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Are antithrombotic agents necessary for head and neck microvascular surgery?

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W. Zhou, W.-B. Zhang, Y. Yu, Y. Wang, C. Mao, C.-B. Guo, G.-Y. Yu, X. Peng: Are antithrombotic agents necessary for head and neck microvascular surgery?. Int. J. Oral Maxillofac. Surg. 2019; 48: 869–874.

Abstract. The aim of this prospective study was to determine the effect of antithrombotic agents in preventing thrombosis after head and neck reconstructive surgery. A randomized clinical trial of referred patients undergoing free flap surgery between February 2015 and July 2017 was conducted. Four hundred and fifty-four patients were randomly assigned to group A ($n = 153$), administered aspirin and low molecular weight dextran; group B ($n = 150$), administered low molecular weight heparin; and group C ($n = 151$), not administered any antithrombotic agent. Patient demographic characteristics, donor site, thrombosis, haematoma, and flap failure were recorded. Coagulation values including platelet count, prothrombin time, and activated partial thromboplastin time were measured during the perioperative period. Repeated-measures ANOVA and the χ^2 test were used for data comparisons. No significant inter-group differences were observed for postoperative microvascular thrombosis ($P = 0.536$) or flap failure ($P = 0.615$) among the three groups. There were more postoperative haematoma revisions in group B than in groups A and C ($P = 0.032$). It is concluded that postoperative antithrombotic agents neither provide a significant improvement in the free flap success rate nor decrease the risk of thrombosis and may increase the risk of haematoma.

Key words: antithrombotic agent; head and neck; microvascular surgery.

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The concept of vascular free tissue transfer was introduced in 1959, and the first vascular free tissue transfer surgery was performed in 1972[1,2]. With the improvement of microsurgery techniques, free tissue transfer has become the most reliable treatment in plastic and reconstructive surgery of the head and neck. Flap success rates have improved immensely, with rates of between 90% and 99% reported in the literature[3–6]. Although the failure rate of microvascular free tissue surgery is low, flap failure is devastating for both the patient and the surgeon when this occurs.

Thrombosis is the leading cause of free flap failure[7,8]. To reduce the possibility of thrombotic occlusion after free flap transfer, surgeons performing reconstructive procedures routinely administer antithrombotic agents. Of these, therapies with aspirin (acetylsalicylic acid), low molecular weight dextran (LMWD), and low molecular weight heparin (LMWH) play a major role in the prevention of thrombosis. Several studies have examined different methods of preventing thrombosis and flap failure; however, clear evidence for

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the clinical benefit of antithrombotic agents has not yet been established[9–13].

This prospective study was performed to estimate and compare the outcomes and complications of free flap transfer surgery in patients who did or did not receive antithrombotic agents postoperatively.

Patients and methods

Study design

A double-blind, controlled, randomized clinical trial was designed and implemented. This prospective randomized clinical trial was approved by the Ethics Committee for Human Experiments at the Peking University School and Hospital of Stomatology. All patients included were aware of the study aims and provided informed consent for participation.

Study sample

The study sample was derived from the population of patients who underwent free tissue transfer surgery at the Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, between February 2015 and July 2017. The inclusion criteria were as follows: (1) use of vascular free tissue reconstruction to repair head and neck defects, (2) normal status in the function of anticoagulation, and (3) no medication history with anticoagulant agents. Patients were excluded from the study if they had significantly abnormal laboratory values or confirmed haemorrhagic tendencies.

Sample size calculation

The expected postoperative thrombosis rate was 2–7%, based on the published literature. It was expected that the rate of thrombosis formation in each group would be the same or less than before. With a two-sided $\alpha = 0.05$ and a power of 90%, it was calculated that at least 135 patients were required for each group. A total of 484 patients were invited to participate in this study. Patient participation and the reasons for withdrawal are summarized in Fig. 1. Finally, the statistical analysis was done for 454 patients. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is given in Fig. 1.

Randomization and antithrombotic agent application

The 454 patients were divided into three groups using a table of random computer-generated numbers. Group A patients ($n = 153$) received 40 mg oral aspirin and 500 ml intravenous injection of dextran-40 (total dose 30 g) once daily for 5 days postoperatively. Group B patients ($n = 150$) were administered postoperative anticoagulation with subcutaneous injection of 4100 U LMWH once daily for 5 days. Group C patients ($n = 151$) received no anticoagulant. All patients underwent anticoagulation with intraoperative topical irrigation of the donor and recipient vessels using heparinized saline solution and were primarily anastomosed in an end-to-end fashion. All procedures were performed at Peking University School and Hospital of Stomatology by the same chief surgeon (X.P.). There was no change in the anastomotic technique throughout the duration of the study.

Study variables

The free flap outcomes of all patients were recorded. Patient demographic characteristics (including age and sex), clinical information, and data on postoperative complications (including haematoma and thrombosis) were collected. For all patients, the three indices of blood coagulation – platelet count, prothrombin time (PT), and activated partial thromboplastin time (APTT) – were measured preoperatively and at 24 h, 48 h, and 120 h postoperatively.

Data analyses

The χ^2 test or Fisher's exact test was performed to identify differences in patient demographics, donor site, haematoma, microvascular thrombosis, and flap loss between the two groups. Repeated-measures analysis of variance (ANOVA) was used for inter-group and intra-group comparisons with respect to coagulation values, including the platelet count, PT, and APTT, during the perioperative period. All measured data were analyzed using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

This prospective study involved 454 consecutive patients (287 male and 167

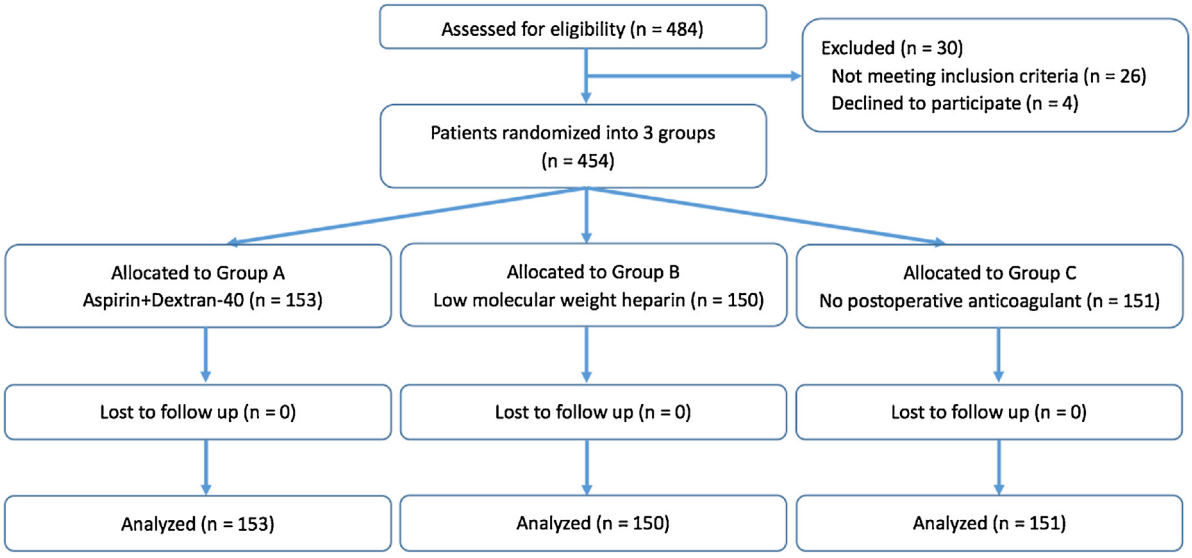

Fig. 1. CONSORT diagram showing the flow of study participants.

Table 1. Characteristics and donor sites of the study patients[a].

	Group A (Aspirin + LMWD)	Group B (LMWH)	Group C (No agent)
Sample size	153	150	151
Age, years (continuous)	49.05 ± 13.60	49.42 ± 14.76	48.89 ± 15.51
Sex (binary), male	91	90	106
Donor site (categorical)			
Fibula flap	86	89	101
ALTF	32	35	25
RFFF	32	22	22
Iliac crest flap	2	3	3
Submental free flap	1	1	0

ALTF, anterolateral thigh flap; LMWD, low molecular weight dextran; LMWH, low molecular weight heparin; RFFF, radial forearm free flap.
[a]Results are presented as the number (*n*), or as the mean ± standard deviation.

female) with a mean age of 49.1 years (range 18–78 years), who underwent free tissue transfer surgery in the head and neck region. The free flaps used for reconstruction included 276 fibula flaps, 92 anterolateral thigh flaps, 76 radial forearm free flaps, eight iliac crest free flaps, and two submental free flaps (Table 1).

Five cases (3.3%) of microvascular thrombosis occurred in group A (aspirin + LMWD), two (1.3%) in group B (LMWH), and four (2.6%) in group C (no agent). No statistically significant inter-group difference was observed with respect to postoperative microvascular thrombosis ($P = 0.536$).

There were four cases (2.6%) of haematoma in group A, 10 (6.7%) in group B, and two (1.3%) in group C. The incidence of haematoma was significantly higher in group B (6.7%) than in groups A and C (2.6% and 1.3%, respectively) ($P = 0.032$). In all haematoma cases, no obvious source of bleeding was found upon re-exploration. All flaps for which haematoma was explored survived.

The free flap success rate was 98.0%, 99.3%, and 98.7% in group A, group B, and group C, respectively. No statistically significant inter-group difference was noted with respect to flap failure ($P = 0.615$) (Table 2).

Coagulation values (platelet count, PT, and APTT) during the perioperative period were measured to investigate the change in coagulation function. The platelet count showed a significant decreasing trend on day 1 postoperative and a returning trend on day 5 postoperative in all three groups. The PT and APTT showed a significant increasing trend on day 1 postoperative and a returning trend on day 5 postoperative in all three groups. The platelet count, PT, and APTT were found to change significantly during the perioperative period in each group (repeated-measures ANOVA, $P < 0.05$). Significant inter-group differences were observed for the change tendency of PT and APTT in group B compared to group A and group C ($P < 0.05$). No significant difference between the groups was observed for the change tendency of the platelet count ($P = 0.172$) (Tables 3–5, Figs. 2–4).

Table 2. Outcomes and complications in the study patient groups.

	Group A (Aspirin + LMWD)	Group B (LMWH)	Group C (No agent)	*P*-value
Sample size (*n*)	153	150	151	
Thrombosis	5	2	4	0.536
Haematoma	4	10	2	0.032*
Flap failure	3	1	2	0.615

LMWD, low molecular weight dextran; LMWH, low molecular weight heparin.
*$P < 0.05$.

Table 3. Patient platelet counts ($\times 10^9$/l) during the perioperative period.

	Group A (Aspirin + LMWD)	Group B (LMWH)	Group C (No agent)
Preoperative	235.14 ± 62.12	249.47 ± 69.77	254.07 ± 84.59
Postoperative			
24 h	209.93 ± 62.74	220.34 ± 64.51	226.31 ± 78.22
48 h	210.71 ± 65.27	210.43 ± 63.69	221.85 ± 74.07
120 h	260.16 ± 80.30	266.87 ± 76.22	271.73 ± 90.14
P-value	$P = 0.172$		

LMWD, low molecular weight dextran; LMWH, low molecular weight heparin.

Discussio

Antithrombotic agents have been used for decades as a regular treatment to decrease thrombosis in microsurgery. At present, most centres performing microsurgery follow their own antithrombotic regimen, based on a combination of aspirin, LMWD, and LMWH. Although the efficacy of postoperative antithrombotic agents in free flap survival is well demonstrated in animal studies, the literature in this regard remains inconsistent[14,15]. Thus far, there is no consensus regarding the standard protocol for preventing thrombosis after head and neck reconstructive surgery. Microsurgeons all over the world have tried different protocols, with different drugs or different dosage regimens, to identify the most effective way to prevent thrombosis after vessel anastomosis in head and neck reconstructive surgery.

Aspirin acts as an antiplatelet agent by irreversibly blocking the enzyme cyclooxygenase on either platelets or endothelium. This decreases the products of arachidonic acid metabolism involved in platelet aggregator and vasoconstrictor[9]. Although the use of aspirin is relatively safe, side effects including bleeding, gastritis, allergic reactions, and nephrotoxicity have been reported[16]. The dosage of aspirin used for the prevention of thrombosis, as reported in the literature, ranges from 81 mg to 325 mg[12,17,18]. Although the dose–effect relationship has been proved in animal trials, the clinical literature demonstrating the relationship between the dosage and effectiveness of aspirin is scarce.

Dextran−40 is a complex polysaccharide made of many glucose molecules and is composed of chains of varying lengths. It is used as an antithrombotic agent to reduce blood viscosity and as a volume expander in anaemia. Risks associated with the use of dextran−40, such as unwanted bleeding, pulmonary oedema, allergic reactions, and acute renal failure, have been reported[19]. These side effects have limited the use of LMWD in the USA and other countries.

In China, low-dose aspirin (40 mg/day) and dextran-40 (30 g/day) are recommended in a textbook and administered in most institutions[20]. Mao et al.[21] reviewed 3140 cases of free flap transfer in the head and neck region performed between May 1999 and May 2015. They used aspirin (40 mg/day) and LMWD (30 g/day) as the prophylactic antithrombotic agents to prevent microvascular thrombosis. An overall free flap success rate of 98.5% was reported, with no general side

Table 4. Patient prothrombin times (PT, s) during the perioperative period.

	Group A (Aspirin + LMWD)	Group B (LMWH)	Group C (No agent)
Preoperative	10.98 ± 0.79	11.11 ± 0.76	11.17 ± 0.78
Postoperative			
24 h	11.43 ± 0.92	11.80 ± 1.04	11.59 ± 1.22
48 h	11.08 ± 0.95	11.59 ± 1.39	11.27 ± 0.96
120 h	10.96 ± 0.77	11.33 ± 1.19	11.06 ± 1.05
P-value			
Group A vs. B	0.015*		
Group A vs. C	0.744		
Group B vs. C	0.013*		

LMWD, low molecular weight dextran; LMWH, low molecular weight heparin.
* $P < 0.05$.

Table 5. Patient activated partial thromboplastin times (APTT, s) during the perioperative period.

	Group A (Aspirin + LMWD)	Group B (LMWH)	Group C (No agent)
Preoperative	28.47 ± 3.56	28.85 ± 4.04	28.91 ± 4.41
Postoperative			
24 h	29.94 ± 4.34	33.05 ± 5.89	30.31 ± 5.22
48 h	30.03 ± 4.91	34.14 ± 6.16	29.91 ± 5.23
120 h	26.61 ± 4.61	29.21 ± 5.78	26.46 ± 4.51
P-value			
Group A vs. B	<0.001*		
Group A vs. C	0.348		
Group B vs. C	<0.001*		

LMWD, low molecular weight dextran; LMWH, low molecular weight heparin.
* $P < 0.05$.

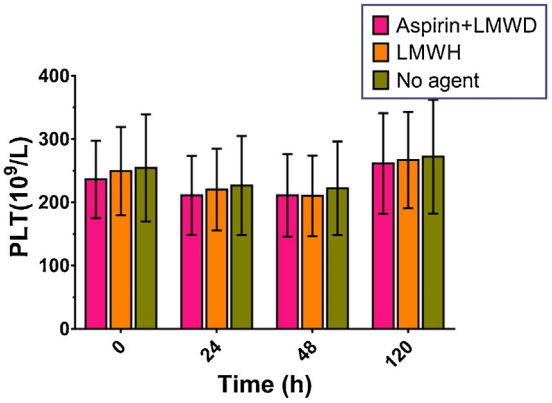

Fig. 2. Platelet counts in the three groups during the perioperative period.

effects, such as pulmonary oedema, gastritis, and allergic reactions, occurring with the use of the combination of aspirin and LMWD. Therefore, the Chinese traditional antithrombotic strategy based on the literature reviews was used in the present study, with low-dose aspirin (40 mg/day) and LMWD (30 g/day) as the antithrombotic agents in group A; again, no general side effects, such as pulmonary oedema, gastritis, and allergic reactions, occurred with the use of this combination. Five cases (3.3%) of venous anastomotic thrombosis occurred postoperatively in patients administered aspirin and LMWD, which resulted in a free flap success rate of 98.0%.

LMWH is the most common regimen used for the prevention of thrombosis. This is a derivative of unfractionated heparin that is prepared through the deaminative hydrolysis of standard heparin into short polysaccharide fragments. These molecules are known to have the same inhibitory effect on active factor X but have a weaker antithrombin (factor II) activity. LMWH has higher bioavailability, a longer plasma half-life, and a steady dose–response relationship when compared to unfractionated heparin. In China, patients undergoing thoracic and abdominal surgery normally receive low-dose LMWH based on their weight (100 IU/kg) to prevent deep vein thrombosis (DVT) and pulmonary embolism (PE). However, most patients who undergo free flap transfer surgery in the head and neck region are actually encouraged to perform early active movement, so the incidence of DVT/PE in patients who have undergone free flap transfer surgery is fairly low. Therefore, LMWH is not regularly used to prevent DVT/PE in these patients. The different anticoagulant treatments used for patients in this study were not to prevent DVT/PE but to prevent thrombosis of the vessel anastomosis.

A brief review of the literature revealed a scarcity of studies on the change in coagulant function following the use of antithrombotic agents in patients undergoing head and neck microvascular surgery. In the present study, the three coagulant indices were measured at 24 h, 48 h, and 120 h postoperative, for the following reasons: (1) the previous literature has indicated that the risk of thrombosis is highest during the first 48 h after surgery (80%) and then decreases to 10% after 72 h[22]; (2) the administration of antithrombotic agents was stopped at 120 h postoperatively. The platelet count showed a significant decreasing trend on day 1 postoperative and a returning trend on day 5 postoperative in all three groups. The PT and APTT showed an increasing trend on day 1 postoperative and a returning trend on day 5 postoperative in all three groups. Although the mechanism of this phenomenon is not entirely clear, it is thought that it is likely associated with the activation of some self-regulatory mechanism or because of the effect of intravenous fluid administration. The significant inter-group differences observed for the change tendency of PT and APTT in group B compared to group A indicate that LMWH is more effective than the other antithrombotic agents for the prevention of thrombosis.

Haematoma and thrombocytopenia are known complications associated with heparin use[23]. In this study, 10 cases (9.9%) of haematoma occurred postoperatively in patients administered LMWH. A significant difference with respect to postoperative haematoma was found for patients administered LMWH ($P = 0.032$). The authors believe that, among common antithrombotic agents, LMWH is the most effective but may increase the risk of haematoma formation at the same time.

Several microsurgeons have reported that the outcomes of anticoagulant use versus non-use are the same, with respect

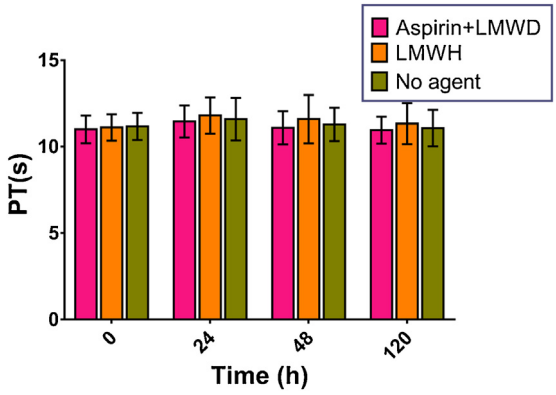

Fig. 3. Prothrombin times in the three groups during the perioperative period.

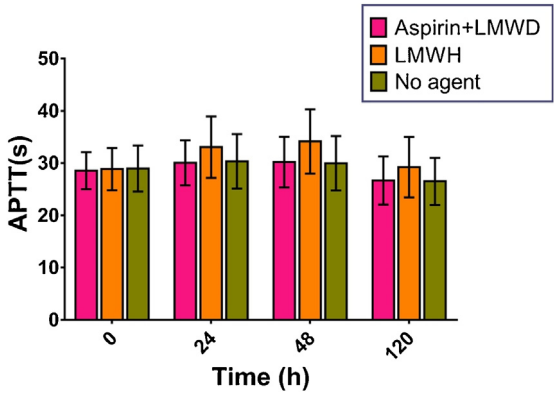

Fig. 4. Activated partial thromboplastin times in the three groups during the perioperative period.

to a variety of anticoagulants. Lighthall et al.[22] reviewed 184 cases in which no anticoagulant agent was used, for which the flap success rate was 94.6%. They concluded that postoperative thromboprophylaxis with aspirin after microvascular free tissue transfer does not provide an improvement in free flap survival. Riva et al.[24] reviewed 836 cases in which no antithrombotic agent was used. Thrombosis occurred in 27 flaps (9.5%) in the dextran-40 group and 74 flaps (8.9%) in the no antithrombotic group. Furthermore, the overall flap loss rate was 6.0% in the dextran-40 group and 5% in the no antithrombotic group. According to their results, antithrombotic therapy with dextran-40 does not have any statistically significant influence on the outcome of free tissue transfer in routine head and neck reconstructive surgery. In the present study, there were seven cases of venous anastomotic thrombosis that occurred postoperatively in patients who were administered antithrombotic agents, eventually leading to a free flap success rate of 98.7%. There were no significant inter-group differences with regard to thrombosis and the flap success rate ($P = 0.536$ and $P = 0.615$, respectively). The authors believe that the use of antithrombotic agents does not decrease the risk of thrombosis or flap failure.

Thus, the important question remains as to the reason each group shared the same free flap outcome. In other words, are antithrombotic agents indeed necessary for head and neck microvascular surgery?

Firstly, in the early stages, the majority of microsurgery procedures were performed in hand surgery. Hence, it is safe to assume that the use of antithrombotic therapy was initiated and performed by hand microsurgeons. With the improvements made in microsurgery techniques, free flap surgeries became popular and reliable, and antithrombotic therapy followed the protocols used in hand microsurgery. The flaps most commonly used for reconstruction in the head and neck region are the fibula flap, anterolateral thigh flap, and radial forearm flap. The arteries of these flaps measure 1.5–2.5 mm, 2–2.5 mm, and 2.5–3.5 mm, respectively, and the veins of these flaps measure 2–4 mm, 1.8–3.3 mm, and 2.5–4 mm, respectively[25]. The most common recipient vessels used for anastomosis are the facial artery, superior thyroid artery, external jugular vein, and branch of the internal jugular vein. The diameters of these vessels normally range from 1.5 mm to 5 mm. In contrast, the diameter of vessels that need to be anastomosed in hand surgeries normally range from 0.2 mm to 1.0 mm. It is clear that the diameters of anastomosed vessels in hand versus head and neck microsurgery are not the same. It is generally believed that the larger the vessel diameter, the lesser is the vessel crisis. In the present study, the low thrombosis rate indicates that the non-use of antithrombotic agents did not lead to more thrombosis events.

Secondly, surgeon experience has been reported to be one of the most important factors associated with flap survival. When free flap transfer surgery was introduced at Peking University School and Hospital of Stomatology, the risk of postoperative complications was relatively high, even with the use of postoperative anticoagulants. With the improvements in surgeon skill, the free flap failure rate decreased gradually. Now, emphasis is placed on the importance of exercise of vascular anastomotic suturing and avoiding pedicle compression, kinking, and twisting during the surgery, rather than the use of postoperative anticoagulants. For patients with preoperative hypercoagulability or a history of irradiation to the head and neck, the use of LMWH as a prophylactic measure is also recommended. Thus far, the clinical data in most reports published in the literature have been derived from multi-centre studies or studies involving different microsurgeons at one institution, which may have affected the investigation of the precise effect of antithrombotic agents. For this reason, all procedures in the present study were performed at Peking University School and Hospital of Stomatology by the same chief surgeon (X.P.). There was no change in the anastomotic technique throughout the duration of the study.

Lastly, excepting intraoperative injury to the vessel epithelium, individual related factors including smoking, previous radiation, hypertension, diabetes, and increasing age may also influence the occurrence of thrombosis in the pedicle of the free vascularized transplant during or after microsurgery. It is recommended that postoperative anticoagulation is administered based on an individual risk assessment.

In conclusion, the use of antithrombotic agents in head and neck microvascular surgery does not decrease the risk of thrombosis formation and may increase the risk of haematoma formation. It is recommended that postoperative antithrombotic agents should not be used routinely, but instead based on an individual risk assessment.

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Competing interests

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

There is no conflict of interests.

Ethical approval

This prospective randomized clinical trial was approved by the Ethics Committee for Human Experiments at the Peking University School and Hospital of Stomatology (PKUSSIRB-2014160100).

Patient consent

Not required.

References

1. Seidenberg B, Rosenak SS, Hurwitt ES, Som ML. Immediate reconstruction of the cervical esophagus by a revascularized isolated jejunal segment. *Ann Plast Surg* 1959;**149**:162–71.
2. McLean DH, Buncke Jr HJ. Autotransplant of omentum to a large scalp defect, with microsurgical revascularization. *Plast Reconstr Surg* 1972;**49**:268–74.
3. Chien W, Varvares MA, Hadlock T, Cheney M, Deschler DG. Effects of aspirin and low-dose heparin in head and neck reconstruction using microvascular free flaps. *Laryngoscope* 2005;**115**:973–6.
4. Eckardt A, Fokas K. Microsurgical reconstruction in the head and neck region: an 18-year experience with 500 consecutive cases. *J Craniomaxillofac Surg* 2003;**31**:197–201.
5. Kruse AL, Luebbers HT, Gratz KW, Obwegeser JA. Factors influencing survival of free-flap in reconstruction for cancer of the head and neck: a literature review. *Microsurgery* 2010;**30**:242–8.
6. Lueg EA. Comparing microvascular outcomes at a large integrated health maintenance organization with flagship centers in the United States. *Arch Otolaryngol Head Neck Surg* 2004;**130**:779–85.
7. Bui DT, Cordeiro PG, Hu QY, Disa JJ, Pusic A, Mehrara BJ. Free flap re-exploration: indications, treatment and outcomes in 1193 free flaps. *Plast Reconstr Surg* 2007;**119**:2092–100.
8. Yii NW, Evans GR, Miller MJ, Reece GP, Langstein H, Chang D, Kroll SS, Wang B, Robb GL. Thrombolytic therapy: what is its role in free flap salvage. *Ann Plast Surg* 2001;**46**:601–4.
9. Conrad MH, Adams Jr WP. Pharmacologic optimization of microsurgery in the new millennium. *Plast Reconstr Surg* 2001;**108**:2088–96. quiz 2097.
10. Dassonville O, Poissonnet G, Chamorey E, Vallicioni J, Demard F, Santini J, Lecoq M, Converset S, Mahdyoun P, Bozec A. Head and neck reconstruction with free flaps: a report on 213 cases. *Eur Arch Otorhinolaryngol* 2008;**265**:85–95.
11. Pohlenz P, Blessmann M, Heiland M, Blake F, Schmelzle R, Li L. Postoperative complications in 202 cases of microvascular head and neck reconstruction. *J Craniomaxillofac Surg* 2007;**35**:311–5.
12. Chernichenko N, Ross DA, Shin J, Chow JY, Sasaki CT, Ariyan S. Arterial coupling for microvascular free tissue transfer. *Otolaryngol Head Neck Surg* 2008;**138**:614–8.
13. Fukuiwa T, Nishimoto K, Hayashi T, Kurono Y. Venous thrombosis after microvascular free-tissue transfer in head and neck cancer reconstruction. *Auris Nasus Larynx* 2008;**35**:390–6.
14. Eom JS, Koh KS, Al-Hilal TA, Park JW, Jeon OC, Moon HT, Byun Y. Antithrombotic efficacy of an oral low molecular weight heparin conjugated with deoxycholic acid on microsurgical anastomosis in rats. *Thromb Res* 2010;**126**:e220–4.
15. Chung TL, Pumplin DW, Holton III LH, Taylor JA, Rodriguez ED, Silverman RP. Prevention of microsurgical anastomotic thrombosis using aspirin, heparin, and the glycoprotein IIb/IIIa inhibitor tirofiban. *Plast Reconstr Surg* 2007;**120**:1281–8.
16. Stephan B, Schenk JF, Nemeh A, Pindur G. The use of antithrombotic agents in microvascular surgery. *Clin Hemorheol Microcirc* 2009;**43**:51–6.
17. Suh JD, Sercarz JA, Abemayor E, Calcaterra TC, Rawnsley JD, Alam D, Blackwell KE. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. *Arch Otolaryngol Head Neck Surg* 2004;**130**:962–6.
18. Disa JJ, Polvora VP, Pusic AL, Singh B, Cordeiro PG. Dextran-related complications in head and neck microsurgery: do the benefits outweigh the risks? A prospective randomized analysis. *Plast Reconstr Surg* 2003;**112**:1534–9.
19. Vos SC, Hage JJ, Woerdeman LA, Noordanus R. Acute renal failure during dextran-40 antithrombotic prophylaxis: report of two microsurgical cases. *Ann Plast Surg* 2002;**48**:193–6.
20. Qiu WL, Zhang Z, Wang DZ. *Theory and practice of oral and maxillofacial surgery.* First edition. Beijing, China: People's Medical Publishing House; 1998: 137–9.
21. Mao C, Peng X, Zhang L. Simplified head and neck reconstructive microsurgical techniques and their clinical applications. *Chin Arch Otolaryngol Head Neck Surg* 2016;**3**:127–8.
22. Lighthall JG, Cain R, Ghanem TA, Wax MK. Effect of postoperative aspirin on outcomes in microvascular free tissue transfer surgery. *Otolaryngol Head Neck Surg* 2013;**148**:40–6.
23. Eley KA, Parker RJ, Watt-Smith SR. Low molecular weight heparin in patients undergoing free tissue transfer following head and neck ablative surgery: review of efficacy and associated complications. *Br J Oral Maxillofac Surg* 2013;**51**:610–4.
24. Riva FM, Chen YC, Tan NC, Lin PY, Tsai YT, Chang HW, Kuo YR. The outcome of prostaglandin-E1 and dextran-40 compared to no antithrombotic therapy in head and neck free tissue transfer: analysis of 1351 cases in a single center. *Microsurgery* 2012;**32**:339–43.
25. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;**133**(6 Suppl):381S–453S.

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