BIO Integration

Patient-controlled Intravenous Analgesia Enhanced Recovery After Surgery by Reducing Length of Hospital Stay in Patients with Oral Squamous Cell Carcinoma Who Underwent Flap Reconstruction: A Propensity Score-matched Study

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Abstract

Background: Patient-controlled intravenous analgesia (PCIA) is an increasingly used method to control postoperative pain. We aimed to investigate the association between PCIA and recovery after flap reconstruction in patients with oral squamous cell carcinoma (OSCC).

Methods: Patients with OSCC who underwent flap reconstruction between 2016 and 2020 were reviewed (n=850). Baseline characteristics were compared between PCIA and non-PCIA groups. Propensity score matching (PSM) (1:4) was introduced to eliminate these confounding factors (n=505). Univariate analysis was performed to compare matched PCIA and non-PCIA group. Univariate and multivariate analyses were performed before and after PSM to identify factors that influenced length of stay (LOS) in hospital. The differences in characteristics of matched and unmatched groups were also compared.

Results: Before PSM, the differences in flap types, smoking status, and radiotherapy history between PCIA and non-PCIA groups were statistically significant (P<0.05). After these factors were matched by PSM, LOS was 1.5 days shorter in the matched PCIA group than in the non-PCIA group (median, 10.5 versus 12.0, P=0.006). There was no significant difference in flap or medical complications, reoperations, or postoperative neutrophil-to-lymphocyte ratio (NLR) between the matched PCIA and non-PCIA groups. Postoperative glucose was lower in the matched PCIA group than in the non-PCIA group (median, 6.70 versus 7.30 mmol/L, P=0.021). Prolonged LOS was associated with postoperative PCIA, flap types, preoperative NLR, intraoperative red blood cell transfusion, fluid infusion rate over 24 h, and postoperative intensive care unit admission (P<0.05).

Conclusions: Patients with OSCC using PCIA after flap reconstruction surgeries have a reduced LOS in hospital compared with those who used conventional postoperative analgesic strategies. Moreover, postoperative glucose increase was lower in the PCIA group than in the non-PCIA group.

Keywords

Patient-controlled intravenous analgesia (PCIA), length of stay (LOS), enhanced recovery after surgery (ERAS), oral squamous cell carcinoma (OSCC).

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Received: June 17 2021
Revised: August 2 2021
Accepted: October 8 2021
Published Online: November 11 2021

Available at: https://bio-integration.org/

Introduction

Postoperative pain occurs in more than 80% of patients who undergo surgical procedures. Among them, 75% of patients report the severity to be beyond moderate [1]. Inadequately controlled pain negatively affects the patient's functional recovery, the risk of post-surgical complications and chronic pain, and, subsequently, the quality of life [2, 3]. Meanwhile, several studies reported that the level of postoperative pain can be unmatched to the parameter of the surgical procedure. For example, dental surgery may cause the same level of pain as thoracotomy [4, 5].

https://bio-integration.org doi: 10.15212/bioi-2021-0018

Conventionally, a patient is given a prescription for postoperative analgesic regimens such as opioid tablets and told to take one every few hours as needed by self-administration. However, this strategy seemed inadequate for pain relief and prompted the risk of reliance on opioid analgesics [6]. Patient-controlled intravenous analgesia (PCIA) devices were invented in 1960s for precise intravenous delivery of a dose of opioids. The pump is activated by the patient, but the dose and time of duration are regulated by their healthcare provider [7]. PCIA is now routinely used in postoperative care in developed countries [8]. According to a survey conducted in China in 2017, the proportion of hospitals using PCIA is 43.8% [9].

Postoperative pain management is also an essential element of enhanced recovery after surgery (ERAS) pathway, which is defined as a multimodal, transdisciplinary care-improvement initiative to promote recovery, reduce complications, and aid in earlier return to normal activities [10–12]. Thus, the length of stay (LOS) in hospital after surgery as well as complications, readmissions, and quality of life are often used as measurements of previous ERAS studies. Multiple ERAS protocols were associated with a reduction in overall complications and LOS of up to 50% compared with conventional perioperative patient [13–15]. Previous studies on postoperative patient-controlled analgesia (PCA) versus conventional analgesic strategy were mainly focused on their effectiveness, whereas patients' recovery indicators, especially LOS, remain controversial [16–18]. However, as an ERAS criteria, LOS is essential for patient emotional feelings. It also has social and economic influences. The median cost per day of patients with oral squamous cell carcinoma (OSCC) after flap construction surgery in our study is CNY 12,516.85 (9,827.89, 13,484.55). According to data published by the National Bureau of Statistics, the annual personal disposable income in China is CNY 32,189, that is to say, even a single-day reduction saves a third of the annual income. Therefore, it is important to elucidate the LOS after flap reconstruction in OSCC patients.

As stressors such as systemic inflammatory and catabolic response may be largely dependent on the nature of a specific surgery, ERAS recommendations are procedure-specific [19]. Thus far, ERAS protocols were mainly designed for gastrointestinal, colorectal, and cardiothoracic surgeries, whereas maxillofacial surgeries were paid little attention to, although flap reconstruction on patients with OSCC was also a major procedure that needed enhanced recovery. In short, after a surgeon removes a tumor and its surrounding lymph nodes, a pedicle flap, which is a part of muscle from limbs with vessels, is transplanted and the vessels are anastomosed. Blood flow to the newly transplanted flap is ensured by blood pressure; however, pain management normally decreases it [20]. Thus, a delicate balance should be achieved by the team of surgeons and anesthetists, which could aid in patient recovery.

Therefore, we aimed to investigate the relationship between PCIA and ERAS measurements by performing a retrospective study on patients with OSCC who underwent flap reconstruction.

Methods

Study design and patient selection

This was a single-center, retrospective study on patient recovery outcomes applying PCIA versus non-PCIA. A total of 850 patients with OSCC who underwent flap reconstruction in Sun Yat-Sen Memorial Hospital from 2016 to 2020 were included. Patients with incomplete clinical data were excluded from analysis. In the PCIA group, 150 mL of sufentanil 100 μg plus dezocine 20 mg and palonosetron 0.25 mg were intravenously administered at the rate of 3 mL/h via a PCA device for postoperative analgesia. In the non-PCIA group, conventional pain control strategy was applied, that is, pain control tablets were given depending on patient requirements.

Ethical approval

The study protocol was approved by the Institutional Review Board of Sun Yat-Sen Memorial Hospital.

Data collection and outcomes

Data on patient demographics, baseline status, intraoperative interventions, and postoperative measurements were collected. Demographic data comprised sex, age, weight, reason for flap, flap types, American Society of Anesthesiology (ASA) status, smoking status, history of radiotherapy, and non-steroidal anti-inflammatory drug administration. Major comorbidities included hypertension, diabetes mellitus, stroke, coronary heart disease, cirrhosis, and other diseases that may potentially influence study outcome. Blood tests measuring hemoglobin (Hb, g/L), albumin (g/L), glucose (mmol/L), C-reactive protein (CRP, mg/L), and the neutrophil-to-lymphocyte ratio (NLR) were performed both 7 days preoperatively and 24 h postoperatively. Intraoperative data included blood loss (mL), duration of surgery (min), red blood cell (RBC) transfusion (units), free-frozen plasma (FFP) transfusion (mL), and urine (mL). The amount and rate of crystalloid and colloid infusion were calculated both intraoperatively and 24 h postoperatively. Postoperative ICU admission was usually a decision made during the operation determined by surgical findings on the severity of the disease and the difficulty of the operation other than PCIA application, and thus, we consider it a postoperative intervention variable rather than an outcome of PCIA. The primary outcome measure was LOS, which was defined as days from operation to discharge. Prolonged LOS (PLOS) was defined as LOS >12 days, and non-PLOS referred to LOS ≤12 days. Secondary outcomes include complications, reoperation rate, and postoperative blood test results. Blood tests were used to compare postoperative blood test level with preoperative baseline level; thus, similar items were tested. Postoperative in-hospital complications were divided into flap and medical complications. Flap complications comprised bleeding,

fistula formation, wound dehiscence, thromboembolism of flap, flap loss, and surgical site infections. Medical complications comprised deep venous thrombosis, pneumonia, pneumothorax, pleural effusion, heart failure, atrial fibrillation, ileus ketoacidosis, and stroke. Reoperation data were collected separately from complications.

Data analysis

The primary objective was to compare patient recovery between the PCIA and non-PCIA groups. Demographic and preoperative baseline characteristics were first compared in a full analysis set (PCIA, n=122; non-PCIA, n=728). Categorical variables were compared by Pearson chi-square test if frequencies were all >5 or by Fisher exact test if any frequency was <5. Continuous variables with normal distribution were compared by Student *t* test. Continuous variables with non-normal distribution were compared by Mann-Whitney *U* test. To eliminate potential selection bias, propensity score matching (PSM) approach was introduced into the analysis. Applied with nearest-neighbor algorithm to match the groups with caliper of 0.034, every PCIA patient was successfully matched with 4 non-PCIA patients. The quality of the match was assessed by recalculating each variable's standardized mean difference (SMD) in the matched sample until SMD ≤10% was achieved when we consider these factors balanced. The balanced factors were demographics (sex, age, weight, flap types, ASA status, smoking status, comorbidities, and radiotherapy history), preoperative blood test results (preoperative Hb, Alb, glucose, and NLR), and intraoperative and postoperative interventions (duration of surgery, intraoperative infusion rate, intraoperative RBC transfusion, and postoperative infusion rate over 24 h and postoperative ICU).

To determine the LOS risk factors, univariate and multivariate analyses were performed on raw and matched data, respectively. Raw data were analyzed by an adjusted multiple logistic regression model to assess independent predictive factors of LOS outcome, and the possibility of PLOS can be calculated by this model. Matched data were analyzed by a conditional logistic regression model only to reassess risk factors of PLOS in the matched pairs. Adjusted odds ratio was calculated to evaluate the impact of confounding factors in both models. Univariate comparison was further conducted in matched non-PCIA versus unmatched patients.

Statistical analyses were accomplished by SPSS version 25.0 software (IBM, Chicago, IL, USA). PSM was run by R software version 3.0.1 with package "nonrandom" (http://www.Rproject.org). A P-value ≤0.05 was considered statistically significant.

Results

The total study population of 850 patients were categorized into two groups according to whether they used PCIA. Baseline characteristics were compared between the groups of 122 patients in the PCIA group and 728 patients in the non-PCIA group (**Table 1**). In the raw data set, the differences of flap types, smoking status, and radiotherapy history were unbalanced between these two groups (P<0.05) (**Table 1**).

To eliminate the diversities of baseline characteristics, PSM was employed by matching PCIA with non-PCIA patients according to demographic characteristics (sex, age, and weight), independent risk factors (flap types, ASA status, smoking status, comorbidities, radiotherapy history, preoperative hemoglobin, albumin, glucose, and NLR), and intervention influence variables (duration of surgery, intraoperative fluid infusion rate, intraoperative RBC transfusion, fluid infusion rate over 24 h, and postoperative ICU). The method resulted in 108 PCIA and 427 non-PCIA matched patients in the present study. Comparison of the matched groups showed that the median LOS was 10.5 (9.0, 13.0) days in the PCIA group and 12.0 (9.0, 14.0) in the non-PCIA group. This difference in median LOS, which was 1.5 days shorter in the matched PCIA group, was statistically significant (P<0.05) (**Table 2**). Moreover, the median postoperative glucose was 6.70 (5.90, 8.00) mmol/L in the PCIA group and 7.30 (6.20, 8.60) mmol/L in the non-PCIA group. This difference in postoperative glucose between the two groups was statistically significant (P<0.05) (**Table 2**). Since the preoperative glucose levels of the two groups were balanced by PSM, this postoperative difference indicates a remarkable increase in glucose after surgery in non-PCIA versus PCIA. Differences of complications, reoperations, and other postoperative blood test results between PCIA and non-PCIA were not statistically significant in this study (**Table 2**).

To determine the risk factors of PLOS, univariate, multiple, and conditional logistic regression models were applied. Univariate analysis suggested that the differences in age, reason for flap, flap types, ASA status, comorbidities, radiotherapy history, preoperative albumin, glucose, CRP, NLR, and blood loss between the two groups were statistically significant (P<0.05). Of the perioperative variables, the differences in intraoperative crystalloid and fluid infusion, intraoperative RBC and FFP transfusion, intraoperative urine, 24-hour postoperative crystalloid infusion, fluid infusion rate over 24 h, postoperative ICU, and postoperative PCIA between the two groups were statistically significant (P<0.05) (**Table 3**). Multivariate analysis found that fibular or anterolateral thigh flap, smoking, radiotherapy history, higher preoperative NLR, longer duration of surgery, faster intraoperative fluid infusion rate, more intraoperative RBC transfusions, slower fluid infusion rate over 24 h, postoperative ICU admission as well as postoperative non-PCIA were independent risk factors of PLOS (P<0.05). Of all, postoperative PCIA was the most important risk factors with respect to PLOS outcome. LOS of non-PCIA patients was 1.677-fold (1.073, 2.621) (P=0.023) more likely to prolong than that of ones using PCIA (**Table 3**).

After PSM, conditional logistic regression analysis suggested that in matched groups, fibular or anterolateral thigh flap, higher preoperative NLR, intraoperative RBC transfusion, slower fluid infusion rate over 24 h, postoperative

Table 1 Univariate Analysis of Demographic Characteristics and Preoperative Laboratory Examinations between the PCIA and Non-PCIA Groups.

	PCIA (n=122)	Non-PCIA (n=728)	Univariate (P-value)
Sex (male)	76 (62.3)	479 (65.8)	0.452
Age (years)	53.39±14.00	55.15±13.74	0.191
Reason for flap			0.055
Osteoradionecrosis	0 (0.0)	32 (4.4)	
Tumor	120 (98.4)	688 (94.5)	
Weight (kg)	59.70±10.63	59.87±11.09	0.874
Flap types			0.018
Fibular	25 (20.5)	189 (26.0)	
Anterolateral thigh	73 (59.8)	327 (44.9)	
Medial lower leg	17 (13.9)	166 (22.8)	
Radial forearm	7 (5.7)	46 (6.3)	
ASA status			0.539
I or II	57 (46.7)	362 (49.7)	
III	65 (53.3)	366 (50.3)	
Smoking status	55 (45.1)	191 (26.2)	<0.001
Comorbidities			
Hypertension	23 (18.9)	151 (20.7)	0.632
Diabetes mellitus	14 (11.5)	58 (8.0)	0.198
Stroke	3 (2.5)	15 (2.1)	0.777
Coronary heart disease	4 (3.3)	27 (3.7)	1.000
Cirrhosis	0 (0.0)	8 (1.1)	0.610
Other	3 (2.5)	44 (6.0)	0.134
Total	35 (28.7)	220 (30.2)	0.733
Radiotherapy history	5 (4.1)	73 (10.0)	0.036
Preoperative			
Hemoglobin (g/L)	132.24±16.72	132.78±18.02	0.757
Albumin (g/L)	37.77±4.22	38.12±4.55	0.426
Glucose	5.00 [4.50, 5.60]	4.80 [4.40, 5.60]	0.735[#]
C-reactive protein (mg/L)	1.38 [0.64, 3.69]	1.58 [0.61, 4.98]	0.516[#]
NLR	2.25 [1.59, 3.20]	2.17 [1.58, 3.09]	0.651[#]

Data are presented as n (%), mean±standard deviation, or median [quartiles].
CI, confidence interval; PCIA, patient-controlled intravenous analgesia; ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio.
[#]Mann-Whitney U test was used.

ICU admission as well as postoperative non-PCIA were independent risk factors of PLOS (P<0.05) (**Table 4**). Postoperative PCIA was also the most important risk factors with respect to PLOS outcome in the matched groups. Non-PCIA patients was 1.815-fold (1.123, 2.935) (P=0.015) more likely to PLOS than PCIA group (**Table 4**).

We further explored the discrepancy between matched and un-matched non-PCIA patients to suggest the applicable limitations in the conclusion of our study. Of the 728 non-PCIA patients, 427 patients were matched in the previous PSM and 301 patients were not. Univariate analysis of the two groups showed that sex, reason for flap, flap types, ASA status, smoking status, radiotherapy history, preoperative albumin, CRP and NLR were statistically different (P<0.05) (**Table 5**). Specifically, the matched non-PCIA group had more tumor patients (96.7% versus 91.4%), fewer osteoradionecrosis patients (1.9% versus 8.0%, P<0.05) and fewer patients with radiotherapy history (3.0% versus 19.9%, P<0.001) than the unmatched non-PCIA group. Besides, matched non-PCIA patients had higher ASA class (class III 54.3% versus 44.5%, P<0.05) than unmatched non-PCIA patients.

Discussion

In our study, we compared the groups of PCIA and non-PCIA patients, and found that flap types, smoking status, radiotherapy history between the two groups were statistically significant. To eliminate these differences, we introduced PSM to choose comparable pairs from the original samples, and found that 1.5 days shorter of median LOS in matched PCIA group compared with non-PCIA was statistically significant. The median postoperative glucose was also statistically significantly lower in PCIA than non-PCIA group (6.70 versus 7.30 mmol/L). To determine the risk factors of PLOS, we performed univariate and multivariate analyses and found that fibular or anterolateral thigh flap, smoking, radiotherapy history, higher preoperative NLR, longer duration of surgery, faster intraoperative fluid infusion rate, more intraoperative RBC transfusions, slower fluid infusion rate over 24 h, postoperative ICU admission, and postoperative non-PCIA were independent risk factors of PLOS. In the matched group, the result of the univariate and multivariate analyses showed that fibular or anterolateral thigh flap, higher preoperative NLR, more

Table 2 Univariate Comparison of Demographics, Perioperative Variables, and Outcomes between the PCIA and Non-PCIA Cohorts Before and After PSM

	Before PSM				After PSM			
	PCIA (n=122)	Non-PCIA (n=728)	Univariate (P-value)	SMD	PCIA (n=108)	Non-PCIA (n=427)	Univariate (P-value)	SMD
Sex (male)	76 (62.3)	479 (65.8)	0.452	4.032	66 (61.1)	255 (59.7)	0.792	2.847
Age (years)	53.39±14.00	55.15±13.74	0.191	14.760	53.69±14.06	54.25±14.08	0.716	3.920
Weight (kg)	59.70±10.63	59.87±11.09	0.874	2.533	59.32±10.91	60.00±11.64	0.568	6.044
Flap types			0.018	5.065			0.988	1.679
Fibular	25 (20.5)	189 (26.0)			24 (22.2)	101 (23.7)		
Anterolateral thigh	73 (59.8)	327 (44.9)			61 (56.5)	234 (54.8)		
Medial lower leg	17 (13.9)	166 (22.8)			16 (14.8)	65 (15.2)		
Radial forearm	7 (5.7)	46 (6.3)			7 (6.5)	27 (6.3)		
ASA status			0.539	8.632			0.820	2.458
I or II	57 (46.7)	362 (49.7)			48 (44.4)	195 (45.7)		
III	65 (53.3)	366 (50.3)			60 (55.6)	232 (54.3)		
Smoking status	55 (45.1)	191 (26.2)	<0.001	44.154	46 (42.6)	163 (38.2)	0.400	9.016
Comorbidities	35 (28.7)	220 (30.2)	0.733	7.584	30 (27.8)	124 (29.0)	0.796	2.799
Radiotherapy history	5 (4.1)	73 (10.0)	0.036	26.368	4 (3.7)	13 (3.0)	0.759	3.651
Preoperative								
Hemoglobin (g/L)	132.24±16.72	132.78±18.02	0.757	1.977	132.48±16.70	132.31±18.66	0.931	0.960
Albumin (g/L)	37.77±4.22	38.12±4.55	0.426	8.742	37.76±4.20	37.77±4.50	0.977	0.318
Glucose	5.00 [4.50, 5.60]	4.80 [4.40, 5.60]	0.735#	1.846	5.00 [4.50, 5.68]	4.80 [3.30, 5.70]	0.796#	3.379
NLR	2.25 [1.59, 3.20]	2.17 [1.58, 3.09]	0.651#	0.157	2.07 [1.58, 3.27]	2.05 [1.49, 2.87]	0.219#	6.990
Duration of surgery (min)	385.00 [318.75, 446.25]	410.00 [330.00, 485.00]	0.048#	21.776	390.00 [320.00, 450.00]	400.00 [325.00, 455.00]	0.641#	3.745
Intraoperative fluid infusion rate (mL/[kg×h]$^{-1}$)	8.78 [8.11, 9.70]	8.78 [7.23, 9.70]	0.910#	9.501	8.78 [8.11, 9.70]	8.78 [7.26, 9.70]	0.691#	0.989
Intraoperative RBC transfusion (units)	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.492#	10.966	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.427#	3.818
Fluid infusion rate over 24 h (mL/[kg×h] $^{-1}$)	3.26 [2.76, 3.86]	3.14 [2.59, 3.77]	0.237#	10.842	3.27 [2.76, 3.86]	3.17 [2.64, 3.79]	0.331#	9.794
Postoperative ICU	5 (4.1)	43 (5.9)	0.423	5.941	5 (4.6)	19 (4.4)	0.936	0.865
Complication								
Flap	12 (9.8)	88 (12.1)	0.475		11 (10.2)	53 (12.4)	0.524	
Bleeding	4	8			4	6		
Fistula formation	3	21			2	13		
Wound dehiscence	0	8			0	6		
Thromboembolism of flap	4	30			4	14		
Flap loss	1	15			1	9		
Surgical site infections	0	8			0	7		
Medical	1 (0.8)	28 (3.8)	0.106		1 (0.9)	14 (3.3)	0.325	
Deep venous thrombosis	1	4			1	2		
Pneumonia	0	11			0	5		
Pneumothorax	0	1			0	1		
Pleural effusion	0	2			0	2		

Table 2 (continued)

	Before PSM				After PSM			
	PCIA (n=122)	Non-PCIA (n=728)	Univariate (P-value)	SMD	PCIA (n=108)	Non-PCIA (n=427)	Univariate (P-value)	SMD
Heart failure	0	4			0	1		
Atrial fibrillation	0	3			0	1		
Ileus	0	1			0	1		
Ketoacidosis	0	1			0	1		
stroke	0	1			0	0		
Total	13 (10.4)	112 (15.4)	0.172		12 (11.1)	66 (15.5)	0.253	
Reoperation	9 (7.4)	50 (6.9)	0.838		9 (8.3)	26 (6.1)	0.399	
LOS (days)	11.0 [9.0, 13.0]	12.0 [10.0, 14.0]	<0.001#		10.5 [9.0, 13.0]	12.0 [9.0, 14.0]	0.006#	
Postoperative								
Hemoglobin (g/L)	109.00 [99.00, 117.00]	111.00 [100.00, 122.00]	0.072#		109.00 [100.00, 117.00]	111.00 [100.00, 123.00]	0.030#	
Albumin (g/L)	28.05 [24.85, 31.68]	29.40 [26.50, 32.25]	0.015#		28.10 [24.63, 31.20]	29.40 [26.50, 32.20]	0.009v	
Glucose	6.70 [5.90, 8.00]	7.20 [6.20, 8.60]	0.033#		6.70 [5.90, 8.00]	7.30 [6.20, 8.60]	0.021#	
NLR	14.65 [10.59, 19.79]	14.52 [9.94, 22.36]	0.810#		14.65 [10.36, 19.79]	14.16 [9.54, 20.17]	0.720#	

Data are presented as n (%), mean±standard deviation, or median [quartiles].
CI, confidence interval; PCIA, patient-controlled intravenous analgesia; ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cell; FFP, free-frozen plasma; NSAID, non-steroidal anti-inflammatory drug; LOS, length of stay.
#Mann-Whitney U test was used.

intraoperative RBC transfusions, slower fluid infusion rate over 24 h, postoperative ICU admission, and postoperative non-PCIA were independent risk factors of PLOS. The differences between the matched and unmatched groups were also presented. The matched non-PCIA group had more tumor patients, fewer osteoradionecrosis patients, fewer patients with radiotherapy history, and higher ASA class than the unmatched non-PCIA group.

Previous studies on ERAS criteria, including LOS, complications, and readmissions, that compared PCA and conventional postoperative analgesia remain controversial. Hudcova and colleagues' 2006 and 2015 meta-analyses reviewed 49 trials with 1725 patients receiving PCA and 1687 patients assigned to a conventional analgesic group. Therein, 10 trials calculated LOS as an observational outcome. Among them, two trials reported that LOS was statistically significantly shorter in the PCA group, one trial favored non-PCA, and seven trials found no statistically significant difference between groups. LOS was 0.18 day shorter in the PCA group, but without statistical significance, and no statistical differences in serious adverse events were found [7, 16]. More recent studies were conducted, albeit in a relatively small number of participants (<100), and results were similar [21–23]. In our study, the reduction in LOS was 1.5 (10.5 versus 12.0, P=0.006) days in PCA, which is a 12.5% reduction in LOS after surgery, whereas flap or medical complications, reoperations, postoperative NLR were not statistically different in the two groups, suggesting that PCA benefits patient recovery and promotes ERAS in length of hospital stay without increasing the risk of short-term flap or medical complications, reoperations, and abnormal postoperative NLR. This result also has a social and economic significance. To our knowledge, the median cost per day of patients in our study is CNY 12,516.85 (9,827.89, 13,484. 55); hence, the cost of a 12-day stay (which is the median LOS in the non-PCIA group) is CNY 150,202.2. A 1.5-day reduction of hospital stay is approximately CNY 18,775.27, which exceeds half of the national annual income per capita (CNY 32,189) according to data released by National Bureau of Statistics [24]. The reduction alleviates the burden on the patient, which, in turn, may improve his emotion and recovery. Furthermore, according to the World Health Organization database, the number of medical doctors per 10,000 population is 19.8 compared with 26.04 in the USA and 58.23 in the UK in the latest update, and thus, bed turnover is more critical in China than in most of the developed countries.

Postoperative glucose is a marker for clinical outcomes. During the fasting state, normal plasma glucose levels maintain between 3.3 and 5.5 mmol/L (60 and 100 mg/dL) [25]. The stress of surgery and anesthesia triggers excessive secretion of catecholamines, cortisol, glucagon, and growth hormone, which disequilibrates hepatic glucose production and utilization in peripheral tissues, causing a hyperglycemic effect [26]. Elevated blood glucose levels may contribute to direct cellular damage such as neutrophil function impairment leading to an overproduction of reactive oxygen species. Free fatty acids are also released to disrupt vascular endothelium. Inflammatory mediators are

Table 3 Univariate and Multivariate Regression Analysis of Demographic and Perioperative Variables between the Non-PLOS and PLOS Groups.

	Non-PLOS (n=390)	PLOS (n=460)	Univariate (P-value)	Multivariate (P-value) (OR; 95% CI)
Sex (male)	246 (63.1)	309 (67.2)	0.221	0.324 (0.826; 0.565, 1.208)
Age (years)	53.27±14.28	56.27±13.21	0.002	0.824 (1.001; 0.988, 1.015)
Reason for flap				
Osteoradionecrosis	8 (2.1)	24 (5.2)	0.013	
Tumor	380 (97.4)	428 (93.0)		
Weight (kg)	59.14±10.72	60.45±11.24	0.085	
Flap types			<0.001	<0.001
Fibular	91 (23.3)	123 (26.7)		0.007 (0.355; 0.168, 0.749)
Anterolateral thigh	221 (56.7)	179 (38.9)		<0.001 (0.231; 0.113, 0.474)
Medial lower leg	65 (16.7)	118 (25.7)		0.421 (0.730; 0.340, 1.571)
Radial forearm	13 (3.3)	40 (8.7)		
ASA status			0.007	0.774 (0.952; 0.680, 1.332)
I or II	212 (54.4)	207 (45.0)		
III	178 (45.6)	253 (55.0)		
Smoking status	102 (26.2)	144 (31.3)	0.099	0.023 (0.646; 0.444, 0.941)
Comorbidities				
Hypertension	65 (16.7)	109 (23.7)	0.011	
Diabetes mellitus	28 (7.2)	44 (9.6)	0.213	
Stroke	7 (1.8)	11 (2.4)	0.547	
Coronary heart disease	11 (2.8)	20 (4.3)	0.237	
Cirrhosis	3 (0.8)	5 (1.1)	0.733	
Other	16 (4.1)	31 (6.7)	0.094	
Total	98 (25.1)	157 (34.1)	0.004	0.293 (0.823; 0.573, 1.183)
Radiotherapy history	20 (5.1)	58 (12.6)	<0.001	0.007 (0.430; 0.233, 0.791)
Preoperative				
Hemoglobin (g/L)	133.59±16.33	131.95±19.00	0.178	0.183 (1.008; 0.996, 1.019)
Albumin (g/L)	38.51±4.36	37.70±4.59	0.009	0.104 (0.996; 0.927, 1.007)
Glucose	4.80 [4.40, 5.55]	5.00 [4.50, 5.70]	0.044#	0.612 (1.029; 0.921, 1.151)
C-reactive protein (mg/L)	1.15 [0.48, 3.53]	1.96 [0.75, 6.63]	<0.001#	
NLR	2.05 [1.51, 2.80]	2.32 [1.68, 3.28]	0.001#	0.046 (1.109; 1.002, 1.227)
Blood loss (mL)	300 [200, 400]	300 [200, 400]	<0.001#	
Duration of surgery (min)	400 [330, 465]	410 [320, 490]	0.109#	0.014 (1.002; 1.000, 1.004)
Intraoperative				
Crystalloid infusion (mL)	2000 [1500, 2500]	2500 [2000, 3000]	<0.001#	
Colloid infusion (mL)	1000 [1000, 1500]	1000 [1000, 1500]	0.603	
Fluid infusion (mL)	3000 [2500, 3500]	3500 [3000, 4000]	0.014#	
Intraoperative fluid infusion rate (mL/[kg×h]$^{-1}$)	8.78 [7.68, 9.70]	8.78 [7.14, 9.70]	0.559	0.046 (1.083; 1.001, 1.171)
Intraoperative RBC transfusion (units)	0.0 [0.0, 1.5]	0.0 [0.0, 2.0]	<0.001#	0.003 (1.189; 1.059, 1.334)
Intraoperative FFP transfusion (mL)	0 [0, 0]	0 [0, 400]	<0.001#	
Intraoperative urine (mL)	700 [450, 1000]	800 [500, 1100]	0.020#	0.067 (1.000; 1.000, 1.001)
24 h postoperatively				
Crystalloid infusion (mL)	3300 [2750, 3775]	3025 [2550, 3650]	0.004#	
Colloid infusion (mL)	1250 [1000, 1500]	1250 [1000, 1500]	0.279#	
Fluid infusion (mL)	4600 [4000, 5250]	4450 [3750, 5150]	0.028#	
Fluid infusion rate over 24 h (mL/[kg×h]$^{-1}$)	3.27 [2.67, 3.93]	3.09 [2.55, 3.72]	0.005#	0.001 (0.695; 0.566, 0.854)
Postoperative ICU	6 (1.5)	42 (9.1)	<0.001	<0.001 (0.162; 0.063, 0.413)
Preoperative NSAID administration	67 (17.2)	77 (16.7)	0.865	0.793 (0.947; 0.632, 1.419)
Vasopressor administration	97 (24.9)	135 (29.3)	0.144	0.560 (1.110; 0.782, 1.576)
Postoperative PCIA	72 (18.5)	50 (10.9)	0.002	0.023 (1.677; 1.073, 2.621)

Data are presented as n (%), mean±standard deviation, or median [quartiles].
LOS <12 days was defined as non-PLOS.
CI, confidence interval; PLOS, prolonged length of stay; ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cell; FFP, free-frozen plasma; NSAID, non-steroidal anti-inflammatory drug; PCIA, patient-controlled intravenous analgesia.
Variables in the multivariable analysis were selected by collinearity diagnostics.
#Mann-Whitney U test was used.

Table 4 Univariate and Adjusted Multivariate Regression Analysis of Demographic and Perioperative Variables with Matched Patients between the Non-PLOS and PLOS Groups

	Non-PLOS (n=271)	PLOS (n=264)	Univariate (P-value)	Multivariate (P-value) (OR; 95% CI)
Sex (male)	145 (53.5)	176 (66.7)	0.002	0.321 (1.286; 0.782, 2.114)
Age (years)	53.52±14.22	54.77±13.90	0.304	0.276 (0.991; 0.975, 1.007)
Flap types			0.001	<0.001
Fibular	58 (21.4)	67 (25.4)		0.008 (0.301; 0.123, 0.734)
Anterolateral thigh	169 (62.4)	126 (47.7)		<0.001 (0.208; 0.089 0.486)
Medial lower leg	35 (12.9)	46 (17.4)		0.150 (0.496; 0.191, 1.287)
Radial forearm	9 (3.3)	25 (9.5)		
ASA status			0.230	0.599 (1.123; 0.729, 1.729)
I or II	130 (48.0)	113 (42.8)		
III	141 (52.0)	151 (57.2)		
Smoking status	89 (32.8)	120 (45.5)	0.003	0.276 (0.764; 0.471, 1.240)
Comorbidities	69 (25.5)	85 (32.2)	0.085	0.536 (0.826; 0.539, 1.379)
Radiotherapy history	4 (1.5)	13 (4.9)	0.027	0.124 (0.366; 0.102, 1.317)
Preoperative				
Hemoglobin (g/L)	133.03±15.68	131.64±20.59	0.382	0.505 (1.005; 0.991, 1.019)
Albumin (g/L)	38.28±4.06	37.25±4.74	0.008	0.087 (0.955; 0.905, 1.007)
Glucose	4.80 [4.50, 5.50]	5.00 [4.40, 5.98]	0.119#	0.509 (1.046; 0.915, 1.196)
NLR	1.98 [1.47, 2.68]	2.23 [1.59, 3.24]	0.012#	0.018 (1.177; 1.029, 1.347)
Duration of surgery (min)	400.00 [330.00, 450.00]	395.00 [316.25, 470.00]	0.577#	0.224 (1.002; 0.999, 1.004)
Intraoperative fluid infusion rate (mL/[kg×h]$^{-1}$)	8.78 [8.09, 9.70]	8.78 [7.15, 9.70]	0.387#	0.205 (1.066; 0.966, 1.176)
Intraoperative RBC transfusion (units)	0.0 [0.0, 0.0]	0.0 [0.0, 2.0]	0.001#	0.007 (1.249; 1.063, 1.466)
Intraoperative urine mL	700 [500, 1000]	700 [500, 1000]	0.399#	0.086 (1.000; 1.000, 1.001)
Fluid infusion rate over 24 h (mL/[kg×h]$^{-1}$)	3.32 [2.77, 3.98]	3.06 [2.54, 3.72]	0.001#	0.004 (0.697; 0.544, 0.894)
Postoperative ICU	3 (1.1)	21 (8.0)	<0.001	0.001 (0.103; 0.028, 0.379)
Preoperative NSAID administration	46 (17.0)	41 (15.5)	0.651	0.991 (0.997; 0.595, 1.670)
Vasopressor administration	66 (24.4)	73 (27.7)	0.385	0.542 (1.149; 0.735, 1.797)
Postoperative PCIA	65 (24.0)	43 (16.3)	0.027	0.015 (1.815; 1.123, 2.935)

Data are presented as n (%), mean±standard deviation, or median [quartiles].
LOS <12 days was defined as non-PLOS.
CI, confidence interval; PLOS, prolonged length of stay; ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cell; FFP, free-frozen plasma; NSAID, non-steroidal anti-inflammatory drug; PCIA, patient-controlled intravenous analgesia.
Variables in the multivariable analysis were selected by collinearity diagnostics.
#Mann-Whitney U test was used.

then recruited, causing immune dysfunctions [27]. Studies have shown that these changes may persist 9 to 21 days after surgery, and inpatient hyperglycemia (>10 mmol/L) are clearly associated to adverse clinical outcomes, including surgical site infections, delayed wound healing, and increased LOS [28–30]. In our study, compared with preoperative glucose baseline, the increase in median of postoperative glucose was 1.2 mmol/L in PCIA and 2.5 mmol/L in non-PCIA, respectively (P=0.021 after PSM). It probably due to the effects of PCIA, which relieves stress response to surgery. However, more indicators, including stress hormones and cytokines, need to be involved to demonstrate our hypothesis.

Moreover, the length of hospital stay is affected by many other factors. In our study, multivariate analysis after PSM showed that, other than PCIA, flap types, intraoperative RBC transfusion, fluid infusion rate over 24 h, and postoperative ICU are independent factors leading to prolonged hospital stay. One reason for prolonged length of hospital stay in patients using lower leg flaps is postoperative restricted mobility. However, as the quality and length of vascularized bone were described as unrivaled by other bone flaps, lower leg flaps were still the most commonly used flap types in clinical practice [31]. Intraoperative RBC transfusion and postoperative ICU both straightforwardly indicate more complications occurred in a patient, thus aggravating a patient's condition and prolonging the hospital stay. The infusion rate of resuscitation fluids is highly variable without a standard in a clinical setting. An explanation to our study result is that rapid administration of colloids increases the plasma concentration of atrial natriuretic peptide, leading to shedding of components

Table 5 Univariate Analysis of Demographic Characteristics and Preoperative Laboratory Examinations between Matched and Unmatched Non-PCIA Patients

	Matched (n=427)	Un-matched (n=301)	Univariate (P-value)
Sex (male)	255 (59.7)	224 (74.4)	<0.001
Age (years)	54.25±14.08	56.44±13.17	0.034
Reason for flap			0.018
Osteoradionecrosis	8 (1.9)	24 (8.0)	
Tumor	413 (96.7)	275 (91.4)	
Weight (kg)	60.00±11.64	59.69±10.27	0.712
Flap types			<0.001
Fibular	101 (23.7)	88 (29.2)	
Anterolateral thigh	234 (54.8)	93 (30.9)	
Medial lower leg	65 (15.2)	101 (33.6)	
Radial forearm	27 (6.3)	19 (6.3)	
ASA status			0.009
I or II	195 (45.7)	167 (55.5)	
III	232 (54.3)	134 (44.5)	
Smoking status	163 (38.2)	28 (9.3)	<0.001
Comorbidities			
Hypertension	81 (19.0)	70 (23.3)	0.160
Diabetes mellitus	40 (9.4)	18 (6.0)	0.096
Stroke	8 (1.9)	7 (2.3)	0.672
Coronary heart disease	13 (3.0)	14 (4.7)	0.259
Cirrhosis	7 (1.6)	1 (0.3)	0.149
Other	22 (5.2)	22 (7.3)	0.229
Total	124 (29.0)	96 (31.9)	0.409
Radiotherapy history	13 (3.0)	60 (19.9)	<0.001
Preoperative			
Hemoglobin (g/L)	132.31±18.66	133.46±17.07	0.399
Albumin (g/L)	37.77±4.50	38.63±4.59	0.013
Glucose	4.80 [4.40, 5.70]	4.90 [4.40, 5.60]	0.709[#]
C-reactive protein (mg/L)	1.41 [0.58, 4.23]	1.89 [0.65, 6.29]	0.037[#]
NLR	2.04 [1.49, 2.87]	2.36 [1.67, 3.43]	<0.001[#]

Data are presented as n (%), mean±standard deviation, or median [quartiles].
CI, confidence interval; ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio.
[#]Mann-Whitney U test was used.

of the endothelial glycocalyx and impairing endothelial barrier function [32]. Thus, a slower postoperative fluid infusion rate could possibly decrease the extravasation of albumin, leading to a slower intravascular volume expansion after major surgery, which eventually results in slower recovery [33]. However, this explanation needs to be further testified.

The limitations of this study include its retrospective nature, which introduces selection bias. In an effort to reduce this bias, we involved a large patient cohort and performed PSM to balance the distribution of study population and interventions unrelated to the goal of this study. We only involved in-hospital short-term complications in this study, whereas long-term complications are still tracked. Besides, the study results are restrictedly applied to OSCC patients after flap reconstruction. Superior postoperative management after other surgeries needs to be further investigated.

In conclusion, our present study suggests that patients with OSCC using PCIA after flap reconstruction surgeries have a reduced in hospital compared with conventional postoperative analgesic strategy without increasing the risk of short-term flap or medical complications, reoperations, and abnormal postoperative NLR. Moreover, postoperative glucose increase in PCIA was lower compared with non-PCIA patients. A more widespread use of PCIA could lead to better recovery of patients, and thus, it provides surgeons and anesthetists an option to deal with this intractable pain after surgery.

Acknowledgement

This work was supported by Guangzhou Science and Technology Planning Project Basic Research Program (no. 202002020002).

Conflicts of Interest

The authors declare that they have no competing interests.

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