Original Article

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Analysis of Risk Factors Predicting Early Postoperative Free Flap Reconstruction Complications in Patients with Head and Neck Cancers

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Objective: This case-control study was conducted to investigate the risk factors for early free flap complications in head and neck cancer patients.

Methods: Patients receiving free flap transfers for reconstruction following the ablation of head and neck cancers admitted to the surgical intensive care unit of E-Da Hospital from 2008 to 2010 were retrospectively reviewed for early postoperative complications (defined as those occurring within postoperative 48 hours). Conditional logistic regression was used to identify the associations of patient characteristics (e.g., demographic and anthropometric parameters, personal history, underlying diseases), hemodynamics, seniority of surgeons with the risk of free flap complications.

Results: Among the 415 patients enrolled in this study, the overall incidence of early flap complications was 6.9% (29/415), including flap hematoma/bleeding (41.9%), total flap necrosis (22.6%), vein thrombosis (16.1%), artery thrombosis (12.9%), and vein graft twisting/kinking (6.5%). After controlling potential confounders (e.g., patient characteristics and surgeon factors), an increased risk of free flap failure was significantly associated with a history of alcohol consumption (odds ratio [OR] = 2.67; 95% confidence interval [CI]: 1.05 – 6.78), a body mass index (BMI) less than 18 kg/m^2 (OR = 3.16; 95% CI: 1.00 – 10.01), and a postoperative systolic blood pressure higher than 180 mmHg (OR = 2.26; 95% CIs: 0.92 – 5.54).

Conclusions: Our results showed that alcohol consumption, a lower BMI, a high postoperative systolic blood pressure, and juniority of surgeons were associated with an increased risk of free flap complications in head and neck cancer patients.

Key words: free flap, head and neck cancer, complication, risk factor

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Introduction

Since its first introduction in 1970s, free flap reconstruction has become the standard reconstruction technique following ablation of head and neck tumors.[1,2] The success rate of free flap transfers has improved substantially from 75% to 85% at the beginning of 1970s and is currently over 90%.[3-5] Nevertheless, free flap failure or complication is disastrous for both clinicians and patients. Bozikov et al. identified thrombosis as the most common complication among patients with head and neck tumors after free flap reconstruction, followed by dehiscence or fistula, infection, and hematoma.[6]

Although previous studies have reported several patient-related risk factors that would adversely affect the outcome of flap reconstruction, the results remain inconsistent. For instance, a previous study showed a three-fold increase in risk of free flap failure in patients aged over 60 years,[4] but other studies demonstrated no significant correlation between age and the probability of free flap failure or complications.[4,7] Moreover, despite the well-reported association of smoking with atherosclerosis and blood flow impairment in flaps,[4,8] studies have failed to show an increased incidence of flap failure or complications in smokers.[9] Similarly, although a previous large-scale analytic review of over two thousand free flap transfers for head and neck reconstruction following cancer resection demonstrated that peripheral vascular disease, preoperative radiotherapy, cardiovascular disease, and diabetes could be possible risk factors for free flap failure,[5] other studies found no significant association of peripheral vascular disease and preoperative radiotherapy with an increased incidence of flap failure or complications.[6,10] Furthermore, in spite of a higher rate of wound infection and dehiscence in patients with diabetes,[11,12] they did not show a significantly increased incidence of thrombosis or flap failure.[13,14]

Besides, preoperative hypovolemia, hypotension, and hypothermia may result in vasospasm, which further predispose the patients to thrombotic complications. Hypertension can also cause vascular anastomosis bleeding and hematoma, causing blood vessel compression and flap failure.[15] Heparin, prostaglandin E1 (PGE1), and dextran are common precautions against platelet aggregation and thrombosis after free flap surgery in patients with head and neck cancers. Although the effectiveness of those agents remains controversial partly because of the wide variation in dosage, a retrospective study reported no significant correlation between the dosage of dextran and the rate of free flap failure.[16]

Through analysis of various factors including individual characteristics of patients as well as perioperative conditions and seniority of operating surgeons, this retrospective case-control study was conducted to comprehensively evaluate the predictors of free flap complications in patients with head and neck cancers.

Patients and Methods

Study population

A total of 415 patients with head and neck cancers who underwent tumor excision and free flap reconstruction by five plastic surgeons and were admitted to surgical intensive care unit (SICU), E-Da Hospital, from January 1, 2008 to August 31, 2010 were enrolled in this study. The protocol and procedures of the present study were approved by the Institutional Review Board of E-Da Hospital.

Study parameters

Information about patient characteristics and medical history, including age, gender, body mass index (BMI), smoking, alcohol and betel nut consumption, hypertension, diabetes, liver cirrhosis, tumor staging, and prior treatment with chemotherapy and/or radiotherapy

was collected from medical records. Perioperative information, including surgical time, use of PGE1 and/or dextran, postoperative hypertension or hypotension, and postoperative laboratory data including white blood cell count , hemoglobin concentration, and platelet count were recorded by two well-trained nursing practitioners. Information on seniority of the operating surgeons was also collected. All medical records were separately reviewed by surgeons and ICU physicians to identify free flap-related complications, namely, flap hematoma/bleeding, venous thrombosis, arterial thrombosis, vein graft twisting/kinking, and total flap necrosis. Only cases agreed on by the two independent reviewers were included. In case of disagreement, a third reviewer was involved till a consensus was reached.

Definitions

Surgeons who were board-certified for periods of 0 – 5, 5 – 10, and over 10 years were defined as junior, middle, and senior, respectively. Hypertension and hypotension were defined as a systolic blood pressure (SBP) > 180 mmHg during the first 24 postoperative hours in the ICU and a SBP < 90 mmHg, respectively. Early postoperative complications were defined as those occurring within postoperative 48 hours. For the current study, habitual alcohol consumption referred to at least one-drink per day regardless of the type of alcohol for over six months. Smoking was defined as tabacco smoking for at least 0.5 pack a day for over six months. A diagnosis of diabetes was made based on a glycated hemoglobin concentration of over 6.5 for over three months. Chewing betel nut was defined as chewing at least 20 betel nuts a day for over a year. Chronic kidney disease was defined as the presence of kidney damage or an estimated glomerular filtration rate less than 60 mL/min/1.73 mt^2, persisting for 3 months or more, irrespective of the cause. A diagnosis of liver cirrhosis was made based on liver biopsy or clinically presence of ascites, variceal hemorrhage, or hepatic encephalopathy.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and compared with the independent samples *t*-test. Categorical data are expressed as numbers and percentage, and the χ^2-tests were employed to determine the significance of the differences. Logistic regression analysis was applied to the estimation of the association of potential risk factors with free flap complications based on odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate regression was performed for independent variables shown by univariate regression analysis to be associated with the risk of early flap complications. All analyses were conducted with the SPSS statistical package for Windows (version 16.0). A two-sided *p* level less than or equal to 0.05 was considered to be statistically significant.

Results

Outcome of the study

Table 1 summarizes the basic demographic and clinical characteristics of 415 patients with head and neck cancers undergoing free flap reconstruction. The mean age of the patients was 51.6 ± 10.6 years. There was a male predominance (95.2%). Postoperative free flap complications were observed in 29 patients (7.0%). The incidence rates of flap complications were as follows: flap hematoma/bleeding (41.9%), total flap necrosis (22.6%), venous thrombosis (16.1%), arterial thrombosis (12.9%), and vein graft twisting/kinking (6.5%). No significant differences in patient characteristics including age, gender, smoking, alcohol and betel nut consumption, hypertension, diabetes, chronic kidney disease, and liver cirrhosis were observed between patients with complications

Table 1. Individual characteristics with free flap complications.

Factors	No. of patients	Complication		Non-complication		*p* value
Age (years-old, mean ± SD)	415	52.3	± 11.1	51.6	± 10.6	0.75
Gender (n, %)	415					0.93
Male		27	(93.1)	368	(95.3)	
Female		2	(6.9)	18	(4.7)	
Body mass index (kg/m^2, mean ± SD)	415	22.1	± 4.2	23.2	± 4.0	0.16
Smoking (n, %)	415					0.17
Yes		24	(82.8)	274	(71.0)	
No		5	(17.2)	112	(29.0)	
Drinking habit (n, %)	415					0.06
Yes		20	(69.0)	196	(50.8)	
No		9	(31.0)	198	(49.2)	
Chewing betel nut (n, %)	415					0.90
Yes		14	(48.3)	191	(49.5)	
No		15	(51.7)	195	(50.5)	
Hypertension (n, %)	415					0.58
Yes		4	(13.8)	67	(17.9)	
No		25	(86.2)	317	(82.1)	
Diabetes (n, %)	415					0.61
Yes		5	(17.2)	47	(12.2)	
No		24	(82.8)	337	(87.8)	
Chronic kidney disease (n, %)	414					0.79
Yes		1	(3.4)	4	(1.0)	
No		28	(96.6)	381	(99.0)	
Liver cirrhosis (n, %)	415					0.92
Yes		1	(3.4)	12	(3.1)	
No		28	(96.6)	374	(96.9)	
Cancer stage (n, %)	338					0.69
Stage I		1	(3.8)	36	(11.5)	
Stage II		9	(34.6)	102	(32.7)	
Stage III		4	(15.4)	50	(16.0)	
Stage IV		12	(46.2)	124	(39.7)	
Tumor recurrence (n, %)	415					0.78
Yes		12	(41.4)	170	(44.0)	
No		17	(58.6)	216	(56.0)	
Prior chemotherapy or radiation therapy (n, %)	415					0.94
Yes		9	(31.0)	117	(30.3)	
No		20	(69.0)	269	(69.7)	
Length of ICU stay (days, mean ± SD)	415	7.0	± 6.3	4.6	± 3.0	0.01
Length of admission (days, mean ± SD)	415	37.8	± 19.5	29.9	± 27.0	0.13

SD: standard deviation; ICU: intensive care unit.

and those without. Besides, there was no statistical difference in the proportions of cancer stages, recurrent tumors, and history of chemotherapy or radiotherapy between the two groups. However, the length of ICU stay for patients with complications (7.0 ± 6.3 days) was significantly higher than that of the non-complication group (4.6 ± 3.0 days, $p = 0.01$).

Peri-operative information of the two groups of patients is presented in Table 2.

Table 2. Peri-operative information with free flap complications.

Factors	No. of patients	Complication		Non-complication		*p* value
Surgeons (n, %)	415					0.16
Surgeon 1 (senior)		4	(13.8)	125	(32,4)	
Surgeon 2 (junior)		10	(34.5)	110	(28.5)	
Surgeon 3 (middle)		2	(6.9)	34	(8.8)	
Surgeon 4 (middle)		4	(13.8)	53	(13.7)	
Surgeon 5 (junior)		9	(31.0)	64	(16.6)	
Operative time (hour, mean ± SD)	415	13.6	± 5.9	12.6	± 5.4	0.34
PGE1 use (n, %)	415					0.38
Yes		11	(37.9)	116	(30.1)	
No		18	(62.1)	270	(69.9)	
Dextran use (n, %)	415					0.73
Yes		20	(69.0)	277	(71.9)	
No		9	(31.0)	108	(28.1)	
Post-operative hypertension (n, %)	415					0.15
Yes		19	(65.5)	199	(57.6)	
No		10	(34.5)	187	(48.4)	
Post-operative hypotension (n, %)	415					0.15
Yes		11	(37.9)	111	(28.8)	
No		18	(62.1)	275	(71.2)	
WBC (10^5, mean ± SD)	415	1.49	± 0.03	1.27	± 0.02	0.50
Hb (mg/dL, mean ± SD)	415	10.4	± 1.8	11.5	± 1.8	0.44
PLT (10^3, mean ± SD)	415	173	± 56.6	203	± 134.7	0.29

PGE1: Prostaglandin E1; WBC: White Blood Cell; Hb: Hemoglobin; PLT: Platelets; SD: standard deviation.

There were no significant differences in operative time, postoperative medications (i.e., use PGE1, dextran), post-operative hemodynamic changes (i.e., hypertension or hypotension), white blood cell count, hemoglobin concentration, and platelet count between the complication and non-complication groups. The complication rates were also not significantly different among the five surgeons. Univariate regression analysis demonstrated an increase in the risk of free flap complications in patients with a lower BMI (less than 18 kg/m^2), alcohol drinking history, and post-operative hypertension (OR: 2.9 [95% CI, 1.1 – 7.7], 2.0 [95% CI, 0.9 – 4.6], and 2.0 [0.9 – 4.5], respectively) (Table 3). A negative association was noted between the seniority of surgeons and the risk of complications ($p < 0.05$). After adjusting for surgeon factors, multivariate analyses showed increased ORs of free flap complications in patients with a lower BMI, alcohol drinking history, and post-operative hypertension.

Discussion

Despite various reported risk factors for free-flap complications in patients with head and neck cancers,[4-7] the results remained inconclusive. In particular, most of the studies did not illustrate the full spectrum of factors associated with flap failure. After comprehensively evaluated the impacts of patient characteristics, peri-operative condition, and the seniority of surgeon on the risk of early flap complications, our study identified drinking habits, being underweight, postoperative hypertension, and surgeon seniority as significant predictors of early free flap complications. Our findings indicated that patients with a lower BMI who un-

Table 3. Logistic regression models applied to estimate the odds ratios and 95% confidence intervals of free flap complications associated with potential risk factors.

Factors	Univariate		Multivariate	
Age				
< 60 years-old	1.0			
≥ 60 years-old	1.2	(0.5 – 2.6)		
Gender				
Female	1.0			
Male	1.6	(0.3 – 7.1)		
Body mass index (BMI)				
BMI ≥ 18	1.0		1.0	
BMI < 18	2.9	(1.1 – 7.7)[#]	3.2	(1.0 – 10.0)[*]
Smoking				
No	1.0			
Yes	1.9	(0.7 – 5.0)		
Drinking habit				
No	1.0		1.0	
Yes	2.0	(0.9 – 4.6)[*]	2.7	(1.1 – 6.8)[#]
Chewing betel nut				
No	1.0			
Yes	0.9	(0.4 – 1.9)		
Hypertension				
No	1.0			
Yes	0.8	(0.3 – 2.3)		
Diabetes				
No	1.0			
Yes	1.2	(0.4 – 3.6)		
Chronic kidney disease				
No	1.0			
Yes	3.5	(0.4 – 32.5)		
Liver cirrhosis				
No	1.0			
Yes	1.2	(0.1 – 9.2)		
Cancer stage				
Stage I	1.0			
Stage II	2.9	(0.4 – 23.6)		
Stage III	2.9	(0.3 – 26.9)		
Stage IV	3.5	(0.4 – 27.9)		
Tumor recurrence				
No	1.0			
Yes	0.8	(0.4 – 1.8)		
Prior chemotherapy or radiation therapy				
No	1.0			
Yes	1.1	(0.5 – 2.5)		
PGE1 use				
No	1.0			
Yes	1.5	(0.7 – 3.4)		

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Table 3. Logistic regression models applied to estimate the odds ratios and 95% confidence intervals of free flap complications associated with potential risk factors (continued).

Dextran use				
No	1.0			
Yes	0.8	(0.4 – 1.9)		
Post-operative hypertension				
No	1.0		1.0	
Yes	2.0	(0.9 – 4.5)*	2.3	(0.9 – 5.5)*
Post-operative hypotension				
No	1.0			
Yes	1.6	(0.7 – 3.5)		
Hb				
Hb ≥ 9 mg/dL	1.0			
Hb < 9 mg/dL	1.6	(0.6 – 4.2)		
Seniority of surgeons				
Senior	1.0		1.0	
Middle	2.5	(0.4 – 15.3)	2.9	(0.5 – 17.2)
Junior	6.0	(1.6 – 22.8)#	5.3	(1.5 – 18.5)#

* $p < 0.1$.
\# $p < 0.05$.
Univariate: all covariates were entered; Multivariate: the covariates that statistically significant in the Univariate were entered; PGE1: Prostaglandin E1; Hb: Hemoglobin.

derwent head and neck surgeries increased the risk of free flap complications. Most patients with head and neck cancers are associated with oral pain and dysphagia, resulting in a poor nutritional status and preoperative morbidities. Since a poor preoperative nutritional status is known to increase the risks of surgery and postoperative complications, postoperative outcome could be improved by adequate preoperative nutritional support.[17]

Moreover, we found a positive correlation between alcohol drinking habits, which was noted in 50.2% of patients, and the risk of early free flap complications. Besides, the results of this study indicated an association between postoperative hypertension and an increased risk of free flap complications, including hematoma or bleeding at the vascular anastomotic sites that constituted up to 42% of free flap complication in this study.

Patient characteristics, including tumor stage, hypertension, diabetes, cirrhosis, prior treatment with surgery or radiation, were not related to an increased risk of free flap complications in our study. A large-scale prospective multi-institutional trial of free flap surgeries and outcomes showed no significant differences in the free flap complications between patients with comorbid diabetes or obesity and those without these conditions.[15] However, other studies demonstrated that diabetes, previous history of radiotherapy following surgery, or higher American Society of Anesthesiologists physical status were significant predictors of free flap complications.[6,8,18-21] Patients with more comorbidities are likely to have a lower tolerance to prolonged anesthesia and operative time that have been reported to be associated with an increased risk of surgical complications and prolonged hospitalization.[22]

Although PGE1 and dextran are frequently used to increase blood flow, decrease viscosity, or prevent microvascular spasm, no significant impact of pharmacologic interventions of PGE1 and dextran on free flap complications was detected in this study. Contrary to

the recommendation of using pharmacological regimens for preventing thrombosis in patients receiving microvascular surgery in the head and neck regions,[23] some studies reported that the use of low-molecular weight dextran or albumin may increase the risks of postoperative comorbidities, the length of hospital stay, and the incidence of adverse flap outcomes.[24,25]

Apart from patient characteristics, the current study also identified surgeon factor as an important predictor of the risk of early free flap complications. We found a significant negative association between the seniority of surgeons and an increased risk of surgical complications, suggesting that surgical skill and experience of surgeons may have a beneficial impact on the reduction of the risk of early free flap complications.

There were several limitations in this study. First, because most of the patients were middle-aged males from a single geographical region, the findings may not be extrapolated to populations with different demographic or geographic backgrounds. Second, since the present study only explored the risk factors for free-flap complications among patients with head and neck cancers, our results may not be applicable to flap reconstructions for other diseases. Thirdly, because we did not analyze the effects of alcohol withdrawal and postoperative blood pressure control on the risk of early flap complications, further investigations are warranted to elucidate these issues. Fourthly, other factors that may affect the study outcomes including the type and location of malignancies, the effect of assistants, the type of anti-hypertensive drugs, the extent of lymph node dissection, the procedures of vein grafting or contralateral vein grafting, and the impact of reoperation (e.g., re-opening or re-anastomosis) were not studied. Finally, although a prolonged operative time and the number of surgeons involved in an operation have been reported to be related to a poor surgical outcome,[8,14,18,25-27] relevant information was not analyzed to support this finding.

Conclusions

In summary, the results of this study demonstrated that the habit of alcohol consumption, being underweight, postoperative hypertension, and a low seniority of surgeons were related to an increased risk of free flap complications. Our findings may provide some insights into the importance of preoperative assessment, the role of surgeons, and postoperative care in reducing the risk of early postoperative free flap complications in patients receiving microvascular surgeries for head and neck cancers.

Author Contributions

Study Design, Becki Wan-Yu Huang, Peng-Chih Wang and Szu-Ying Chen; Data Collection, Yu-Wei Huang, Yi-Ming Wang and Hsiang-Shun Shih; Statistical Analysis, Becki Wan-Yu Huang and Peng-Chih Wang; Data Interpretation, Szu-Ying Chen, Yu-Wei Huang, Yi-Ming Wang and Hsiang-Shun Shih; Manuscript Preparation, Becki Wan-Yu Huang and Peng-Chih Wang; Literature Search, Becki Wan-Yu Huang; Funding Acquisition, Peng-Chih Wang and Szu-Ying Chen.

Founding

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Informed Consent Statement

This study was approved by Institutional Review Board of E-Da Hospital.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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