

A Simple Way to Measure Glucose and Lactate Values During Free Flap Head and Neck Reconstruction Surgery

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Purpose: Evaluation of flap blood flow is necessary to detect flap blood flow abnormalities and perform salvage surgery. This study determined whether intra-flap blood glucose and lactate values measured with a simple instrument could detect impaired blood flow during head and neck reconstruction.

Materials and Methods: We prospectively analyzed 82 cases of head and neck cancer reconstruction (62 men and 20 women; mean age, 64.0 years [range, 20 to 88 years]), of which 74 had impeded blood flow. Glucose and lactate levels were regularly measured over a period of 48 hours, from the time of flap elevation, as predictor variables. Blood flow obstruction was the outcome variable. Other study variables included primary site, flap type, gender, age at operation, height, weight, body mass index, presence or absence of diabetes, ischemia time, and operative time. Logistic analysis, using glucose and lactate values at the time of blood flow failure, was performed. Cutoff values were calculated using a receiver operating characteristic analysis.

Results: The breakdown of the flaps was as follows: 20 free jejunum, 19 anterolateral thigh, 12 fibular, 11 radial forearm, 8 rectus abdominis myocutaneous, and 4 other flaps. Congestion was observed in 8 of the 82 flaps, including 3 anterolateral thigh flaps, 3 radial forearm flaps, 1 free jejunum flap, and 1 rectus abdominis myocutaneous flap. The intra-flap blood glucose values in the normally progressing cases gradually decreased until 16 hours postoperatively and thereafter recovered to normal levels. Intra-flap blood lactate values increased until 8 hours postoperatively and subsequently decreased. The odds ratio during congestion was only significantly different for lactate (odds ratio, 2.55, P = .014), and the cutoff values for sensitivity and specificity were 4.2 mmol/L and 6.7 mmol/L, respectively.

Conclusions: Intra-flap blood glucose and lactate values may reflect the transition of the postoperative circulation of free flaps. During congestion, lactate values change more sensitively than blood glucose values.

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The free flap survival rate has been stabilizing, at 94 to 99%,¹ but the rate of salvage surgery in treating impaired blood flow is poor, at 34 to 73%.¹ Over time, impaired blood flow becomes irreversible.² Leaving impaired blood flow untreated can result in

serious complications such as massive bleeding due to ruptured sutures or spread of infection to the carotid artery, particularly in head and neck reconstruction. As such, evaluation of flap blood flow is necessary to detect abnormalities and perform salvage

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surgery immediately. The evaluation method for flap blood flow often relies on the visual impression of a physician or co-medical practitioner. Patients who have undergone head and neck reconstruction often have a free flap in the oral cavity, which is difficult to observe, so visual evaluation of blood flow is difficult. Therefore, persons who evaluate blood flow need more training. This may be possible in a large facility but is impossible in a small facility. If standard parameters exist that reflect flap blood flow, we believe that diagnostic capability will not differ between institutions. In this study, we will identify numerical values that reflect flap blood flow.

Among the numerous evaluation methods for flap blood flow, a method that measures intra-flap glucose and lactate values using microdialysis has been devised.³⁻⁵ Microdialysis involves the use of an embedded catheter in the flap tissue (eg, skin, muscle, or fat) to measure the target substance and can be used for buried flaps; however, it requires professional expertise.⁴

Currently, the primary methods indicated for evaluating flap blood flow are visual examination and clinical findings such as those from the pinprick test.⁶ However, these methods vary widely depending on the evaluator's experience and level of objectivity. Furthermore, the pinprick test can only be used for accessible flaps.⁷ Ideally, blood flow evaluation should be simple and objective with no variance due to occupation or experience. Despite various studies on flap blood flow evaluation methods,^{3,8-11} no standard has been established yet because the methods use expensive instruments or ones that are complicated to operate.

Recent reports have suggested that blood flow abnormalities can possibly be detected early through measurement of blood glucose and lactate values.^{4,12} This prospective study was conducted to determine whether intra-flap blood glucose and lactate values measured with a simple instrument could detect impaired blood flow during head and neck reconstruction. We prospectively analyzed intra-flap blood glucose and lactate values in patients who had undergone resection of head and neck cancer with free flap reconstruction and correlated these values with flap blood flow obstruction.

Materials and Methods

PATIENTS

This prospective cohort study was conducted with the approval of the ethics committee of Jikei University School of Medicine (reception No. 25-250-7385) and in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki. The research design and methods were explained to the patients before surgery, and they provided written consent for inclusion in the study.

The patients were recruited from Jikei University School of Medicine. A total of 82 cases (62 men and 20 women) of resection of head and neck cancer with free flap reconstruction were performed between October 2013 and September 2014. The mean age of the patients was 64 years (range, 20 to 88 years).

Patients were included in the study if they had undergone reconstruction with free flap surgery and provided written consent to participate. Patients were excluded if they did not provide written consent or the attending clinician considered them inappropriate candidates for the study. Other exclusion criteria included cardio-cerebrovascular abnormalities or serious organ dysfunction during the follow-up period that required emergency treatment, as well as an inability to collect blood samples, such as in cases with buried or intraoral flaps in which the opening was insufficient for the sensor tip.

STUDY DESIGN

As glucose and lactate measurements were determined in samples taken from the free jejunum,⁵ our study involved analyzing blood glucose and lactate levels from the free flap and free jejunum. For the free flap measurement, the flap surface was pricked with a 25-gauge LS Lancet needle (Nipro, Osaka, Japan) and a small amount of blood was extracted (a technique similar to the pinprick test; Fig 1).

For the free jejunum flap measurement, blood was collected from the serosal side of the monitor flap. Approximately 0.3 mL of blood was collected from the same site, and the blood glucose and lactate values were measured with a portable measuring instrument (Lactate Pro2 for lactate and Medisafe for glucose; Arkray, Kyoto, Japan). The flap color was observed during the measurement, and impeded blood flow was determined on the basis of the clinical findings, such as flap color, capillary refill, turgor, temperature, and pinprick testing. Intraoperative measurements were obtained at 2 points: at the time of flap vein obstruction and immediately after the anastomosis of flap blood vessels (at the time of reperfusion). On the basis of the measurement methods of Henault et al,⁴ postoperative measurements were obtained at the time of wound closure and 2, 4, 8, 12, 16, 20, 24, 36, and 48 hours after wound closure.

On the basis of the study of Setala et al,¹³ we used the value from the time of flap vein obstruction as the reference value and tracked the subsequent transitions in the measured values. When blood flow was determined to be obstructed, the value immediately before the salvage surgical procedure was used as the final measurement value.



FIGURE 1. Blood extraction procedure for capillary glucose and lactate measurements in flap monitoring of free jejunal flaps.

Kishi et al. Measurement of Glucose and Lactate Values. J Oral Maxillofac Surg 2019.

VARIABLES

Samples and possible variables related to the results were defined as follows: primary sites, flap types, gender, age at operation, height, weight, body mass index, presence or absence of diabetes, ischemic time of free flaps, and operative time. Blood glucose and lactate levels were measured immediately before reoperation as predictor variables to study their effect on blood flow obstruction, which was the outcome variable. Primary site was included as a variable because flap size was predicted to differ according to reconstruction site. Flap type was measured on the basis of the differences in the volumes of the dermis, fat, and muscle comprising the flaps.

STATISTICAL ANALYSIS

Continuous quantitative data are presented as mean \pm standard deviation. Differences in the measured values between the 2 measurement times were calculated using the Wilcoxon rank sum test. Linear regression analysis was used for the correlation between the continuous variables of time and the average of the measured values. Univariate and multivariate logistic regression analyses were used for the prediction ability of impeded blood flow. Owing to the small sample size, the glucose and lactate values

are described individually for all patients who had congestion.

The level of statistical significance was set at $P \leq .05$. Stata software (version 13; StataCorp, College Station, TX) was used for the statistical analysis.

Results

The breakdown of the 82 cases was as follows: 25 lingual, 17 hypopharyngeal, 12 esophageal, 9 maxillary, 7 oropharyngeal, 2 lower gingival, 2 upper gingival, 2 floor-of-mouth, and 6 other cancer cases (2 parotid adenocarcinoma cases, 2 submaxillary adenocarcinoma cases, 1 case of ear canal cancer, and 1 case of squamous cell carcinoma of the head).

Seventy-four flaps had no impeded blood flow. The breakdown of the flaps was as follows: 20 free jejunum, 19 anterolateral thigh, 12 fibular, 11 radial forearm, 8 rectus abdominis myocutaneous, and 4 other flaps. Congestion developed in 8 flaps, categorized as follows: 3 anterolateral thigh flaps, 3 radial forearm flaps, 1 free jejunum flap, and 1 rectus abdominis myocutaneous flap.

The intraoperative ischemic time for the 82 flaps was 85 ± 23 minutes, and the time from reperfusion to wound closure was 71 ± 13 minutes. The characteristics of the study participants are shown in Table 1. Cases were categorized as normal or congestive, and no bias was found in the breakdown of the 2 groups. For normal glucose and lactate values (74 cases), the mean values just before clamping were indicated, and for congestive glucose and lactate values (8 cases), the mean values before the repeated surgical procedure were indicated (Table 2). Salvage surgery was performed for the 8 cases with congestion. Figure 2 shows the transitions in mean blood glucose and lactate values in the 74 cases that progressed normally. Figure 3 shows the transitions in the 8 cases of congestion, organized by patient.

GLUCOSE VALUES

Blood glucose values were measured in the 74 cases that progressed normally (Fig 2). The blood glucose value from the time of flap vein obstruction to immediately after reperfusion decreased from 7.0 \pm 2.1 to 6.3 ± 2.6 mmol/L, and this result was significantly different (P = .004, Wilcoxon rank sum test). This value temporarily decreased relative to the amount of time after surgery (r = 0.68, P = .03, linear regression analysis), with the lowest value, 6.1 ± 1.6 mmol/L, at 16 hours postoperatively (P = .005). It subsequently increased at 20 hours postoperatively and recovered to the reference level, at 6.7 ± 1.7 mmol/L (P = .35), after which it remained higher than the reference value (Fig 2).

Participant	Normal	Congestion	Р
Characteristic	(n = 74)	(n = 8)	Value
Gender, n			.41
Female	19	1	
Male	55	7	
Age at operation, yr			.44
Mean	63.7	67.1	
SD	11.9	10.3	
Range	22-88	53-82	
Height, cm			.57
Mean	163	161	
SD	0.1	0.056	
Range	144-182	154-173	
Weight, kg			.73
Mean	57.9	56.5	
SD	13.9	9.23	
Range	27.0-132	42-73	
BMI			.97
Mean	21.6	21.6	
SD	3.68	2.71	
Range	12.0-39.9	15.8-24.8	
DM, n			.31
Yes	9	2	
No	65	6	

Table 1. BACKGROUND CHARACTERISTICS OF STUDY PARTICIPANTS

Abbreviations: BMI, body mass index; DM, diabetes mellitus; SD, standard deviation.

Kisbi et al. Measurement of Glucose and Lactate Values. J Oral Maxillofac Surg 2019.

LACTATE VALUES

Lactate values were measured in the 74 cases that progressed normally (Fig 2). The lactate value from the time of flap vein obstruction to immediately after reperfusion increased significantly from 2.4 ± 1.6 to $6.3 \pm 4.5 \text{ mmol/L}$ (P < .001, Wilcoxon rank sum test). This value temporarily increased relative to the amount of time after surgery (r = 0.97, P < .05), peaking at $4.9 \pm 4.1 \text{ mmol/L}$, at 8 hours postoperatively (P < .001). It subsequently decreased, reaching $3.06 \pm 2.44 \text{ mmol/L}$ at 36 hours postoperatively, and recovering to the same level at the time of flap vein obstruction (P = .21; Fig 2).

CASES OF CONGESTION

The final measurement value of lactate in the cases of congestion (n = 8) was higher than that at the time of flap vein obstruction in all 8 cases. Meanwhile, although the final measurement value of blood glucose was lower than that at the time of flap vein obstruction in 6 cases, it was the same as the value at the time of flap vein obstruction in case 4 and was higher in case 8 (Fig 3).

The mean final measurement values in the cases of congestion were 3.99 ± 2.83 and 9.18 ± 4.01 mmol/ L for blood glucose and lactate, respectively (Table 2). Table 3 shows the results of the multivariate analysis. Logistic regression analysis was conducted using the final measurement value in cases of

Table 2. COMPARISON OF STUDY VARIABLES AND FLAP BLOOD FLOW STATUS			
Participant Characteristic	Normal $(n = 74)$	Congestion $(n = 8)$	P Value
Ischemia time, minutes			.068
Mean	87	72	.000
SD	31	16	
Range	32-186	49-107	
Operative time, minutes			.09
Mean	473	374	
SD	156	36	
Range	237-858	338-402	
Glucose value, mmol/L			<.00001
Mean	7.03	3.99	
SD	2.06	2.83	
Range	2.39-13.7	1.11-8.11	
Lactate value, mmol/L			.0003
Mean	2.44	9.18	
SD	1.61	4.01	
Range	0.50-7.50	4.2-15.7	

Note: For normal glucose and lactate values (74 cases), the mean values just before clamping are indicated, and for congestive glucose and lactate values (8 cases), the mean values before the repeated surgical procedure are indicated.

Abbreviation: SD, standard deviation.

Kisbi et al. Measurement of Glucose and Lactate Values. J Oral Maxillofac Surg 2019.

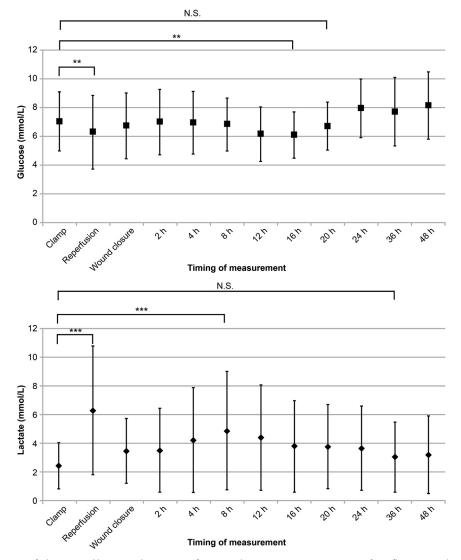


FIGURE 2. Comparison of glucose and lactate values at reperfusion and various postoperative times from flap artery clamping. Asterisks indicate statistically significant findings: **P < .01 and ***P < .001. Abbreviation: NS, not significant.

Kisbi et al. Measurement of Glucose and Lactate Values. J Oral Maxillofac Surg 2019.

congestion and the value at the time of flap vein obstruction for the cases that progressed normally. Univariate analyses were performed for patient factors, blood glucose value, and lactate value to exclude confounding factors. A receiver operating characteristic (ROC) analysis was conducted using the value from the time of flap vein obstruction and the final measurement value, and the cutoff values and their respective sensitivities and specificities were calculated. In the patients who had congestion, the final measurement value with high sensitivity and specificity was considered the cutoff value.

The results showed significant differences for hypopharyngeal cancer and the blood glucose and lactate values. Another multivariate analysis was conducted for the 3 factors, and the results showed that the odds ratio (OR) for the blood glucose value was 0.58 (95% confidence interval, 1.20 to 2.87), which was not significantly different (P = .14; Table 3). Meanwhile, the OR for the lactate value was 2.55 (95% confidence interval, 1.28 to 2.38), which was significantly different (P = .014; Table 3). Ischemia and operative times also were included in Table 3 as parameters that were expected to affect the disturbance of the flap blood flow.

In this study, an ROC analysis was performed only on the lactate values, which showed a significant difference in the multivariate analysis. The results of the ROC analysis of the lactate values were as follows: sensitivity and specificity of 100% and 63.9%, respectively, with a cutoff value of 4.2 mmol/L or greater, and 75.0% and 90.5%, respectively, with a cutoff value of 6.7 mmol/L or greater (area under the curve, 0.91; 95% confidence interval, 0.92-1.00; Table 4).

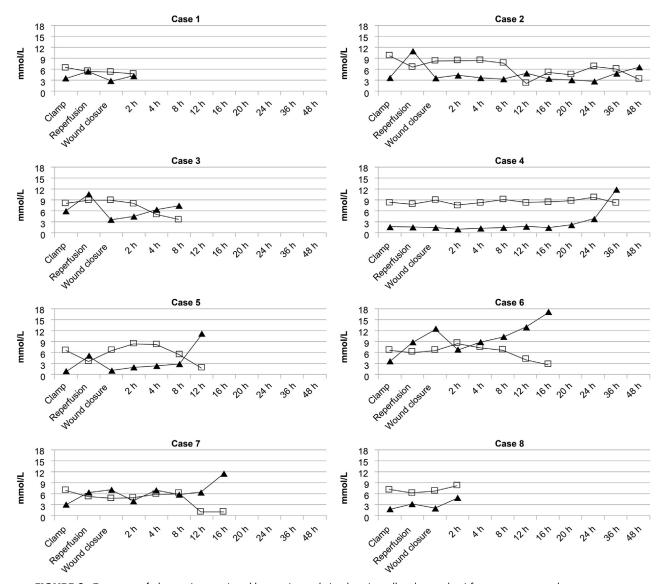


FIGURE 3. Transition of glucose (squares) and lactate (triangles) values (in millimoles per liter) from intraoperatively to congestion. *Kisbi et al. Measurement of Glucose and Lactate Values. J Oral Maxillofac Surg 2019.*

Discussion

Although it has been reported that a simple blood glucose-measuring device detects flap blood flow disturbance, only a few reports have compared the detection capability of a simple lactic acidmeasuring device. The purpose of this study was to verify whether the value indicated by the simple lactate-measuring instrument detected blood flow disorder in flaps. To do this, first, we statistically analyzed whether flaps without blood flow obstruction showed a steady trend. Second, we verified whether the change in the event of blood flow disturbance was significant. As a result, the values fluctuated even in the flaps without blood flow obstruction. Moreover, our study showed that lactate value, rather than blood glucose value, statistically significantly detected blood flow obstruction.

The simple measuring instrument detected a significant decrease in the blood glucose value and an increase in the lactate value with regard to intraoperative ischemia (eg, that occurring from flap vein obstruction to reperfusion) and postoperative congestion. These results suggest that the simple measuring instrument is useful in evaluating flap blood flow.

The characteristics of the blood glucose and lactate values in the flaps without impeded blood flow were as follows: The blood glucose values temporarily decreased postoperatively, increased after 16 hours, recovered to the reference level at 20 hours, and surpassed the reference value thereafter. The lactate

Table 3. LOGISTIC REGRESSION TO EXAMINE ASSO-CIATION BETWEEN CLINICAL FACTORS AND ATTAIN-ING FLAP CONGESTION: MULTIVARIATE ANALYSIS OF DATA

Factor	OR	95% CI	P Value
Ischemia time	0.98	0.92-1.05	.66
Operative time	1.0	0.43-1.10	.6
Glucose value	0.58	1.20-2.87	.14
Lactate value	2.55	1.28-2.38	.014

Abbreviations: CI, confidence interval; OR, odds ratio.

Kisbi et al. Measurement of Glucose and Lactate Values. J Oral Maxillofac Surg 2019.

values temporarily increased postoperatively, decreased after 8 hours, and recovered to the reference level at 36 hours postoperatively.

Setala et al¹⁴ reported transitions similar to the temporary postoperative decrease in blood glucose values and increase in lactate values. They speculated that the tissue was in a transient anaerobic metabolic state until the post-reperfusion flap tissue adapted to the new perfusion pattern. Unlike lactate values, after the blood glucose values increased to higher than the upper limit for temporary decreases, they remained higher than the reference value. Jyränki et al¹⁵ also reported that the blood glucose value increased over time. The cause was not clear, but findings indicated that the intra-flap blood glucose value temporarily decreased when insulin was administered, suggesting that generally, it is easily influenced by the blood glucose value of the body.¹⁵ On the basis of this, the intra-flap blood glucose was possibly driven up by an increase in the blood glucose value of the body, which was caused by a postoperative stress reaction or transfusion, as the intra-flap circulation stabilized. This finding showed that blood glucose value transitions are unstable, even in flaps without impeded blood flow.

Table 4. RECEIVER OPERATING CHARACTERISTIC CURVE ANALYSIS OF LACTATE VALUES IN PREDICTING IMPEDED BLOOD FLOW

Lactate Cutoff Value	Sensitivity, %	Specificity, %	Area Under ROC Curve
\geq 4.2 mmol/L	100	63.9	0.905
$\geq 6.7 \text{ mmol/L}$	75.0	90.5	
\geq 7.6 mmol/L	62.5	90.5	
\geq 11.1 mmol/L	50.0	100	

Abbreviation: ROC, receiver operating characteristic.

Kisbi et al. Measurement of Glucose and Lactate Values. J Oral Maxillofac Surg 2019.

Several reports described the effects of blood flow obstruction on blood glucose and lactate values. Heden and Sollevi¹⁶ showed that tissue hypoxia caused lactate values to increase and blood glucose values to decrease at the same time during ischemia. Furthermore, in this study, a statistically significant decrease in glucose value and an increase in lactate value were observed from ischemia to reperfusion. This finding suggested that even portable measuring instruments can detect blood flow disturbance in flaps. Setala et al¹⁴ reported that blood glucose values decreased 2 to 8 hours before clinical findings emerged and lactate values increased 1 to 12 hours before the findings of congestion. However, this study did not clarify which value first reacted to the congestion. By contrast, unmetabolized lactate accumulation,⁵ a pressure increase within the capillaries, and an arterial blood flow rate with a decrease during congestion have been speculated to cause a supply shortage of blood glucose.¹⁷ Accordingly, we can surmise that the lactate value increases first, followed later by the decrease in the blood glucose value.

Some of our patients were diagnosed as having impeded blood flow because their blood glucose values were higher than the reference value, although this only occurred in 2 cases. In addition, only the lactate value showed a significant difference in the logistic interpretive analysis. These results show that lactate values respond more significantly than blood glucose values during congestion. Several studies on lactate cutoff values in flaps with impeded blood flow have been published.^{4,15,18} On the basis of the animal testing performed by Setala et al,¹⁸ intra-flap lactate values of greater than 9.3 mmol/L (sensitivity, 93%; specificity, 91%) indicated impeded blood flow. Meanwhile, Jyränki et al¹⁵ reported in a clinical study that the lactate values in flaps without impeded blood flow were lower than 7 mmol/L, whereas Henault et al⁴ used greater than 6.4 mmol/L (sensitivity, 100%; specificity, 96.9%) as the cutoff value. In an experimental case, the optimum cutoff values for sensitivity and specificity were calculated to be greater than 4.2 mmol/L and greater than 6.7 mmol/L, respectively. Kindermann et al¹⁹ reported that the speed at which lactate was produced exceeded the speed at which it was metabolized when the blood lactate value exceeded 4.0 mmol/L, causing it to accumulate. In addition, Henning et al²⁰ reported that the blood lactate values of patients with life-threatening ischemia were greater than 4.0 mmol/L. Bakker et al²¹ reported that the blood lactate values of patients with life-threatening multiorgan failure were greater than 6.6 mmol/L. Our blood lactate cutoff value was close to the critical values reported by Henning et al and Bakker et al, which was an effective indicator of whether a patient would survive.

However, a wide variation in blood glucose and lactate value transitions was observed among our results, which may possibly be due to individual differences among the patients in our cohort. Therefore, in the future, we may need to reassess our method of correcting the values we obtained using our glucose- and lactate-measuring instruments.

In 1998, Röjdmark et al³ measured intra-flap blood glucose and lactate values to evaluate flap blood flow. In addition, Sorensen⁵ used those values for free jejunum flaps. Most previous studies that measured blood glucose and lactate values inside the flap tissue used microdialysis.^{3,5,13-16,18} Microdialysis is a method used during surgery in which a catheter is embedded in the flap tissue (eg, skin, muscle, or fat) to measure the target substance. This allows for continuous measurement and excellent objectivity, but the complicated procedure and need for professional management have been cited as having disadvantages.⁴ By contrast, a study by Sakakibara et al¹² examined blood glucose values in free flaps with a simple measuring instrument. In 2014, another study examined the usefulness of measuring lactate using the same method.⁴ The major advantage of the simple measuring instrument is its ability to measure quickly and easily. However, one of the drawbacks of simple measuring instruments is that they can only evaluate flaps exposed on the body surface, whereas microdialysis can evaluate buried flaps.

In our study, the number of cases that progressed normally was greater than the number of cases with impeded blood flow. A previous study showed that diabetes mellitus increased the risk of postoperative complications by 1.76 (OR) and resulted in a flap failure rate of 2.05% in patients with head and neck free flap reconstruction.²² Diabetes mellitus was present in 15% of patients with failed free flap head and neck reconstruction. In our study, the overall flap failure rate was 9.76% (8 of 82 cases), with 25% of these patients (2 of 8) having diabetes. The prevalence of diabetes mellitus among the cases of flap failure was higher in our study than in the previous study. However, we cannot conclude whether diabetes was the cause of the flap failure, as 1 patient had a thrombus at the venous anastomotic site and the other had a twist in the anastomotic vein, which constituted a physical cause.

Thus, we conclude that setting a highly reliable cutoff value remains difficult. However, a simple measuring instrument can be used to obtain objective information quickly and easily in cases in which an inexperienced observer is unsure of whether blood flow is impeded based on clinical findings. In such instances, the cutoff values reported in past studies^{4,14,17} and in this study can be a good reference. Indeed, previous studies showed good accuracy of handheld glucometers and lactatemeasuring devices in monitoring glucose and lactate levels in critically injured or ill patients.^{23,24} Moving forward, we must attempt to determine whether blood flow is impeded by referencing measured values rather than clinical findings and then performing salvage surgery. Accumulating data when the blood flow is impeded is essential in accomplishing this.

STUDY LIMITATIONS

We are cognizant that metabolic abnormalities can arise in patients with cancer, causing lactic acid impairment in solid tumors, and that hepatic dysfunction is common in patients with chronic alcoholism. Furthermore, diabetic treatment may impair the lactic acid macroenvironment. However, for this study, we did not obtain patient data to assess these issues. As an aside, as far as we can ascertain, previous studies in the literature did not address these issues. Nevertheless, these issues could potentially be evaluated in future studies.

We used a simple measuring instrument to determine the intra-flap blood glucose and lactate values from the time of flap vein obstruction to 48 hours after the operation in 82 cases of reconstruction for head and neck cancer using free flaps. Our results suggest that lactate values responded more sensitively than blood glucose values during congestion, and a simple lactate-measuring instrument can possibly easily and quickly evaluate flap blood flow.

Objective information can be easily added to subjective clinical findings by using portable measuring instruments when evaluating flap blood flow. A study of more cases is urgently needed to increase the reliability of the cutoff value.

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