hematoma rate with increased APTT after intravenous heparin therapy in free flaps in the head and neck. The applied intravenous heparin dose corresponded to 5,000-10,000 IU per day, a lower dose than intravenous therapy in our UFH group. In this group, 6.6% major hematomas occurred, which was statistically significant compared to the control group without heparin ($p = 0.04$)[15]. In contrast, hematomas requiring revision in our UFH group were only 4.6%. However, Numajiri et al[15] could not prove an influence on flap survival, which is in agreement with our and other results[5].

The results presented must be interpreted considering their retrospective nature, in which the selection of perioperative anticoagulation was not randomized. However, by using a long observation period from 2004 to 2023 with 355 free reconstructions, we were able to include a large number of patients who had a similar distribution of relevant oncological, medical, and surgical parameters to reduce the inevitable selection bias. Only the distribution of free flap types and the presence of preoperative heart failure differed significantly between groups. However, these factors did not seem to influence postoperative complications, so a comparison between the perioperative anticoagulation regimens was still possible.

Furthermore, there was no negative control group in our overall cohort to prove the superiority of anticoagulant therapy over patients without postoperative thromboprophylaxis. However, in our opinion, the conduct of such a prospective study should be critically questioned because tumor disease already represents an independent risk factor for the development of thrombosis. Furthermore, studies[12,27-29] show an increased risk of venous thromboembolism in major tumor surgery in the head and neck region, which is why thrombosis prophylaxis is recommended in this situation in the German guideline[22].

On the other hand, it was not possible to include a group with several anticoagulants. However, in a literature review by Kaciulyte et al[11] they described a postoperative standardized pro-weight antithrombotic protocol, applying a combination of dextran and heparin in their unit. This should reduce platelet aggregation and thrombin activity as well as increase blood flow through fluid expansion. Nevertheless, due to the increased systemic complications, dextran is only of minor importance in current antithrombotic medication[24].

Additionally, there is a clear limitation in the lack of monitoring of postoperative anticoagulants. Although a standardized, APTT-independent UFH dosage was part of the treatment protocol of group C, a significant range of postoperative coagulation parameters was shown. This could be due to the weight-independent dosing, even though other studies[15] have also shown differences in APTT with weight-dependent heparin dosing. Our evaluation did not reveal a significant association between postoperative bleeding and APTT; this could also be due to the small number of hemorrhagic events requiring revision in the UFH group. LMWH therapies were also not controlled by anti-Xa measurement in our evaluation, so we cannot comment on the association of postoperative complications and possible individual overdose in these groups.

After reviewing our results and their classification in the current literature, we recommend postoperative thromboprophylaxis after microvascular reconstruction following surgery in the head and neck. According to the current guideline[22], LMWH should be used in preference to UFH because LMWH has improved pharmacologic properties, a lower risk of side effects, better bioavailability with a longer half-life, and reasonable practicality for once-daily administration[30]. In this context, additional preoperative administration does not pose an increased risk of bleeding and might prevent thrombosis, so this therapeutic regimen can be recommended.

Conclusions

The use of LMWH with additional preoperative administration does not appear to confer a disadvantage in terms of postoperative bleeding events with the same flap success rates compared with postoperative LMWH therapy alone. There also is not an increased risk of thrombosis compared with UFH therapy. Consequently, LMHW can be administered with preoperative application to risk-adapted thromboprophylaxis.

Conflict of Interest

All authors declare that they have no financial support or relationship that may pose a conflict of interest.

Authors' Contributions

Contributions to conception and design: MS, HT, and MK; contributions to data acquisition and interpretation: HT, MS, and MK; contributions to the performance of all statistical analyses: HT and MS; contributions to the drafting of the manuscript: MS and HT; contributions to critical revision of the manuscript: HT, MK, SM, MB, RR, MA, HI, and MS. All of the authors have read and approved the final manuscript.

Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics Approval

All procedures performed in this study involving human participants followed the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval (approval number 170_20Bc) was given by the Clinical Research Ethics Committee of the Medical Faculty (Friedrich Alexander University of Erlangen-Nuremberg, Germany) on June 9, 2020.

Informed Consent

Informed consent was obtained from all study participants.

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