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ARTIGO ORIGINAL

Perioperative Predictors of Free Flap Damage in Head and Neck Surgery: A Retrospective Cohort Study

Preditores Peri-operatórios de Lesão de Retalho Livre em Cirurgia de Cabeça e Pescoço: Estudo Restrospetivo de Coorte

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Keywords
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Palavras-chave
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ABSTRACT

Introduction: Microvascular free flap surgery improves survival and life quality. However, we lack knowledge on the best anesthesia approach. We aimed to identify predictors of flap damage.

Material and Methods: Eighty-seven patients submitted to head and neck free flap surgery were analyzed. The primary endpoint was flap damage (composite of complete flap loss, wound infection and 30-day re-intervention).

Results: Flap damage occurred in 18.6% patients (n = 16). Body mass index was significantly different between groups. Patients with flap damage had a median body mass index of 20.56 [IQR 4.01] compared to 22.03 [IQR 5.02] in the control group. Body mass index had a significant discriminatory power for predicting flap damage (AUC 0.67 CI: 0.54-0.81). With a cut-off body mass index of 21, lower body mass index patients were at increased risk for flap damage (OR 3.96; CI: 1.24- 12.69). They were more frequently mechanically ventilated > 48 hours (56.3% *vs* 17.4%, $p < 0.05$) or received postoperative blood transfusion (56.3% *vs* 20,3%, $p < 0.05$). They had longer ICU (6.5 IQR 6 *vs* 4 IQR 4, $p < 0.05$) and in-hospital stays (37.5 IQR 36 *vs* 18 IQR 17, $p < 0.05$).

Discussion: Nutritional status should be a priority during patient selection. The association to mechanical ventilation, postoperative blood transfusion and prolonged in-intensive care unit stays reinforces the need for optimal postoperative care.

Conclusion: Body mass index, mechanical ventilation, postoperative blood transfusion, longer intensive care unit and in-hospital stays were predictors of flap damage. Anesthesiologists should assume a coordinated perioperative medicine. Further studies are needed to clarify relevant practices.

RESUMO

Introdução: A cirurgia de retalho livre microvascular melhora sobrevida e qualidade de vida. Contudo, desconhecemos a sua melhor abordagem anestésica. Pretendemos identificar preditores de lesão de retalho.

Métodos: Analisaram-se 87 doentes. O *endpoint* primário foi lesão do retalho (variável composta de perda total do retalho, infeção da ferida e re-intervenção a 30 dias).

Resultados: A lesão do retalho ocorreu em 18,6% dos doentes (n = 16). A diferença de índice de massa corporal (IMC) foi estatisticamente significativa. Doentes com lesão de retalho apresentaram IMC de 20,56 [IQR 4,01] comparado a 22,03 [IQR 5,02]. O IMC teve poder discriminativo como preditor de lesão de retalho (AUC 0,67 CI:0,54-0,81). Com um limite de IMC de 21, doentes com IMC inferior tiveram maior risco (OR 3,96; CI: 1,24- 12,69). Estes doentes foram mais frequentemente ventilados mecanicamente > 48 horas (56,3% *vs* 17,4%, $p < 0,05$) ou transfundidos no pós-operatório (56,3% *vs* 20,3%, $p < 0,05$). Apresentaram maior tempo de internamento na unidade de cuidados intensivos (6,5 IQR 6 *vs* 4 IQR 4, $p < 0,05$) e no hospital (37,5 IQR 36 *vs* 18 IQR 17, $p < 0,05$).

Discussão: O estado nutricional deve ser uma prioridade. A associação a ventilação mecânica, transfusão no pós-operatório e internamento prolongado na unidade de cuidados intensivos reforça a importância da otimização dos cuidados pós-operatórios.

Conclusão: O índice de massa corporal, a ventilação mecânica, a transfusão sanguínea pós-operatória, o internamento em UCI

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e admissão hospitalar prolongados foram preditores de lesão do retalho. Há benefício na adoção de uma medicina peri-operatória estruturada. Estudos futuros são benéficos para esclarecer quais as práticas médicas relevantes.

INTRODUCTION

Microvascular free flap surgery is currently the main technique to ensure head and neck cancer treatment and reconstruction. Primarily started in 1958, it has quickly expanded its popularity enabling reconstructions otherwise impossible, and improving survival and functional outcomes.[1]

Nevertheless, free flap losses still occur at rates between 1% - 5%.[1,2]

Free flap anesthesia has mainly been based on physiological principles and empirical experience, since evidence-based protocols are lacking.[3,4] The complexity of the microvascular circulation, the balance between ischemic time and reperfusion injury, the length of surgery as well as the patients' comorbidities make anesthetizing these patients a delicate challenge. Further studies on free flap anesthesia may contribute to improve the success rate, by defining methods that target appropriate global and regional hemodynamics.[5]

The primary aim of this study was to analyze the perioperative period and identify predictors of flap damage, thus serving as a hypothesis generator study for further work on this subject, ultimately to improve patient care. The secondary aim was to describe the anesthetic care of patients submitted to head and neck free flap reconstruction at our institution, one leading Portuguese oncology and surgical reference center.

METHODS

We conducted a retrospective cohort study in our institution between January 2015 and April 2017 and all patients submitted to head and neck free flap surgery between January 2015 and April 2017 were included (systematic sample method). Patient medical data was revised and patients with insufficient intraoperative and postoperative recorded data were, afterwards, excluded. Only patients from the chosen sample with complete medical data regarding peri-operative data were analyzed.

All patients signed the informed consent for the procedure and for anonymous data analyzes. The ethics and investigation committee gave its approval with the protocol number 78/2018 on the 4th June 2018.

Clinical records were analyzed for patient's demographics, clinical characteristics, pre and intraoperative blood work, intraoperative drugs and anesthesia details. The postoperative period was analyzed in terms of length of stay in the intensive care unit (ICU), total hospital stay, in-hospital mortality, medical complications, surgical complications and flap loss. The primary endpoint of the study was flap damage, a composite endpoint of flap loss, wound infection and 30-day re-intervention.

On November 2017, a non-systematic literature review was performed in the PubMed database with the following terms: free flap, anesthesia, head and neck, microvascular free tissue, enhanced recovery after surgery and perioperative surgical home in different combinations. On July 2018, a brief literature review was made to include any recent publication relevant on the subject. Searches were limited to English and Portuguese language. Relevant references from the chosen articles were also included. All relevant papers to our work were carefully read and are quoted in this narrative.

Statistical analysis was performed using SPSS software® (SPSS 23, IBM).

Categorical variables are presented as absolute numbers and percentages and compared using Pearson x^2.

Continuous variables are presented as mean +- standard deviation or median with 25th and 75th percentiles for normal and non-normal distribution respectively. Normality was tested using the Kolmogorov-Smirnov test. For normal distributed variables the t-student test was used for comparison between groups. For non-normal distributed variables, the non-parametric Mann-Whitney test was chosen. Regarding statistical significant data, we applied a continuity correction for categorical variables with less than five expected count.

An α level of 0.05 was assumed to be statistical significant.

RESULTS

In 2016, our institution performed 7219 elective surgeries, 2096 were head and neck surgery.[6] Ninety cancer patients were submitted to free flap reconstruction in the chosen timeframe. Three patients (3.4%) were excluded due to incomplete data, and 87 patients (96.6%) were included in the final analysis.

In our population, 77.9% (n = 67) underwent primary treatment whereas 22.1% (n = 20) had been resected during previous surgery. The major donor sites were radial forearm (48.8%, n = 43) and fibula (31.4%, n = 27) although others were also used (19.8%, n = 17).

Regarding intraoperative data, all patients had a total intravenous anesthesia. Standard ASA, BIS (bispectral index) and neuromuscular monitoring plus urine output and invasive arterial pressure were performed routinely. During surgery, fluid balance was titrated according to conventional fluid management and blood pressure was controlled through fluids and ephedrine. Other vasopressors, such as noradrenalin, were not used intraoperatively.

Flap damage, a composite endpoint of complete flap loss, wound infection and 30-day re-intervention, occurred in 18.6% patients (n = 16). Complete flap loss was the most severe complication and occurred in 2.3% of patients (n = 2). Regarding mortality, only one patient died at 30 days, whereas 5.8% (n = 5) died at 90 days.

Preoperative predictors of flap damage

The mean age of the population was 52.3 +- 11.8 years old and 77.9% were male (n = 67).

Of the 87 patients, 67.4% (n = 58) were classified as ASA II and 26.7% (n = 23) as ASA III. Performance status was outlined from clinical records according to the clinical frailty score7 and 91.8% (n = 80) were considered to be very fit, well or managing well. Nevertheless, 19.8% (n = 17) had an involuntary weight loss bigger than 5 kg in the last twelve months. Median body mass index (BMI) was 21.6 [IQR 18].

In terms of cardiovascular risk factors, 51.2% (n = 44) were active smokers and 60.5% (n = 53) had at least one cardiovascular comorbidity (hypertension, cardiac failure, percutaneous coronary intervention, coronary artery bypass graft, diabetes or past stroke).

When comparing clinical and preoperative data between patients with and without flap damage (Table 1), patient weight and BMI were significantly different between subjects with or without flap damage. Patients with flap damage had a median BMI of 20.56 [IQR 4.01] which compared to 22.03 [IQR 5.02] in patients without flap damage ($p < 0.05$). A ROC curve was analyzed (Fig. 1) and preoperative BMI had a significant discriminatory power for flap damage, with an area under the curve of 0.67 [CI 0.54-0.81]. Patients with a BMI below 21 had an odds ratio for flap damage of 3.96 [CI: 1.24 – 12.69].

Other important clinical variables such as ASA classification, frailty score, creatinine or hemoglobin levels, and cardiovascular risk factors were not significant different between groups. Median preoperative creatinine was 0.79 [IQR 0.18], median preoperative hemoglobin 13.7 [IQR 2.2] and median preoperative hematocrit 41[IQR 5.9] (Table 1).

Intraoperative predictors of flap damage

Median anesthesia duration was 9 hours [IQR 2] and median surgery duration was 7 hours [IQR 2]. Median crystalloid administration was 4450 mL [IQR 1750], median blood loss was 800 mL [IQR 500] and median fluid balance was positive in 2368 mL [IQR 1940].

Group comparison for intraoperative variables is summarized in Table 2.

Postoperative predictors of flap damage

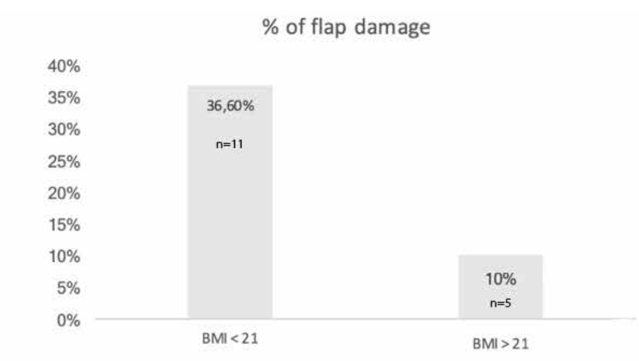
Patients underwent the immediate postoperative period in the intensive care unit (ICU). The median length of stay in the ICU was 4 days [IQR 5] and median hospital stay was 21 days [IQR 19]. The majority of patients had a tracheostomy performed (65.1%, n = 56 patients).

Table 1. Characterization of clinical and demographic data according to the occurrence of flap damage

	Total	No flap damage	Flap damage	*p*-value
Male sex (%)	67 (77.9%)	54 (77.1%)	13 (81.3%)	0.128
Mean age (±SEM)	55.26 (SD 11.79)	55.09 (±1.399)	56	0.781
Median weight (IQR)	60 (18)	62 (17)	53 (18)	**0.045**
Median height (IQR)	1.68 (0.13)	1.69 (0.13)	1.66 (0.11)	0.055
ASA (%)				0.227
ASA I	5 (5.8%)	4 (5.7%)	1 (6.3%)	-
ASA II	58 (67.4%)	48 (68.6%)	10 (62.5%)	-
ASA III	23 (26.7%)	18 (25.7%)	5 (31.3%)	-
Median body mass index (IQR)	21.6 (18)	22.03 (5.02)	20.56 (4.01)	**0.033**
Race (%)				0.236
caucasian	80 (93%)	65 (92.9%)	15 (93.8%)	-
afro-american	5 (5.8%)	4 (5.7%)	1 (6.3%)	-
other	1 (1.2%)	1 (1.4%)	0	-
Active smoking habits (%)	44 (51.2%)	36 (51.4%)	8 (50%)	0.061
Cardiovascular morbidities (any) (%)	52 (60.5%)	42 (60%)	10 (62.5%)	0.064
Number of comorbidities (%)				0.971
0	12 (14%)	10 (14.3%)	2 (12.5%)	-
1	32 (37.2%)	27 (38.6%)	5 (31.3%)	-
2	27 (31.4%)	22 (31.4%)	5 (31.3%)	-
3	12 (14%)	9 (12.9%)	3 (18.8%)	-
4	3 (3.5%)	2 (2.9%)	1 (6.3%)	-
Chronic obstructive pulmonary desease (%)	24 (27.9%)	19 (27.1%)	5 (31.3%)	0.129
Clinical frailty (%)				7.4
Very fit	8 (9.4%)	8 (11.6%)	0	-
Well	31 (36.5%)	21 (30.4%)	10 (62.5%)	-
Managing well	39 (45.9%)	33 (47.8%)	6 (37.5%)	-
Vulnerable	7 (8.2%)	7 (10.1%)	0	-
Alcoholism (%)	38 (44.2%)	31 (44.3%)	7 (43.8%)	0.062
Alcohol withdrawal syndrome (%)	6 (7%)	5 (7.1%)	1 (6.3%)	0.066
Weight loss > 5kg (%)	17 (19.8%)	12 (17.1%)	5 (31.3%)	1.804
Chronic steroid use (%)	1 (1.2%)	0	1 (6.3%)	4.426
Previous chemotherapy (%)	2 (2.3%)	1 (1.4%)	1 (6.3%)	1.333
Previous radiotherapy (%)	4 (4.7%)	3 (4.3%)	1 (6.3%)	0.113
Median pre-operative hemoglogin (IQR)	13.7 (2.2)	13.7 (2.3)	14.15 (1.9)	0.784
Median pre-operative hematocrit (IQR)	41 (5.9)	41 (5.9)	42.5 (5.8)	1
Median pre-operative creatinine (IQR)	0.79 (0.18)	0.79 (0.2)	0.76 (0.19)	0.538
Median pre-operative glycemia (IQR)	99 (19)	99 (19)	97 (27)	0.303
Pre-operative median arterial pressure (IQR)	99 (21)	100 (21)	98.5 (23)	0.383

QR - interquartile range; SEM - standard error of the mean

Vasopressor support with noradrenalin was used in 38.1% (n = 32) to a maximum of 14 days of use. Postoperative complications were recorded and included cardiac arrest,



BMI	Odds ratio	*p*-value
BMI < 21	3.96 [CI 1.24 - 12.69]	0.02
BMI > 21	0.2525 [CI 0.08 - 0.81]	0.02

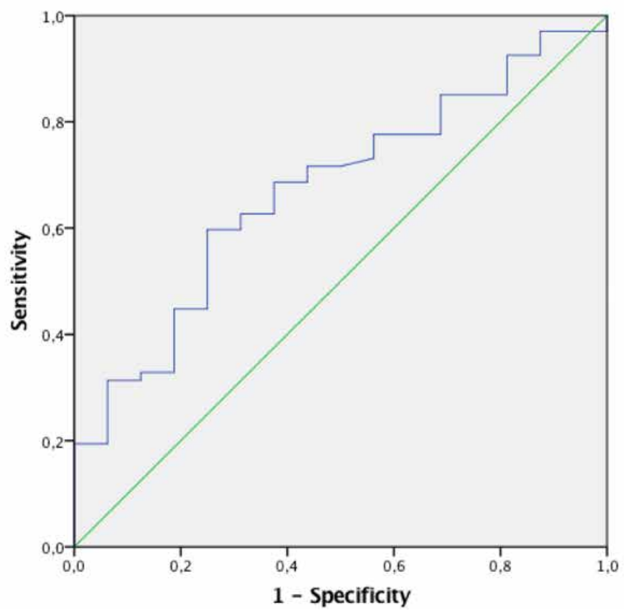


Figure 1. BMI as a predictor of flap damage

thromboembolic events (myocardial infarction, pulmonary embolism, deep venous thrombosis or stroke), bleeding in the first 72 hours, infection (pneumonia, sepsis or urinary tract infection), respiratory failure (reintubation or mechanical ventilation >48 hours) or kidney failure (acute kidney injury) (Table 3). In our series, 45.3% (n = 39) patients had a postoperative complication.

Patients with flap damage were more frequently submitted to mechanical ventilation >48 hours (56.3% *vs* 17.4%, $p < 0.05$) or received blood transfusion (56.3% *vs* 20.3%, $p < 0.05$). They also had longer ICU (6.5 IQR 6 *vs* 4 IQR 4, $p < 0.05$) and in-hospital stays (37.5 IQR 36 *vs* 18 IQR 17, $p < 0.05$).

DISCUSSION

Free flap technique is a safe and reliable procedure for head and neck reconstructive surgery. The perioperative mortality in our series of 87 patients was 1.2% which is comparable to other large series of free tissue surgery (2.1%).[8] Flap damage was identified in 18.6% patients and flap loss in 2.3% patients

Table 2. Distribution of intraoperative variables according to the occurrence of flap damage

	Total	No flap damage	Flap damage	*p*-value
Anaesthesia duration (IQR)	9 (2)	8.75 (2)	9 (1)	0.903
Surgery duration (IQR)	7(2)	7 (2)	7 (2)	0.625
Donor site location (%)				3.9
radial forearm	42 (48.8%)	36 (51.4%)	6 (37.5%)	-
fibula	27 (19.8%)	23 (32.9%)	4 (25%)	-
other	17 (19.8%)	11 (15.7%)	6 (37.5%)	-
Intraoperative blood transfusion (%)	29 (33.7%)	24 (27.9%)	5 (5.8%)	1.082
Urine output (IQR)	89.5 (73.8)	85 (85)	100 (50)	0.888
Volume of crystalloid (IQR)	4450 (1750)	4400 (2200)	4500 (1000)	0.891
Volume of colloid (IQR)	0 (500)	250 (500)	0 (500)	0.438
Blood loss (IQR)	800 (500)	800 (500)	950 (600)	0.979
Insensitive loss (IQR)	851 (304)	870 (318)	816 (272)	0.288
Fluid balance (IQR)	2367.5 (1940)	2385 (2486)	2338 (878)	0.528

Table 3. Distribution of postoperative variables according to the occurrence of flap damage

	Total	No flap damage	Flap damage	*p*-value	*p*-value (continuity correction)
Median lenght of ICU stay (IQR)	4 (5)	4 (4)	6.5 (6)	**<0.001**	-
Median lenght of hospital stay (IQR)	21 (19)	18 (17)	37.5 (36)	**<0.001**	-
Tracheostomy (%)	56 (65.1%)	46 (65.7%)	10 (62.5%)	0.06	-
Vasoactive drug (%)	32 (38.1%)	24 (35.3%)	8 (50%)	1.19	-
Cardiac arrest (%)	1 (1.2%)	1 (1.4%)	0	0.235	-
Thromboembolic events (%)	0	0	0	-	-
Blood transfusion in first 72h (%)	23 (27.1%)	14 (20.3%)	9 (56.3%)	**0.01**	**0.009**
Infection (%)	17 (20%)	10 (14.5%)	7 (43.8%)	6.949	-
sepsis	7 (8.2%)	3 (4.3%)	4 (25%)	**0.022**	0.28
pneumonia	15 (17.6%)	10 (14.5%)	5 (31.3%)	2.5	-
urinary tract	1 (1.2%)	1 (1.4%)	0	0.235	-
Acute kidney failure (%)	5 (5.9%)	3 (4.3%)	2 (12.5%)	1.559	-
Respiratory failure (%)	22 (25.9%)	13 (18.8%)	9 (56.3%)	9.475	-
reintubation	4 (4.7%)	3 (4.3%)	1 (6.3%)	0.105	-
mechanical ventialtion>48h (%)	21 (24,7%)	12 (17.4%)	9 (56.3%)	**0.003**	0.03
Postoperative medical complication (%)	39 (45.9%)	25 (36.2%)	14 (87.5%)	13.749	-

giving a total success rate of 9.7% which is also comparable to other institutions.[9]In our population, patients with a preoperative BMI of 21 or less had a 4 fold increased risk of developing flap damage. The burden of poor nutritional status has been frequently associated to postoperative infection rate, immune function and tissue healing.[10] This is of utmost importance in patients who undergo major resection and reconstruction. Interestingly, Khan *et al*,[11] in a recent retrospective cohort study suggested the effects of BMI should be evaluated in the specific population of interest to determine the nature of the effect of elevated BMI. This is in line with the concept of obesity paradox, indicating a possible protective effect of mild to moderate obesity when compared with underweight or morbidly obese patients.[11] The obesity paradox has been shown in a variety of clinical scenarios ranging from hemodialysis to cardiac surgery.[12-14]

The evaluation of BMI and nutritional status should be a priority during patient selection and every attempt should be made to optimize patients from a nutritional point of view. Rehabilitation programs before major cancer surgery are still not broadly available. Our study suggests that poor preoperative nutritional status is an important predictor of flap damage. The use of pre- and postoperative oral nutritional supplements have been shown to improve handgrip strength, pulmonary function and insulin resistance as a result of ameliorating the metabolic stress response.[10,15] Future studies evaluating optimal preoperative BMI in these patients and whether nutritional supplements and target BMI can improve patient outcomes should be conducted in the near future.

Nowadays, anesthesiologists face considerable challenges from an ageing population. However, advanced age was not a flap damage predictor supporting the current knowledge and evidence that major surgery success is not different between the young and elderly population. However, our sample size was small to completely exclude any age effect on surgical outcomes.[9,16]

The intraoperative use of vasopressors is a matter of on-going debate in microvascular surgery. It is widely suspected that the use of vasoconstrictive agents potentially leads to peripheral vasospasm, thrombosis, reduced flap perfusion, and, ultimately, flap failure.[17] In our surgical center, it is current practice not to administer vasopressor perfusions intraoperatively. However, vasoactive drug perfusions are routinely administered when needed in the ICU. We have found no association between the use of such drugs and the occurrence of flap damage, which is in line with current literature on this topic.[17,18] In fact, Scholz *et al*[18] randomized a population of free flap head and neck patients in three groups that received dobutamine infusions of 2, 4 and 6 $\mu g.kg^{-1}.min^{-1}$. Mean and maximum blood flow increased significantly in the anastomosed artery at dobutamine infusions of 4 and 6 $\mu g.kg^{-1}.min^{-1}$ and this was accompanied by increased cardiac output. The authors suggested that improved blood flow and cardiac output may improve free flap perfusion.

The use of vasoactive drugs in free flap surgery continues to be a subject of intense debate and more evidence is needed in order to understand their role in this type of surgery and their in-class differences. However, our findings suggest that they may not be associated with increased flap damage.

ICU stay and the presence of medical complications can impact the success of free flap surgery. We have found an association between mechanical ventilation and blood transfusion with higher rates of flap damage. This association reinforces the need for optimal postoperative care with the goal of minimizing the incidence of medical complications.

We included study variables from the entire perioperative period aiming to describe our current practice and highlight the importance of preoperative and postoperative care in the success of free flap surgery. Anesthesiologists should assume perioperative medicine and not only be limited to intraoperative management if patients' outcomes are to be improved. Pioneering models such as Perioperative Surgical Home (PSH), the Enhancement Recovery After Surgery (ERAS) or a Multi-Disciplinary Team (MDT) approach are gaining importance in many developed countries.[19]

This type of coordinated care is of special importance for the head and neck oncology kind of patients who are typically frail and multimorbid. Indeed, in our study in-hospital length of stay of 21 days [IQR 19] is considerably higher than a 14.55 days' length of stay in a head and neck free flap surgery population after an ERAS implementation approach (versus 18 days' length of stay in the same study, in the control group).[15] We consider a best-value measure to integrate our future patients in an ERAS approach or even in a Perioperative Surgical Home circuit which follows the patients since the initial decision to undergo surgery until the postoperative care. Successfully implemented ERAS programs have been associated with a 35% to 40% reduction in length of hospital stay. This benefit has been observed without a concurrent increase in postoperative complications or hospital readmissions.[19]

We acknowledge the limitation of our work in several domains. We have performed a retrospective observational study and recording bias is an important limitation, although every effort was made to minimize missing data. We have had access to patient medical records and we opted to collect only objective information that was clearly written although we know there is some operator-variability and we also could not access to every relevant variable. We reckon that our sample size is small and associations with small effect size might not be statistical significant in these conditions. We recognize also that our sample is heterogeneous in patient co-morbidities and tumor type and only represents one surgical center, which highly limits its generalization to other centers. A wider sample, including surgeries performed in previous years, may have minimized this limitation. However, heterogeneity would, in our opinion, be wider as the current treatments at the time (surgical and medical) as well as the medical themes were different. Even though, we have chosen to put in every variable even if some are of low numbers hoping this work can serve as a guide to future investigations. However, in spite of these limitations, we have shown important factors in perioperative medicine that might influence the success of free flap head and neck surgery. We hope that further studies and interventions, with multiple centers and wider samples, may be designed based on our findings in order to develop evidence-based practices and improve patient outcomes in reconstructive surgery.

CONCLUSION

Free flap anesthesia is a clinical challenge and evidence-based protocols are lacking. In our study, body mass index, mechanical ventilation, postoperative blood transfusion, longer ICU and in-hospital stays were predictors of flap damage. Anesthesiologists should assume a coordinated perioperative medicine. Further studies are needed to find which practices are relevant in improving patient care and free flap survival.

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Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
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Conflitos de interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de financiamento: Não existiram fontes externas de financiamento para a realização deste artigo
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
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