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Application of gabapentin in multimodal analgesia after free anterolateral thigh flap repair surgery

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Abstract: **Objective** To investigate the efficacy of perioperative oral gabapentin in multimodal analgesia following free anterolateral thigh flap repair surgery, and its impact on pain, anxiety, depression, and fatigue in patients. **Methods** A total of 104 patients who underwent free anterolateral thigh flap repair surgery in the Department of Hand Surgery, Wuxi Ninth People's Hospital from January to June 2024 were selected and randomly divided into a control group (n=52) and a study group (n=52). Both groups received patient-controlled intravenous analgesia (PCIA) postoperatively with sufentanil 2 μg/kg combined with tropisetron 6 mg. The study group received oral gabapentin 0.6 g one hour before surgery and 0.9 g daily for four consecutive days postoperatively. while the control group took inactive capsules with the same appearance in exactly the same way as the research group. Resting Visual Analog Scale (VAS) scores, Pittsburgh Sleep Quality Index (PSQI) , Hospital Anxiety and Depression Scale (HADS) , and Christensen Fatigue Score were recorded preoperatively and at 24, 48, and 72 hours postoperatively. Adverse reactions (dizziness, nausea and vomiting, vascular crisis) within 72 hours postoperatively, as well as serum levels of inflammatory factors [interleukin (IL)-6, tumor necrosis factor (TNF)-α] and nerve growth factor (NGF) , were monitored. **Results** Compared to the control group, the study group showed significantly lower resting VAS score at 24, 48, and 72 hours postoperatively (P<0.01) . The PSQI and Christensen Fatigue Score at 48 and 72 hours postoperatively, and the HADS score at 72 hours postoperatively, were significantly lower in the study group than in the control group (P<0.05). Postoperative levels of IL-6 and TNF-α were significantly lower in the study group (P<0.05) , while NGF levels were significantly higher. at 24, 48 and 74 hours postoperatively (P<0.05) Compared with the control group, the study group had a lower rate of rescue analgesia use [5.77% (3/52) *vs* 34.62% (18/52), χ^2 =13.425, P=0.002], fewer daily rescue analgesia administrations [(0.6±0.3) times *vs* (1.8±0.7) times, t=11.362, P<0.01], lower total sufentanil consumption [(12.5±2.1) μg/kg *vs* (18.3±3.4) μg/kg, t=10.466, P<0.01], and fewer postoperative PCIA attempts [(8.2±1.5) times *vs* (14.7±2.8) times, t=14.756, P<0.01]. There was no statistically significant difference between the two groups in the incidence of adverse reactions such as dizziness, nausea and vomiting, and vascular crisis (P>0.05). **Conclusion** Gabapentin combined with multimodal analgesia can effectively relieve pain, anxiety, and fatigue, improve sleep quality, modulate inflammatory responses, and promote nerve regeneration after free anterolateral thigh flap repair surgery, demonstrating good safety.

Keywords: Gabapentin; Multimodal analgesia; Skin flap repair surgery; Patient controlled intravenous analgesia; Fatigue; Anxiety; Inflammatory response; Nerve growth factor

Free anterolateral thigh flap repair is a complex surgical procedure. Postoperative pain may cause local muscle tension in patients, affect blood supply to the flap, and increase the risk of vascular crisis [1-2]. Effective pain management can alleviate patients' muscle tension, improve blood perfusion of the flap, facilitate early functional exercise, and promote recovery [3]. Traditional analgesic regimens mainly rely on opioids, which are associated with multiple side effects such as nausea, vomiting, and respiratory depression [4]. In recent years, multimodal analgesia regimens have gradually attracted attention. By combining multiple non-opioid drugs, they achieve more effective analgesic effects while reducing the use of opioids [4].

Gabapentin is a gamma-aminobutyric acid (GABA) analog, which is widely used in the treatment of neuropathic pain. Its mechanisms of action include inhibiting neuroinflammatory response and regulating neurotransmitter levels, among others [5]. This study aims to investigate the application effect of gabapentin in multimodal analgesia after free anterolateral thigh flap repair, and evaluate its impacts on postoperative pain, anxiety, sleep quality, fatigue, and biomarkers, so as to provide new insights for clinical practice.

1 Subjects and Methods

1.1 Study Subjects

A total of 104 patients who underwent free anterolateral thigh flap repair in the Department of Hand Surgery of Wuxi Ninth People's Hospital from January to June 2024 were selected. The enrolled patients were randomly divided into a control group and a study group using a random number table method, with 52 cases in each group.

(1) Inclusion criteria: ① aged 16 to 80 years old; ②American Society of Anesthesiologists (ASA) classification grade I to II; ③no severe cardiopulmonary dysfunction; ④no mental disorders.

(2) Exclusion criteria: ①long-term preoperative use of analgesics, sedatives (such as benzodiazepines) or anti-anxiety drugs; ②allergy to gabapentin; ③pre-existing severe sleep disorders or anxiety and depression symptoms before surgery.

Patients and their families were informed of the content of this study and voluntarily signed the informed consent form. The study was approved by the Ethics Committee of Wuxi Ninth People's Hospital (approval number: KS2025028).

1.2 Methods

This study adopted a double-blind design, and all patients received general anesthesia. Anesthesia induction: Intravenous injection of propofol (Jiangsu Yingke Biopharmaceutical, National Drug Approval No. H20203504, 20 mL: 0.2 g) 1-2 mg/kg, sufentanil (Yichang Humanwell Pharmaceutical, Hubei; National Drug Approval No. H20054171, 1 mL: 50 μg) 0.3-0.5 μg/kg, and rocuronium bromide (Guangdong Xinghao Pharmaceutical, National Drug Approval No. H20103235, 5 mL: 50 mg) 0.6-0.9 mg/kg. After endotracheal intubation, a ventilator was connected for assisted breathing. Anesthesia maintenance: Inhalation of 1%-2% sevoflurane (Lunan Betate Pharmaceutical, National Drug Approval No. H20244849, 100 mL), and intermittent intravenous injection of sufentanil 0.1-0.2 μg/kg. The depth of anesthesia was adjusted according to the patient's vital signs. Intraoperative indicators such as heart rate, blood pressure, blood oxygen saturation, and end-tidal carbon dioxide partial pressure were monitored to ensure the stability of the patient's vital signs. During the study period, benzodiazepines or other drugs with sedative/anti-anxiety effects were prohibited to avoid interference with the results of the Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression Scale (HADS) scores.

Both groups of patients received patient-controlled intravenous analgesia (PCIA) after surgery [6-7]. The analgesic pump contained sufentanil 2 μg/kg and tropisetron (Hainan Lingkang Pharmaceutical, National Drug Approval No. H20060287, 5 mg) 6 mg, diluted to 100 mL with normal saline. The background infusion rate was 2 mL/h, the single PCIA dose was 2 mL, and the lockout time was 15 min. Patients in the study group orally received 0.6 g of gabapentin (Zhejiang Yongtai Pharmaceutical, National Drug Approval No. H20223322, 0.1 g) 1 h before surgery, and orally took 0.9 g of gabapentin daily for 4 consecutive days after surgery. Patients in the control group orally received inactive capsules with exactly the same appearance, color, and administration method as gabapentin 1 h before surgery and daily after surgery for 4 consecutive days.

If the patient's postoperative resting Visual Analogue Scale (VAS) score was ≥4 points (based on the moderate pain threshold [4]) and the pain was not effectively relieved by PCIA (the VAS score decreased by less than 2 points within 15 minutes after a single press [7]), 50 mg of flurbiprofen axetil (Beijing Tide Pharmaceutical, National Drug Approval No. H20041508, 5 mL: 50 mg) was intravenously injected once every 6-8 h, with the maximum daily dose not exceeding 200 mg. The frequency, dose, and corresponding time points of rescue analgesic drug use was recorded in the case report form (CRF), and included as covariates in the model during statistical analysis to control for their potential impact on the study results.

1.3 Observation Indicators

1.3.1 Scale Scores

The following scale evaluations were performed on patients before surgery, and at 24 h, 48 h, and 72 h after surgery, and the scores were recorded. The Visual Analogue Scale (VAS) score was used to evaluate pain, the Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality [8], the Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression [9], and the Christensen Fatigue Score was used to evaluate the degree of fatigue [10].

1.3.2 Biomarker Detection

Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of inflammatory factors [interleukin (IL)-6, tumor necrosis factor (TNF)-α] and nerve growth factor (NGF) in the serum of patients at 24 h, 48 h, and 72 h after surgery.

1.3.3 Adverse Reactions

The occurrence of adverse reactions such as dizziness, nausea and vomiting, and vascular crisis within 72 h after surgery was recorded.

1.4 Statistical Methods

SPSS 26.0 software was used for data analysis. Measurement data conforming to normal distribution were expressed as $\bar{x}\pm s$. For repeated measurement indicators, a linear mixed model was used to analyze the time effect, group effect, and time×group interaction effect. The Bonferroni method was used for simple effect analysis. Skewed distributed measurement data were expressed as M (P_{25}, P_{75}). Comparisons between multiple time points were performed using generalized estimating equations, and pairwise comparisons were performed using the Mann-Whitney U test. Count data were expressed as case (%), and comparisons were performed using the χ^2 test. A P value < 0.05 was considered statistically significant.

2 Results

2.1 Comparison of Pain, Sleep Quality, Anxiety and Depression, and Fatigue Scores

Analysis using the linear mixed model showed that there were significant time effects, group effects, and

time×group interaction effects in the postoperative VAS, PSQI, HADS, and Christensen fatigue scores (P<0.01). The VAS scores of the study group at 24 h, 48 h, and 72 h after surgery were significantly lower than those of the control group (P<0.05). Compared with the control group, the PSQI scores of the study group at 48 h and 72 h after surgery were significantly reduced (P<0.05). Compared with the control group, the HADS score of the study group at 72 h after surgery was significantly reduced (P<0.05). Compared with the control group, the Christensen fatigue scores of the study group at 48 h and 72 h after surgery were significantly reduced (P<0.05), as shown in **Table 1**.

2.2 Comparison of Biomarker Levels

There was no statistically significant difference in the preoperative serum levels of IL-6, TNF-α, and NGF between the two groups of patients (P>0.05). Repeated measures analysis of variance showed that the time effects, group effects, and interaction effects of IL-6, TNF-α, and NGF levels were all statistically significant (P<0.01). The levels of IL-6 and TNF-α in the study group at 24 h, 48 h, and 72 h after surgery were significantly lower than those in the control group. The NGF levels of the two groups of patients peaked at 72 h after surgery, and the study group was significantly higher than the control group at all postoperative time points (P<0.01), as shown in **Table 2**.

2.3 Comparison of Postoperative Rescue Analgesia, Opioid Consumption, and Number of PCIA Presses

Compared with the control group, the study group had a lower rate of postoperative rescue analgesia use [5.77% (3/52) *vs* 34.62% (18/52), χ^2=13.425, P=0.002] and fewer daily uses [(0.6 ± 0.3) times *vs* (1.8 ± 0.7) times, t=11.362, P<0.01]. Within 72 h after surgery, the total consumption of sufentanil in the study group was (12.5±2.1) μg/kg, which was significantly lower than that in the control group [(18.3±3.4) μg/kg, t=10.466, P<0.01]. The number of postoperative PCIA presses in the study group was (8.2±1.5) times, which was significantly less than that in the control group [(14.7±2.8) times, t=14.756, P<0.01].

2.4 Adverse Reactions

There were no statistically significant differences in the incidence rates of adverse reactions such as dizziness, nausea and vomiting, and vascular crisis within 72 h after surgery between the two groups of patients (P>0.05) as shown in **Table 3**.

Tab.1 Comparison of perioperative VAS, PSQI, HADS and Christensen Fatigue Score between two groups [n=52, point, M (P_{25}, P_{75})]

Time point	VAS		PSQI		HANDS		Christensen fatigue score	
	Control group	Study group	Control group	Study group	Control group	Study group	Control group	Study group
Preoperatively	6.0(5.0,8.0)	6.0(5.0,6.5)	18.0(15.0,20.0)	16.0(12.0,19.0)	20.0(16.5,25.0)	18.0(15.0,21.5)	7.0(5.0,9.0)	5.0(3.0,7.0)
24 h postoperatively	4.0(2.0,5.0)^{b}	2.0(1.5,2.0)^{ab}	12.0(9.5,15.5)^{b}	11.0(6.5,16.5)^{b}	14.0(10.0,18.0)^{a}	10.0(5.0,16.5)^{b}	5.0(2.0,7.5)^{b}	2.0(1.0,5.0)^{ab}
48 h postoperatively	4.0(2.0,5.0)^{b}	1.0(0.0,1.0)^{abc}	12.0(10.0,19.0)^{b}	8.0(4.5,13.0)^{abc}	11.0(9.5,18.0)^{a}	8.0(4.0,13.5)^{b}	5.0(2.0,6.0)^{b}	1.0(1.0,2.5)^{abc}
72 h postoperatively	3.0(1.0,3.5)^{b}	0.0(0.0,0.5)^{abcd}	10.0(8.0,12.0)^{bc}	5.0(3.0,10.5)^{abcd}	11.0(7.0,15.5)^{a}	5.0(2.0,10.0)^{abc}	2.0(1.0,5.0)^{bc}	0.0(0.0,1.0)^{abcd}
χ^2/P $_{group}$ value	96.390/<0.001		10.650/0.001		14.430/<0.001		27.620/<0.001	
χ^2/P $_{time}$ value	101.000/<0.001		28.200/<0.001		16.460/<0.001		33.440/<0.001	
χ^2/P $_{interaction}$ value	3.879/0.010		1.098/0.351		0.293/0.831		0.104/0.958	

Note: Compared with the same group preoperatively, ^{a}P<0.05; Compared with the control group at the same time point, ^{b}P<0.05; Compared with the same group at 24 hours postoperatively, ^{c}P<0.05; Compared with the same group at 48 hours postoperatively, ^{d}P<0.05.

Tab.2 Comparison of perioperative biomarker levels between two groups (n=52, $\bar{x}\pm s$)

Time point	IL-6(pg/mL)		TNF-α(pg/mL)		NGF(pg/mL)	
	Control group	Study group	Control group	Study group	Control group	Study group
Preoperatively	25.3±4.1	24.8±3.9	15.6±2.3	15.2±2.1	216.6±26.9	217.5±34.5
24 h postoperatively	135.4±14.3^{a}	98.5±10.2^{ab}	62.7±7.8 ^{a}	45.2±6.1^{ac}	220.1±24.8	241.6±24.0^{ac}
48 h postoperatively	120.5±15.2^{ab}	85.3±12.6^{abc}	58.4±8.7^{ab}	42.1±7.3^{abc}	214.6±23.6	244.6±21.3^{ac}
72 h postoperatively	95.8±11.7^{abc}	70.1±9.8^{abc}	40.3±6.5^{abc}	30.5±5.2^{abc}	225.8±27.6^{b}	250.4±29.4^{abc}
χ^2/P $_{group}$ value	45.678/<0.001		56.789/<0.001		10.250/<0.001	
χ^2/P $_{time}$ value	120.345/<0.001		98.234/<0.001		8.860/<0.001	
χ^2/P $_{interaction}$ value	18.901/0.012		22.345/0.008		3.860/0.011	

Note: Compared with the same group preoperatively, ^{a}P<0.05; Compared with the control group at the same time point, ^{b}P<0.05; Compared with the same group at 24 hours postoperatively, ^{c}P<0.05.

Tab.3 Comparison of postoperative adverse reactions between two groups [n=52, case(%)]

Group	Dizziness	Nausea and vomiting	Vascular crisis
Control group	10(19.23)	8(15.38)	4(7.69)
Study group	8(15.38)	4(7.69)	2(3.84)
χ^2 value	0.269	1.507	0.177
***P* value**	0.604	0.220	0.674

3 Discussion

This study explored the application effect of gabapentin in multimodal analgesia after free anterolateral thigh flap repair through a randomized controlled trial. The results showed that the combined use of gabapentin significantly improved postoperative pain,

anxiety, fatigue and sleep quality, regulated the levels of biomarkers related to inflammatory response and nerve regeneration, and did not increase the risk of adverse reactions.

As a GABA analog, gabapentin mainly exerts an analgesic effect by binding to the α2δ subunit of voltage-gated calcium channels and inhibiting neurotransmitter release [5,11], which can assist in postoperative pain management [12]. The results of this study showed that gabapentin significantly reduced the postoperative VAS score, indicating that it has a good effect in postoperative pain management. In addition, the serum levels of IL-6 and TNF-α in the study group were significantly reduced after surgery, suggesting that gabapentin may alleviate postoperative pain by inhibiting neuroinflammatory response. In this study, VAS ≥ 4 points combined with ineffective PCIA (VAS reduction less than 2 points) was used as the trigger condition for rescue analgesia. This standard refers to the Clinical practice guidelines for postoperative pain management in adults (2024 edition) [13], aiming to balance comfort of patient and the objectivity of research results. Although the use rate of rescue analgesia in the study group was lower than that in the control group, the interference with inter-group differences was minimized by including it as a covariate in the linear mixed model analysis. Future studies can further optimize the control of confounding factors through stratified design or matching analysis.

Postoperative anxiety and depression are important factors affecting patient recovery[14]. In this study, the postoperative HADS score of the study group decreased, indicating that gabapentin can not only relieve postoperative pain, but also improve the anxiety of patients. The postoperative Christensen fatigue score of the study group was significantly reduced, supporting the value of gabapentin in comprehensive postoperative management [15]. This may be related to the regulatory effect of gabapentin on neurotransmitters [5,11], and further studies can explore its potential mechanism in neuroprotection and psychological rehabilitation.

Postoperative inflammatory response is an important factor affecting patient recovery [16-17]. This study detected the levels of IL-6, TNF-α and NGF in serum after surgery, and found that gabapentin can significantly reduce the levels of inflammatory factors and increase the level of NGF. Through linear mixed model analysis, this study confirmed that gabapentin not only reduced the overall level of postoperative pain (group effect), but also significantly changed the trend of pain over time (interaction effect), indicating that its analgesic effect is time-dependent. In addition, multi-time point biomarker detection showed that IL-6 and TNF-α peaked at 24 h after surgery, and the study group effectively blocked the inflammatory cascade by inhibiting the early inflammatory response and continuous regulation. The dynamic increase of NGF suggests that gabapentin may accelerate tissue repair by promoting nerve regeneration.

In this study, gabapentin combined with PCIA not only improved postoperative pain and psychological state, but also significantly reduced the total consumption of sufentanil and the number of PCIA presses, further verifying the clinical advantage of multimodal analgesia in reducing opioid dependence through the synergistic effect of non-opioid drugs. This result is consistent with previous studies [18-19], suggesting that gabapentin has important value in optimizing postoperative analgesia strategies. Meanwhile, studies have shown that multimodal analgesia regimens can reduce the use of opioids, reduce postoperative adverse reactions, and significantly improve postoperative pain, anxiety, fatigue and sleep quality by combining a variety of non-opioid drugs [20], further verifying the clinical advantage of multimodal analgesia in reducing opioid dependence through the synergistic effect of non-opioid drugs. This indicates that multimodal analgesia regimens have broad application prospects in postoperative pain management [21-22].

The limitations of this study include the relatively small sample size and short follow-up duration. Although the use of preoperative sedative or anxiolytic medications was restricted through exclusion criteria, postoperative over-the-counter sedative medication use by patients was not fully monitored. Future studies may further expand the sample size, extend the follow-up period, explore the role of gabapentin in long-term postoperative rehabilitation, and strictly control for confounding factors related to the use of sedative and anxiolytic medications. In addition, animal experiments and cell experiments can be combined to further investigate its mechanism of action, providing a more solid theoretical foundation for clinical application.

The gabapentin combined multimodal analgesia regimen exhibits a significant analgesic effect after anterolateral thigh free flap repair surgery. It can improve postoperative anxiety, depression, and fatigue states, regulate inflammatory responses and nerve regeneration, accelerate patient recovery, and has good safety. This study provides a new perspective for postoperative pain management, and gabapentin is expected to become an important component of multimodal analgesia regimens.

Conflict of Interest None

Reference

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·临床麻醉专题·论著·

加巴喷丁在游离股前外侧皮瓣修复术后多模式镇痛中的应用

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摘要：目的 探讨围手术期口服加巴喷丁在游离股前外侧皮瓣修复术后多模式镇痛中的应用效果，及对患者疼痛、焦虑抑郁、疲劳的影响。**方法** 选取2024年1月至6月无锡市第九人民医院手外科接受游离股前外侧皮瓣修复术的患者104例，随机分为对照组（n=52）和研究组（n=52）。两组术后均采用患者静脉自控镇痛（PCIA），药物为舒芬太尼2 μg/kg联合托烷司琼6 mg。研究组术前1 h口服加巴喷丁0.6 g，术后连续4天每日口服加巴喷丁0.9 g。对照组用与研究组完全同样的方法服用外观一致的无活性胶囊。记录术前及术后24 h、48 h、72 h的静息VAS评分、匹兹堡睡眠质量指数（PSQI）、医院焦虑抑郁量表（HADS）、Christensen疲劳评分，监测术后72 h内不良反应（头晕、恶心呕吐、血管危象）及血清炎症因子[白细胞介素（IL）-6、肿瘤坏死因子（TNF）-α]和神经生长因子（NGF）水平。**结果** 与对照组相比，研究组术后24 h、48 h、72 h的静息VAS评分显著降低（P<0.01）。研究组术后48 h、72 h的PSQI和Christensen疲劳评分以及术后72 h的HADS评分均显著低于对照组（P<0.05）。研究组术后24 h、48 h、72h的IL-6、TNF-α水平均显著低于对照组（P<0.05），而NGF水平显著高于对照组（P<0.05）。与对照组比较，研究组术后补救镇痛使用率更低[5.77%（3/52） *vs* 34.62%（18/52），χ^2=13.425，P=0.002]、单日使用次数更少[（0.6±0.3）次 *vs*（1.8±0.7）次，t=11.362，P<0.01]、舒芬太尼总消耗量更少[（12.5±2.1）μg/kg *vs*（18.3±3.4）μg/kg，t=10.466，P<0.01]及术后PCIA按压次数更少[（8.2±1.5）次*vs*（14.7±2.8）次，t=14.756，P<0.01]。两组术后头晕、恶心呕吐、血管危象不良反应发生率差异无统计学意义（P>0.05）。**结论** 加巴喷丁联合多模式镇痛可有效缓解游离股前外侧皮瓣修复术后疼痛、焦虑及疲劳，改善睡眠质量，调节炎症反应并促进神经再生，具有良好的安全性。

关键词： 加巴喷丁；多模式镇痛；皮瓣修复术；患者静脉自控镇痛；疲劳；焦虑；炎症反应；神经生长因子
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Application of gabapentin in multimodal analgesia after free anterolateral thigh flap repair surgery

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Abstract: Objective To investigate the efficacy of perioperative oral gabapentin in multimodal analgesia following free anterolateral thigh flap repair surgery, and its impact on pain, anxiety, depression, and fatigue in patients. **Methods** A total of 104 patients who underwent free anterolateral thigh flap repair surgery in the Department of Hand Surgery, Wuxi Ninth People's Hospital from January to June 2024 were selected and randomly divided into a control group (n=52) and a study group (n=52). Both groups received patient-controlled intravenous analgesia (PCIA) postoperatively with sufentanil 2 μg/kg combined with tropisetron 6 mg. The study group received oral gabapentin 0.6 g one hour before surgery and 0.9 g daily for four consecutive days postoperatively, while the control group took inactive capsules with the same appearance in exactly the same way as the research group. Resting Visual Analog Scale (VAS) scores, Pittsburgh

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Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), and Christensen Fatigue Score were recorded preoperatively and at 24, 48, and 72 hours postoperatively. Adverse reactions (dizziness, nausea and vomiting, vascular crisis) within 72 hours postoperatively, as well as serum levels of inflammatory factors [interleukin (IL)-6, tumor necrosis factor (TNF)-α] and nerve growth factor (NGF), were monitored. **Results** Compared to the control group, the study group showed significantly lower resting VAS score at 24, 48, and 72 hours postoperatively (P<0.01). The PSQI and Christensen Fatigue Score at 48 and 72 hours postoperatively, and the HADS score at 72 hours postoperatively, were significantly lower in the study group than in the control group (P<0.05). Postoperative levels of IL-6 and TNF-α were significantly lower in the study group (P<0.05), while NGF levels were significantly higher at 24, 48 and 74 hours postoperatively (P<0.05). Compared with the control group, the study group had a lower rate of rescue analgesia use [5.77%(3/52) *vs* 34.62%(18/52), χ^2=13.425, P=0.002], fewer daily rescue analgesia administrations[(0.6±0.3)times *vs* (1.8±0.7)times, t=11.362, P<0.01], lower total sufentanil consumption [(12.5±2.1)μg/kg *vs* (18.3±3.4)μg/kg, t=10.466, P<0.01], and fewer postoperative PCIA attempts [(8.2±1.5)times *vs* (14.7±2.8)times, t=14.756, P<0.01]. There was no statistically significant difference between the two groups in the incidence of adverse reactions such as dizziness, nausea and vomiting, and vascular crisis (P>0.05). **Conclusion** Gabapentin combined with multimodal analgesia can effectively relieve pain, anxiety, and fatigue, improve sleep quality, modulate inflammatory responses, and promote nerve regeneration after free anterolateral thigh flap repair surgery, demonstrating good safety.

Keywords: Gabapentin; Multimodal analgesia; Skin flap repair surgery; Patient controlled intravenous analgesia; Fatigue; Anxiety; Inflammatory response; Nerve growth factor

游离股前外侧皮瓣修复术是一种复杂的外科手术，术后疼痛可能导致患者局部肌肉紧张，影响皮瓣的血运，增加血管危象的发生风险[1-2]。有效的疼痛管理可以减轻患者的肌肉紧张，改善皮瓣的血流灌注，有助于患者早期进行功能锻炼，促进康复[3]。传统镇痛方案主要依赖阿片类药物，但其副作用较多，如恶心、呕吐、呼吸抑制等[4]。近年来，多模式镇痛方案逐渐受到关注，其通过联合多种非阿片类药物，实现更有效的镇痛效果，同时减少阿片类药物的使用[4]。

加巴喷丁是一种γ-氨基丁酸(gamma-aminobutyric acid，GABA)类似物，广泛用于神经病理性疼痛的治疗，其作用机制包括抑制神经炎症反应、调节神经递质水平等[5]。本研究旨在探讨加巴喷丁在游离股前外侧皮瓣修复术后多模式镇痛中的应用效果，评估其对术后疼痛、焦虑、睡眠质量、疲劳及生物标志物的影响，为临床实践提供新的思路。

1　对象与方法

1.1　*研究对象*　选取2024年1月至6月在无锡市第九人民医院手外科接受游离股前外侧皮瓣修复术的患者104例，按照随机数字表法将参与患者随机分为对照组和研究组，每组各52例。(1) 纳入标准：①年龄16~80岁；②美国麻醉医师协会(American Society of Anesthesiologists，ASA)分级Ⅰ~Ⅱ级；③无严重心肺功能障碍；④无精神障碍。(2) 排除标准：①术前长期使用镇痛药物、镇静药物(如苯二氮䓬类)或抗焦虑药物；②对加巴喷丁过敏；③术前存在严重睡眠障碍或焦虑抑郁症状。

患者及其家属对本研究内容了解并自愿签署知情同意书，且研究经无锡市第九人民医院伦理委员会审批通过(批准文号：KS2025028)。

1.2　*方法*　本研究采取双盲设计，所有患者均接受全身麻醉。麻醉诱导：静脉注射丙泊酚(江苏盈科生物制药，国药准字H20203504，20 mL∶0.2 g)1~2 mg/kg、舒芬太尼(湖北宜昌人福药业，国药准字H20054171，1 mL∶50 μg)0.3~0.5 μg/kg、罗库溴铵(广东星昊药业，国药准字H20103235，5 mL∶50 mg)0.6~0.9 mg/kg，气管插管后连接呼吸机辅助呼吸。麻醉维持：吸入1%~2%七氟烷(鲁南贝特制药，国药准字H20244849，100 mL)，间断性静脉注射舒芬太尼0.1~0.2 μg/kg，根据患者生命体征调整麻醉深度。术中监测心率、血压、血氧饱和度、呼气末二氧化碳分压等指标，确保患者生命体征平稳。研究期间禁止使用苯二氮䓬类或其他具有镇静/抗焦虑作用的药物，以避免对匹兹堡睡眠质量指数(Pittsburgh sleep quality index，PSQI)和医院焦虑抑郁量表(Hospital Anxiety and Depression Scale，HADS)评分的结果造成干扰。

两组患者术后均采用患者静脉自控镇痛(patient-controlled intravenous analgesia，PCIA)[6-7]，镇痛泵药物为舒芬太尼2 μg/kg、托烷司琼(海南灵康制药，国药准字H20060287，5 mg)6 mg加生理盐水稀释至

100 mL，背景输注速率2 mL/h，单次PCIA剂量2 mL，锁定时间15 min。研究组患者于术前1 h口服加巴喷丁（浙江永太药业，国药准字H20223322，0.1g）0.6 g，术后，每日口服加巴喷丁0.9 g，连续服用4天。对照组患者于术前1 h、术后每日口服外观、颜色、服用方式与加巴喷丁完全一致的无活性胶囊，连续服用4天。

若患者术后静息视觉模拟量表（Visual Analogue Scale，VAS）评分≥4分（基于中度疼痛阈值[4]），且通过PCIA未能有效缓解疼痛（单次按压后15分钟内VAS评分降低幅度不足2分[7]），则静脉注射氟比洛芬酯（北京泰德药业，国药准字H20041508，5 mL∶50 mg）50 mg，每6~8 h一次，单日最大剂量不超过200 mg。补救镇痛药物的使用次数、剂量及对应时间点均记录于病例报告表（case report form，CRF），并在统计分析中作为协变量纳入模型，以控制其对研究结果的潜在影响。

1.3 观察指标

1.3.1 量表评分 于术前、术后24 h、48 h、72 h对患者进行以下量表评估，记录分数。采用VAS评分评估疼痛，采用PSQI评估睡眠质量[8]，采用HADS评估焦虑抑郁[9]，采用Christensen疲劳评分评估疲劳程度[10]。

1.3.2 生物标志物检测 利用酶联免疫吸附试验检测术后24 h、48 h及72 h患者血清中的炎症因子[白细胞介素（interleukin，IL）-6、肿瘤坏死因子（tumor necrosis factor，TNF）-α]和神经生长因子（nerve growth factor，NGF）水平。

1.3.3 不良反应 记录术后72 h内头晕、恶心呕吐、血管危象等不良反应的发生情况。

1.4 统计学方法 采用SPSS 26.0软件进行数据分析。符合正态分布的计量资料以$\bar{x}\pm s$表示。重复测量指标采用线性混合模型分析时间效应、组别效应及时间×组别交互效应。Bonferroni法进行简单效应分析。偏态分布的计量数据以$M(P_{25},P_{75})$表示，多时间点间比较采用广义估计方程，两两比较采用Mann-Whitney U检验。计数资料以例（%）表示，比较采用χ^2检验。P<0.05为差异有统计学意义。

2 结 果

2.1 疼痛、睡眠质量、焦虑抑郁、疲劳评分比较 线性混合模型分析显示，术后VAS、PSQI、HADS及Christensen疲劳评分存在显著的时间效应、组别效应及时间×组别交互作用（P<0.01）。研究组术后24 h、48 h、72 h的VAS评分均显著低于对照组（P<0.05）。与对照组相比，研究组术后48 h、72 h的PSQI评分显著降低（P<0.05）。与对照组相比，研究组术后72 h的HADS评分显著降低（P<0.05）。与对照组相比，研究组术后48 h、72 h的Christensen疲劳评分显著降低（P<0.05），见表1。

2.2 生物标志物水平比较 两组患者术前血清中的IL-6、TNF-α及NGF水平差异无统计学意义（P>0.05）。重复测量方差分析显示，IL-6、TNF-α及NGF水平的时间效应、组别效应及交互效应均有统计学意义（P<0.01）。研究组术后24 h、48 h及72 h的IL-6和TNF-α水平显著低于对照组。两组患者NGF水平在术后72 h达到峰值，且术后各时间点研究组均显著高于对照组（P<0.01）。见表2。

2.3 术后补救镇痛、阿片类药物消耗量及PCIA按压次数比较 与对照组比较，研究组术后补救镇痛使用率更低[5.77%（3/52）*vs* 34.62%（18/52），χ^2=13.425，P=0.002）、单日使用次数更少[（0.6 ± 0.3）次 *vs*（1.8 ± 0.7）次，t=11.362，P<0.01]。术后72 h内，研究组患者舒芬太尼总消耗量为（12.5±2.1）μg/kg，显著低于对照组的（18.3±3.4）μg/kg（t=10.466，P<0.01）。研究组术后PCIA按压次数为（8.2±1.5）次，明显少于对照组的（14.7±2.8）次（t=14.756，P<0.01）。

2.4 不良反应 两组患者术后72 h内头晕、恶心呕吐、血管危象等不良反应的发生率差异均无统计学意义（P>0.05）。具体结果见表3。

表1 两组围手术期VAS、PSQI、HADS及Christensen疲劳评分比较 [n=52，分，$M(P_{25},P_{75})$]

Tab.1 Comparison of perioperative VAS, PSQI, HADS and Christensen Fatigue Score between two groups [n=52, point, $M(P_{25},P_{75})$]

时间点	VAS		PSQI		HADS		Christensen疲劳评分	
	对照组	研究组	对照组	研究组	对照组	研究组	对照组	研究组
术前	6.0(5.0,8.0)	6.0(5.0,6.5)	18.0(15.0,20.0)	16.0(12.0,19.0)	20.0(16.5,25.0)	18.0(115.0,21.5)	7.0(5.0,9.0)	5.0(3.0,7.0)
术后24 h	4.0(2.0,5.0)^{b}	2.0(1.5,2.0)^{ab}	12.0(9.5,15.5)^{b}	11.0(6.5,16.5)^{b}	14.0(10.0,18.0)^{b}	10.0(5.0,16.5)^{b}	5.0(2.0,7.5)^{b}	2.0(1.0,5.0)^{ab}
术后48 h	4.0(2.0,5.0)^{b}	1.0(0,1.0)^{abc}	12.0(10.0,19.0)^{b}	8.0(4.5,13.0)^{abc}	11.0(9.5,18.0)^{b}	8.0(4.0,13.5)^{b}	5.0(2.0,6.0)^{b}	1.0(1.0,2.5)^{abc}
术后72 h	3.0(1.0,3.5)^{b}	0(0,0.5)^{abcd}	10.0(8.0,12.0)^{bc}	5.0(3.0,10.5)^{abcd}	11.0(7.0,15.5)^{b}	5.0(2.0,10.0)^{abc}	2.0(1.0,5.0)^{bc}	0(0,1.0)^{abcd}
$\chi^2/P_{组间}$值	96.390/<0.001		10.650/0.001		14.430/<0.001		27.620/<0.001	
$\chi^2/P_{时间}$值	101.000/<0.001		28.200/<0.001		16.460/<0.001		33.440/<0.001	
$\chi^2/P_{交互}$值	3.879/0.010		1.098/0.351		0.293/0.831		0.104/0.958	

注：与对照组同时间点比较，^{a}P<0.05；与同组术前比较，^{b}P<0.05；与同组术后24 h比较，^{c}P<0.05；与同组术后48 h比较，^{d}P<0.05。

表 2　两组术后生物标志物水平比较　（n=52，$\bar{x}\pm s$）

Tab2　Comparison of perioperative biomarker levels between two groups　（n=52，$\bar{x}\pm s$）

时间点	IL-6（pg/mL）		TNF-α（pg/mL）		NGF（pg/mL）	
	对照组	研究组	对照组	研究组	对照组	研究组
术前	25.3±4.1	24.8±3.9	15.6±2.3	15.2±2.1	216.6±26.9	217.5±34.5
术后 24 h	135.4±14.3[a]	98.5±10.2[ac]	62.7±7.8[a]	45.2±6.1[ac]	220.1±24.8	241.6±24.0[ac]
术后 48 h	120.5±15.2[ab]	85.3±12.6[abc]	58.4±8.7[ab]	42.1±7.3[abc]	214.6±23.6	244.6±21.3[ac]
术后 72 h	95.8±11.7[abc]	70.1±9.8[abc]	40.3±6.5[abc]	30.5±5.2[abc]	225.8±27.6[b]	250.4±29.4[abc]
$F/P_{组间}$值	45.678/<0.001		56.789/<0.001		10.250/<0.001	
$F/P_{时间}$值	120.345/<0.001		98.234/<0.001		8.860/<0.001	
$F/P_{交互}$值	18.901/0.012		22.345/0.008		3.860/0.011	

注：与对照组同时间点比较，[a]P<0.05；与同组术前比较，[b]P<0.05；与同组术后 24 h 比较，[c]P<0.05。

表 3　两组术后不良反应比较　［n=52，例（%）］

Tab.3　Comparison of postoperative adverse reactions between two groups　［n=52，case（%）］

组别	头晕	恶心呕吐	血管危象
对照组	10（19.23）	8（15.38）	4（7.69）
研究组	8（15.38）	4（7.69）	2（3.84）
χ^2值	0.269	1.507	0.177
P值	0.604	0.220	0.674

3　讨　论

本研究通过随机对照试验探讨了加巴喷丁在游离股前外侧皮瓣修复术后多模式镇痛中的应用效果，结果显示加巴喷丁的联合使用显著改善了术后疼痛、焦虑、疲劳及睡眠质量，并调节了炎症反应与神经再生相关生物标志物水平，同时未增加发生不良反应的风险。

加巴喷丁作为一种GABA类似物，主要通过结合电压门控钙通道α2δ亚单位，抑制神经递质释放，从而发挥镇痛作用[5,11]，可以辅助术后疼痛管理[12]。本研究结果显示，加巴喷丁显著降低了术后VAS评分，表明其在术后疼痛管理中具有良好的效果。此外，研究组术后血清中IL-6和TNF-α水平显著降低，提示加巴喷丁可能通过抑制神经炎症反应来减轻术后疼痛。本研究采用VAS≥4分联合PCIA无效（VAS降低不足2分）作为补救镇痛触发条件，该标准参考了《成人术后疼痛管理临床实践指南（2024版）》[13]，旨在平衡患者舒适度与研究结果的客观性。尽管研究组补救镇痛使用率低于对照组，但通过将其作为协变量纳入线性混合模型分析，已最大程度减少其对组间差异的干扰。未来研究可进一步通过分层设计或匹配分析优化混杂因素的控制。

术后焦虑和抑郁是影响患者康复的重要因素[14]。本研究中，研究组术后HADS评分降低，表明加巴喷丁不仅能缓解术后疼痛，还能改善患者的焦虑情绪。研究组术后Christensen疲劳评分显著降低，支持加巴喷丁在术后综合管理中的价值[15]。这可能与加巴喷丁对神经递质的调节作用有关[5,11]，进一步研究可探索其在神经保护和心理康复中的潜在机制。

术后炎症反应是影响患者康复的重要因素[16-17]。本研究检测了术后血清中的IL-6、TNF-α和NGF水平，发现加巴喷丁能够显著降低炎症因子水平，同时提高NGF水平。通过线性混合模型分析，本研究证实加巴喷丁不仅降低了术后疼痛的总体水平（组别效应），还显著改变了疼痛随时间的变化趋势（交互作用），表明其镇痛效果具有时间依赖性。此外，多时间点生物标志物检测显示，IL-6和TNF-α在术后24 h达到峰值，而研究组通过抑制早期炎症反应及持续调节，有效地阻断了炎症级联反应。NGF的动态升高则提示加巴喷丁可能通过促进神经再生加速组织修复。

本研究中，加巴喷丁联合PCIA不仅改善了术后疼痛及心理状态，还显著降低了舒芬太尼的总消耗量及PCIA按压次数，进一步验证了多模式镇痛通过非阿片类药物协同作用减少阿片依赖的临床优势。这一结果与既往研究[18-19]一致，提示加巴喷丁在优化术后镇痛策略中具有重要价值。同时研究显示，多模式镇痛方案通过联合多种非阿片类药物，减少阿片类药物的使用，降低术后不良反应，显著改善了术后疼痛、焦虑、疲劳和睡眠质量[20]，进一步验证了多模式镇痛通过非阿片类药物协同作用减少阿片依赖的临床优势，这表明多模式镇痛方案在术后疼痛管理中具有广阔的应用前景[21-22]。

本研究的局限性在于样本量较小，且随访时间较短，虽通过排除标准限制了术前镇静/抗焦虑药物的使用，但未完全监测术后患者是否自行服用非处方镇静药物。未来研究可进一步扩大样本量，延长随访时间，探讨加巴喷丁在术后长期康复中的作用，并严格管控镇静/抗焦虑药物使用的混杂因素。此

外，可结合动物实验和细胞实验，深入研究其作用机制，为临床应用提供更坚实的理论基础。

加巴喷丁联合多模式镇痛方案在游离股前外侧皮瓣修复术后具有显著的镇痛效果，能够改善术后焦虑、抑郁和疲劳状态，调节炎症反应和神经再生，加速患者康复，且安全性良好。本研究为术后疼痛管理提供了新的思路，加巴喷丁有望成为多模式镇痛方案中的重要组成部分。

利益冲突　无

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