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Inhibitory Effect of Remifentanil on Intraoperative Stress Response in Burn Patients Undergoing Escharotomy and Skin Grafting

Doudou Zhao[1], Yancheng Huang[2], Yu Lai[2], Ye Fang[1], Tingyu Pan[1], Rui Xu[1] and Enjun Lei[1,*]

[1]Department of Anesthesiology, First affiliated hospital of Nanchang University, Nanchang, Jiangxi, 330031, China
[2]Medicine Graduate School, Nanchang University, Nanchang, Jiangxi, 330031, China

* ***Corresponding author:*** Enjun Lei, Department of Anesthesiology, First Affiliated Hospital of Nanchang University, No. 17, Yongwaizheng Street, Donghu District, Nanchang, Jiangxi, 330031, China. Email: leienjun@126.com

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Abstract

Background: Burns are among the most life-threatening forms of trauma requiring timely and effective treatment.
Objectives: The present study aimed to assess the inhibitory effect of remifentanil on the stress response of burn patients undergoing escharectomy and skin grafting.
Methods: A total of 52 patients undergoing burn scab removal surgery were selected and randomly assigned to two groups: remifentanil group (group R) and fentanyl (group F). Anesthesia induction: Group R was administered an intravenous injection of propofol, rocuronium, and remifentanil, while Group F received an intravenous injection of propofol, rocuronium, and fentanyl. After tracheal intubation, group R was injected intravenously with remifentanil and propofol to maintain anesthesia. Group F was induced with fentanyl. Thereafter, the patient's blood pressure and heart rate (HR) were recorded. Subsequently, their carotid artery blood was withdrawn, and they were tested for epinephrine (E), norepinephrine (NE), and blood glucose. Finally, the patients' eye-opening time and extubation time at the end of anesthesia were recorded.
Results: After anesthesia induction, the mean artery pressure, HR, and E in group R were lower than those in group F. There was no statistically significant difference between the levels of NE in the two groups. Nonetheless, the eye-opening time and extubation time in group R were significantly shorter than those in group F.
Conclusion: Compared to fentanyl, remifentanil can more effectively reduce the stress response of surgery and anesthesia. It can integrate anesthetic drugs with blood pressure control. Furthermore, this method is simple, effective, safe, and reliable.

Keywords: Adrenaline, Burns, Intraoperative stress response, Norepinephrine, Remifentanil

1. Background

As serious external injuries, burns cause damage to the skin and serious systemic reactions, resulting in metabolic disorders and dysfunctions of various organs, including hypovolaemia, hypothermia, metabolic, and immune system disturbances, as well as increased susceptibility to infection (1-6). Among them, post-burn stress is one of the most important aspects affecting patients' recovery and life safety. The stress response not only makes it more challenging to treat the patient but may also cause hypoxic/ischemic shock (7, 8). Therefore, timely and effective treatment and attention to stress reactions are of paramount importance for burn patients.

A wide array of studies compared the clinical effects of fentanyl and remifentanil in different operations in terms of hemodynamics and cortisol secretion. Research demonstrated that high doses of remifentanil depressed the epinephrine (E) response to pneumoperitoneum and surgery, indicating no general activation of the sympathetic nervous system. Neither a low dose nor a high dose of remifentanil depressed the norepinephrine (NE) response during pneumoperitoneum, suggesting the centrally independent release of NE (9). Furthermore, a mean remifentanil infusion of 0.49 microgram/kg/min is as effective as a mean alfentanil infusion of 1.99 micrograms/kg/min in suppressing intraoperative responses (10).

Doubling the remifentanil infusion to 0.5 microgram/kg/min before the major stress event improves response suppression and lowers intraoperative use of remifentanil without prolonging recovery time. Remifentanil allows faster awakening times than alfentanil; nonetheless, preemptive administration of postoperative analgesics is recommended to facilitate discharge (10). Some researchers pointed out that hemodynamic properties associated with remifentanil extend to a broader context (11). Moreover, intraoperative blood loss during spinal surgery decreased in patients who received remifentanil as an opioid adjuvant (12).

Based on clinical data, an anesthetic regimen combining propofol and remifentanil attenuates two indicators of the stress response more efficiently than an isoflurane-remifentanil combination (13). Moreover, the combined use of sufentanil and remifentanil stabilizes perioperative hemodynamics and reduces stress hormone levels (14). Nevertheless, there is a dearth of studies on the effect of remifentanil underlying the stress response of surgical anesthesia in burn patients.

Therefore, we aimed to explore the role of remifentanil underlying the stress response of burn patients undergoing escharectomy and skin grafting. In this study, we compared the specific indicators of stress response in 52 burn patients with early scab removal under fentanyl and remifentanil treatment. Our research might provide a novel direction for the safe operation of burn patients.

2. Objectives

The present study aimed to assess the inhibitory effect of remifentanil on the stress response of burn patients undergoing escharectomy and skin grafting.

3. Methods

Research location

This study was conducted at First Affiliated Hospital of Nanchang University from January 2020 to January 2021. A total of 52 patients admitted to our hospital at this time were selected for the study and accompanying controlled trials.

General information

From January 2020 to January 2021, First Affiliated Hospital of Nanchang University used remifentanil/fentanyl and propofol intravenously to implement general anesthesia for 52 burn patients with early scab removal. Intraoperative blood pressure control was performed, and satisfactory clinical anesthesia effects were achieved. Patients were randomly assigned to the remifentanil-propofol group (group R) and the fentanyl-propofol group (group F), with 26 cases each. The contents of this study are in compliance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanchang University. The inclusion criteria entailed patients undergoing burn scab surgery selected according to ASA II-III grading (15) (aged 18-60 years old, burn area 40% -70%, 3-10 days after burn, the cause of injury was flame burn and hot steam burn). A total of 74 patients met these requirements. On the other hand, the exclusion criteria were as follows: the absence of any severe heart, lung, brain diseases, adrenal gland disease, endocrine or metabolic diseases, and hormone therapy before the operation. After screening, we finalized 52 cases for the study.

Methods of anesthesia

The peripheral vein and central vein were established after the patients entered the room. The peripheral vein was used for drug administration, and the central vein was utilized for blood sampling. The induction of anesthesia for the two groups of patients is as follows: group R remifentanil 0.6-0.8 μg/kg, the infusion time should be more than 60 sec, and the administration should be completed within 2 min. Group F received fentanyl 3-4 μg/kg intravenously 2 min before intubation.

Group R received an intravenous injection of remifentanil 0.1-0.2 μg/-(kg▪min) and continuous propofol 4-6 mg/-(kg▪h) infusion via an infusion pump to maintain anesthesia. Group F was supplemented with fentanyl 0.25 μg/kg and continuous propofol 4-6 mg/-(kg▪h) infusion every half an hour via an infusion pump. Fentanyl was stopped 30 min before the end of the operation, and remifentanil and propofol were stopped when preparing for bandaging. Intravenous analgesia pump after operation: Sufentanil (50 μg), ondansetron (16 mg), and normal saline (60 ml, 2 ml/h). The patients were followed up 2 and 24 h after operation to observe the effect of anesthesia.

Monitoring and collection

Routine femoral artery catheterization before anesthesia, continuous monitoring and recording of femoral artery systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP). The systolic blood pressure, diastolic blood pressure, MPA, and heart rate (HR) were recorded from both groups of patients at six time points: before anesthesia induction (T1), 1 min after induction (T2), 1 min after tracheal intubation (T3), 10 min after surgery (T4), 20 min after surgery (T5), and 1 min after extubation (T6). At the same time, 1 ml of blood sample was collected from the central vein immediately, and the blood glucose (GLU) level was quickly detected with a blood GLU meter. Moreover, the NE and E radioimmunoassay kits (NE: IBL Germany, RE59242, E: Wuhan Kesitan Biotechnology Co., Ltd, CSJ105275H.) were used to detect the concentrations of NE and E.

Statistical processing

Statistical analysis was performed using SPSS software (version 19.0). All of the continuous data were expressed as mean± standard deviation. Attribute data were reported as percentages. Two independent-sample t-tests were used to compare the variable data between the groups. Moreover, comparisons between multiple groups were made using repeated measures ANOVA and the least significant difference test. In this study, $P<0.05$ was considered to be statistically significant.

4. Results

There was no statistically significant difference between the two groups of patients in terms of age, weight, burn area, and burn time (Table 1). The dosage of propofol was not statistically significant ($P=0.39$), and the dosage of remifentanil (0.58±0.30) was not statistically significant compared to the dosage of fentanyl (0.34±0.08). No serious events occurred during anesthesia and surgery; moreover, no abnormalities were observed in the ECG. The anesthesia time of the two groups of patients was similar; however, the recovery time of group R was significantly shorter than that of the fentanyl group. There was a statistically significant difference between the time from the end of the operation to the patient's eye-opening and the time for extubation in group R (6.43±2.637 vs. 0.29±3.147) compared to the fentanyl group (10±3.347 vs. 15.33±3.204) (*P*<0.01; Table 2).

Impact on mean arterial pressure

The MAP of the two groups decreased significantly after induction, and it was lower in group R (P<0.05) and remained below the basic value during the operation. Group F had an increase in the recovery period (T5, T6); nonetheless, the difference was not statistically significant.

The overall MAP value of group R was lower than that of group F; however, there was no difference between the groups; only the difference between T3 and T1 after intubation was statistically significant (*P*<0.05, Figure 1 and Table 3).

Table 1. Comparison of baseline data between the two groups of patients

Group	Case	Age (year)	BMI (kg/m²)	Burn area (%)	Burn time (h)
R	26	36.32 ± 2.18	18.25±4.28	28.64 ± 2.27	78.15 ± 8.15
F	26	36.40 ± 3.20	18.31 ± 3.26	28.32 ± 2.43	78.10 ± 8.06
t-value		0.105	0.057	0.491	0.022
P-value		0.917	0.955	0.626	0.982

Burn area: Estimated according to the "Rule of Nine": 9% of the body surface area for the head, 18% for the front of the torso, 18% for the back of the torso, 18% for the leg, 9% for an arm, and 1% for the genitals and perineum. Burn time: time from burn to admission.

Table 2. Comparison of anesthesia between the two groups

Group	Propofol dosage (mg/kg)	Remifentanil/fentanyl dosage (μg/kg)	Anesthesia time (min)	Recovery time (h)	Eye-opening time (h)	Extubation time (h)
R	42.15±6.23	0.58±0.30	83.02± 4.03	5.26±3.22	6.43± 2.637	0.29±3.147
F	41.02 ± 6.15	0.34±0.08	84.00±4.05	9.24± 4.41	10±3.347	15.33±3.204
t-value	0.658	3.941	0.875	3.717	4.272	17.080
P-value	0.513	<0.001	0.386	<0.001	<0.001	<0.001

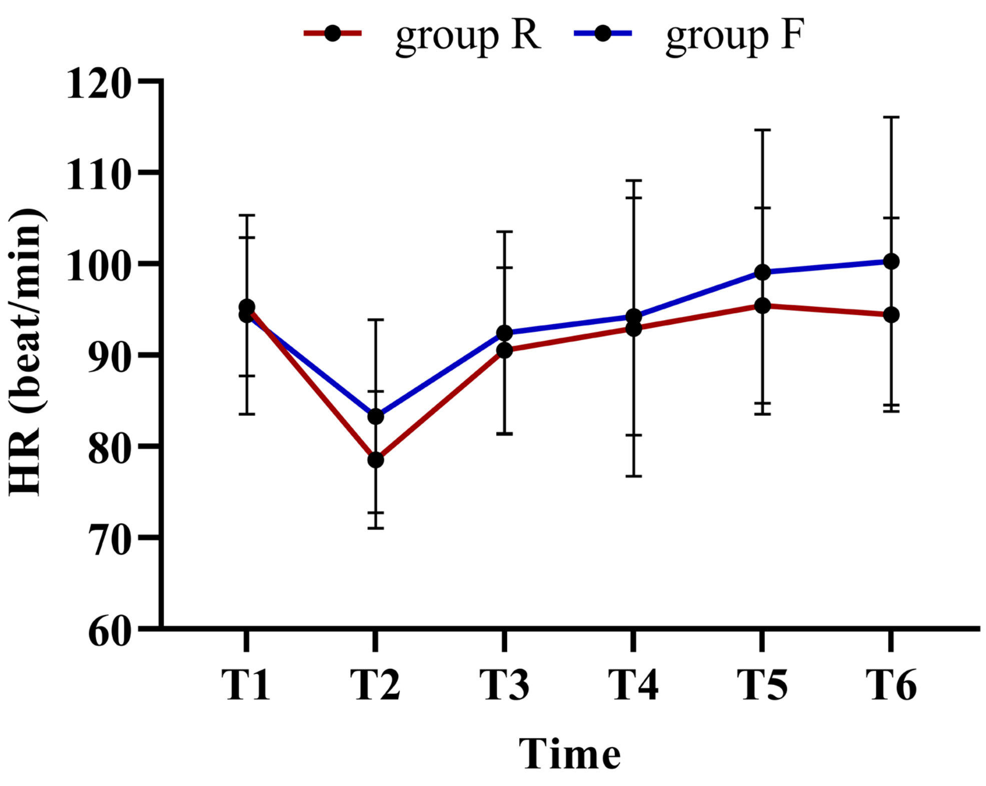

Figure 1. Changes in heart rate at various points in time

Table 3. Comparison of vital signs at each time point between the two groups of patients

Group	MAP (mmHg)	HR (/min)	GLU (mmol/L)	E (ng/ml)	NE (ng/ml)

R	T1	95.3±.6	105±10.9	8.8±2.11	30.6±4.16	113.1±31.14
	T2	78.5 ± 7.5*a	115.9±16.1a	8.3±2.30	30.1± 4.41	108.1±27.17
	T3	90.5 ± 9.1a	108±9.4	7.9±1.89	29.5±3.02	111.9±27.29
	T4	92.9 ± 16.2	95.1±13.9a	7.6±1.84a	29.1±4.42*	106.8±21.09
	T5	95.4 ± 10.7	92.6±18.5a	8.2±2.10	28.3±4.87*	102.9±19.00
	T6	94.4 ± 10.6	101.6±16.1	9.9±2.27	29.5±4.12	109.5±30.78
F-value		9.520	9.103	3.962	0.932	0.503
P-value		<0.001	<0.001	0.002	0.462	0.773
F	T1	94.4 ± 10.9	109.6±10.7	8.6±2.86	32.0±5.13	113.9±38.78
	T2	83.3 ± 10.6*a	116.9±17.8a	8.3±2.60	31.1±5.51	111.6±36.63
	T3	92.4 ± 11.1	119.1±13.1	8.3±2.38	31.8±6.16	105.8± 22.179
	T4	94.2 ± 13.0	101.8±17.2	8.4±2.70	32.6±5.07	111.567±27.47
	T5	99.1 ± 15.6	98.3±16.4	8.5±2.67	32.1±6.11	109.4±31.13
	T6	100.3 ± 15.8	98.8±15.7	10.1±2.3a	32.2±6.24	119.6±34.15
F-value		5.616	9.268	1.873	0.199	0.536
P-value		<0.001		0.102	0.963	0.749

Impact on heart rate

The basic HR before anesthesia was 109.6±10.7 in group F and 105.4±10.9 in group R, demonstrating no statistically significant difference between the groups. The HR increased significantly after the induction of anesthesia (116.9±17.8, 115.9±10.9), which was different from the basal HR at the T1 time point (P<0.01). The HR began to decrease after induction, except for group F, in which HR still increased after intubation; however, it was not statistically significant. In group R, the HR at T4 and T5 were significantly lower than the basic value at T1, and the difference was statistically significant (P<0.01; Figure 2 and Table 3).

Impact on blood glucose

The basic blood GLU levels at T1 of the two groups were relatively similar (8.6±2.86mmol/L in group F, 8.8±2.11 mmol/L in group R). In group F, the blood GLU level was relatively stable between T2-T5 but increased significantly at the time point of T6 compared to T1 after extubation (P<0.05). After induction, the blood GLU decreased in group R and maintained until extubation, and significantly decreased at the T4 time point compared to T1 (P<0.05; Figure 3 and Table 3).

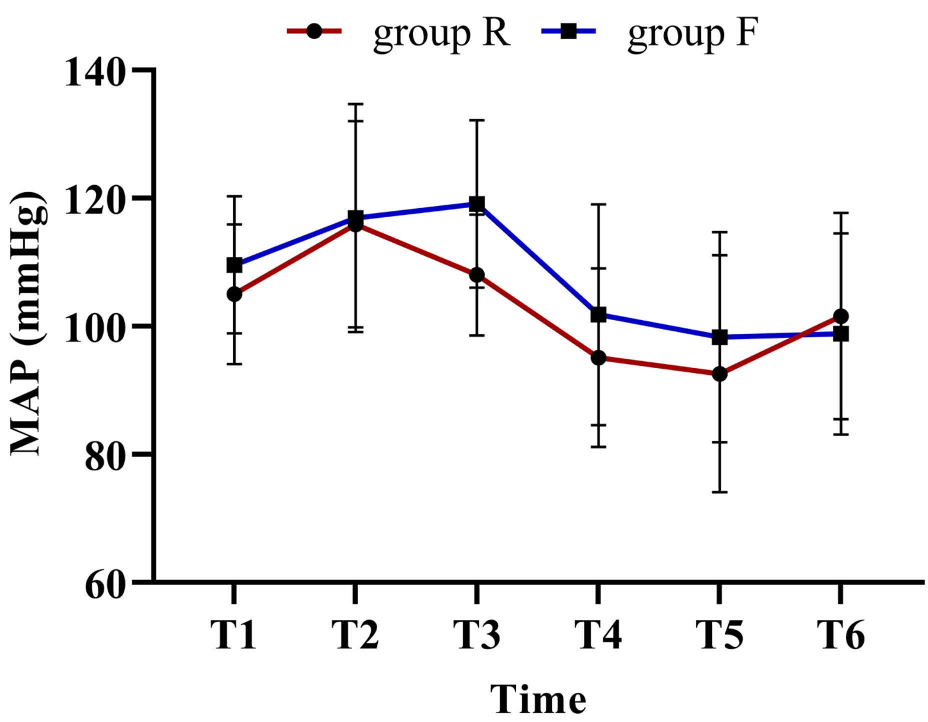

Figure 2. Changes in mean arterial pressure at various points in time

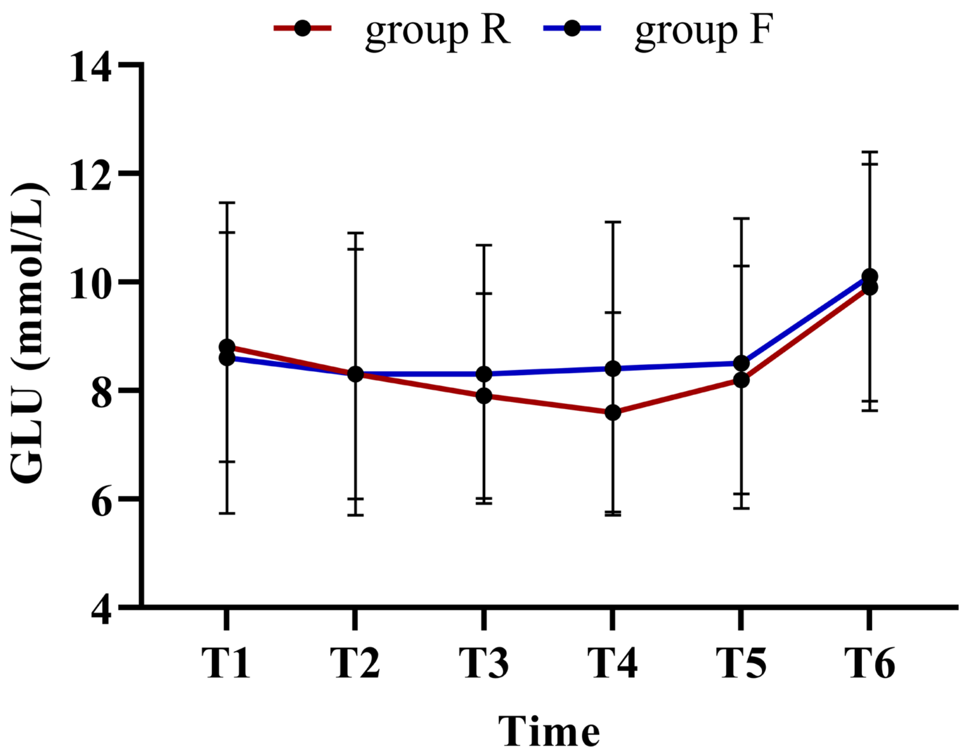

Figure 3. Changes in blood glucose at various points in time

Impact on epinephrine and norepinephrine

The NE values of the two groups before anesthesia induction were 113.1±31.42 pg/ml in group R and 113.9±38.78 pg/ml in group F. After induction, the NE values of the two groups were lower than the basic value, except for group F at the time point of T6 (119.6±35.15); nonetheless, these changes were not statistically significant (P>0.05). There was no difference in the basic level at the T1 time point of the E value between the two groups. The E value of group F did not change significantly during the operation, and the E value of group R was significantly lower than that of group F at the time points of T4 and T5 (P<0.05; Figure 4 and Table 3).

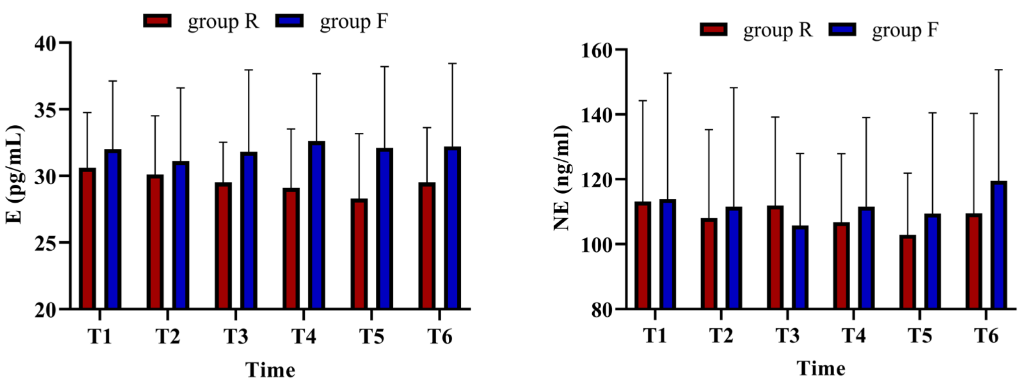

Figure 4. Changes in epinephrine and norepinephrine at various points in time

Discussion

In this study, the E level of group R was significantly lower than that of group F at the time points of T4 and T5 (P<0.05), and the MAP value of group R was lower than that of group F. In general, it was suggested that remifentanil can inhibit sympathetic nerve release of adrenaline to inhibit cardiovascular response and control blood pressure. The NE values of the two groups before anesthesia induction were obtained at 113.1±31.42 (group R) and 113.9± 38.78 (group F). After induction, the NE values of the two groups were lower than the basic value, except for group F at the T6 time point (119.6±35.15); nonetheless, these changes were not statistically significant ($P>0.05$). The release of NE during surgery is closely related to the degree of trauma. The trauma site stimulates the central NE activation system through afferent signals, such as pain or hormone regulation. The change of E in the circulation reflects the activity of the renal medulla (4, 16-18).

After severe burns, the body undergoes high metabolic changes, which are mainly manifested as increased body temperature, high hemodynamics, protein loss, fat dissolution, increased oxygen consumption, and immunosuppression, resulting in increased morbidity and mortality (19). The increased levels of catecholamines, glucagon, and cortisol are thought to cause this reaction and the subsequent series of reactions (20). Clinical trials (16-18) reported that urinary NE, E, and cortisol immediately increase significantly after severe burns. Moreover, NE increases tenfold in the early stage after burn, E increases 4 to 5 times, and urine cortisol level increases 8-10 times. Under normal circumstances, the body is controlled by negative feedback regulation. Nevertheless, after severe burns, this protective regulation of the body is destroyed, causing a significant increase in stress hormones. For burn patients, early scab removal surgery is not only a process of receiving treatment but also a process of suffering trauma. Surgery and anesthesia will cause a stronger stress response (13); therefore, it is beneficial to reduce the stress response of burn patients during operation.

In this experiment, it was observed that the HR of the two groups decreased after the operation started but increased significantly after induction. This is inconsistent with the results of multiple previous studies (21-23). It may be that participants in the previous research were all patients with normal volume, and this experiment was adopted by burn patients who were under capacity. After induction, the HR increased, MAP decreased, and the secretion of catecholamines did not increase. It is not considered that the stress response is enhanced; nonetheless, the blood vessel dilation is caused by insufficient return blood volume. Opioids have a significant effect on the cardiovascular system due to their high affinity for μ receptors. They reduce the HR through the central vagus nerve. This effect depends on the dose and delivery speed of opioids (24, 25). Therefore, for patients with hypovolemia before anesthesia, a small dose of remifentanil should be used for slow intravenous infusion.

Opioids have always been considered to have a dose-dependent inhibitory effect on sympathetic nerve activity. Studies have confirmed that remifentanil, which is significantly stronger than other opioids, has the effect of lowering blood pressure and HR (24, 26). There was no significant difference in the levels of NE between the two groups in this experiment, indicating that the effect of remifentanil on blood pressure and HR is not entirely exerted through the inhibition of sympathetic nerves. In order to ensure the blood perfusion of all organs in burn patients, standard controlled blood pressure reduction was not implemented during the operation. Therefore, it is not ruled out that insufficient dosage will affect the analysis of catecholamine levels. In addition, the sample size of this study was small, which may influence the accuracy of the results. It is suggested that these problems be avoided as much as possible in future studies.

6. Conclusion

In conclusion, compared with fentanyl, remifentanil has a better effect on scab removal surgery for burn patients. It can effectively inhibit the stress response during the operation, the hemodynamics are more stable, and the anesthetic drug and blood pressure control are integrated. The method is simple, safe, and reliable, with accurate effects. The present study might provide a theoretical basis for drug control in the safe operation process of burn patients.

Acknowledgments

Not applicable.

Footnotes

Conflicts of Interest: All authors declare that they have no financial or nonfinancial conflict of interest.
Author Contribution: Enjun Lei designed the study,Doudou Zhao and Yancheng Huang wrote the manuscript,Yu Lai and Ye Fang collected and analyzed data,Tingyu Pan and Rui Xu,revised the manuscript. All authors read and approved the final submitted manuscript.
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Ethical Statements: The study protocol was approved by the Ethics Committee of First Affiliated Hospital of Nanchang University.

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