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ORIGINAL RESEARCH

Impact of Analgesic Modalities on Postoperative Breakthrough Pain Following Anterior Cruciate Ligament Reconstruction: A Retrospective Study

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Background: Effective postoperative pain management is vital for the recovery, mobility, and quality of life of patients undergoing anterior cruciate ligament reconstruction (ACLR) surgery. Our retrospective analysis aims to identify factors affecting postoperative breakthrough pain after ACLR, with a focus on analgesic modalities.

Methods: This retrospective study included 848 patients who underwent ACLR surgery at Peking University Third Hospital from January 1, 2019, to September 30, 2022. After applying exclusion criteria, patients were categorized into four groups: general anesthesia with femoral nerve block (Group G + F, n = 156), general anesthesia alone (Group G, n = 129), spinal anesthesia with femoral nerve block (Group S + F, n = 314), and spinal anesthesia alone (Group S, n = 249). The collected data included demographic details, analgesic methods, and the timing of the first pain relief request. Statistical analysis was performed using the chi-square test and multivariable logistic regression to evaluate intergroup differences and the effect of covariates.

Results: A significant difference was found in the timing of the first analgesic request among the groups ($p < 0.001$). Group G and Group S requested their initial postoperative analgesics sooner than Groups G + F and S + F, respectively ($p < 0.001$). Multivariable analysis showed that gender was associated with postoperative breakthrough pain (odds ratio [OR] 0.502; 95% confidence interval [CI] 0.307 to 0.821). Postoperative routine use of non-steroidal anti-inflammatory drugs (NSAIDs) also reduced breakthrough pain incidence (OR 0.286; 95% CI 0.182 to 0.451). Breakthrough pain at 12 and 24 hours post-surgery was associated with prolonged hospital stays ($p = 0.001$ and 0.006, respectively).

Conclusion: The administration of a single-shot femoral nerve block (FNB) significantly delayed the first request for analgesia after ACLR, without leading to prolonged hospitalization. Factors associated with postoperative breakthrough pain during hospitalization included gender, regular NSAID use, and analgesic modality selection.

Keywords: arthroscopic anterior cruciate ligament reconstruction, postoperative breakthrough pain, risk factors

Introduction

According to statistics, more than 400,000 patients worldwide undergo surgical treatment for anterior cruciate ligament (ACL) injuries each year.[1] Arthroscopic anterior cruciate ligament reconstruction (ACLR), a widely adopted surgical approach for ACL injuries globally, combines the benefits of minimal invasiveness, accelerated recovery, and reduced complication rates. However, procedures such as surgical incisions, creation of bone tunnels, and graft harvesting can all contribute to postoperative pain in patients.[2] Although anesthesiologists employ strategies such as nerve blocks and analgesic administration to alleviate postoperative pain, some patients may experience breakthrough pain. This condition impedes early mobilization, thereby increasing the risk of joint stiffness and persistent pain, which not only hinders the rehabilitation process and diminishes quality of life but also elevates overall healthcare costs.[3,4]

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Breakthrough pain (BTP) is a transitory exacerbation of pain that occurs on a background of otherwise controlled pain.[5] The considerable individual variability in postoperative breakthrough pain is multifactorial, stemming from differences in age, pain sensitivity, psychological state, and genetics.[6–9] International research on breakthrough pain has predominantly focused on obstetric patients and cancer pain patients, with very limited studies addressing postoperative breakthrough pain in knee surgery patients. A meta-analysis on pain management following ACLR demonstrated that nerve blocks significantly reduce postoperative pain and opioid consumption.[10] However, another meta-analysis on pain management following ACLR arrived at a contradictory conclusion, indicating that Femoral Nerve Block (FNB) has not been proven to significantly impact patients' pain scores.[11] Additionally, in clinical practice, many patients still experience severe breakthrough pain despite the implementation of these analgesic measures. Therefore, this retrospective study aims to investigate the effects of different analgesic modalities on breakthrough pain following arthroscopic ACLR.

Methods

Ethics Approval

This study was approved by the Institutional Review Board and Ethics Committee of Peking University Third Hospital (IRB00006761-M2024102) and registered at ChiCTR.org (ChiCTR2500107686). This retrospective study was granted a waiver of informed consent by the Institutional Review Board and Ethics Committee. The study protocol adhered strictly to the ethical principles outlined in the Declaration of Helsinki. All procedures were implemented to ensure participant safety, maintain confidentiality of data, and comply with recognized international research standards.

Patient Selection and Data Extraction

A retrospective review of medical records was conducted for all patients who underwent ACLR from the inception of the electronic medical record system on January 1, 2019, to September 30, 2022. To mitigate selection bias, the initial data extraction included all patients who underwent ACLR during the study period. The initial screening identified 1157 eligible patients during the study period. The inclusion criteria were: American Society of Anesthesiologists (ASA) Physical Status Classification I or II and age 18 ~ 60 years. Exclusion criteria included abnormal preoperative routine laboratory tests or coagulation profile, use of anticoagulants or antiplatelet agents within two weeks prior to surgery and ACLR performed with an autograft other than hamstring tendons. To avoid potential confounding, only the first ACLR surgery per patient during the study period was included; all revision procedures were excluded. This approach prevented the assessment of post-revision pain from being contaminated by the patient's prior ACLR experience. A total of 309 patients were excluded, leaving 848 patients for the final analysis. These 848 patients were divided into four groups: 156 patients in the general anesthesia combined with single-shot femoral nerve block group (Group G + F), 129 patients in the simple general anesthesia group (Group G), 314 patients in the spinal anesthesia combined with single - shot femoral nerve block group (Group S + F), and 249 patients in the simple spinal anesthesia group (Group S) (Figure 1). The choice of anesthesia was made following detailed counseling by the anesthesiologist regarding the advantages and disadvantages of neuraxial versus general anesthesia, with the final decision based on patient preference.

At Peking University Third Hospital, patients undergoing ACLR during the study period were managed according to standardized intraoperative and postoperative analgesia protocols. Intraoperative analgesia comprised a single-shot FNB (20 mL of 0.3% ropivacaine) and an intravenous nonsteroidal anti-inflammatory drug (NSAID) (flurbiprofen ester, 50 mg). The intraoperative analgesic plan was determined through shared decision-making: the anesthesiologist detailed the options to the patient, who then decided whether to proceed with its implementation. Postoperative analgesia comprised scheduled oral etoricoxib (60 mg daily) as well as the option of intravenous NSAIDs (flurbiprofen ester 100 mg twice daily or parecoxib sodium 40 mg daily). For postoperative breakthrough pain, oral oxycodone-acetaminophen was administered as needed based on a 10-point visual analog scale (VAS). Specifically, a VAS score of 4 ~ 6 was treated with 5 mg oxycodone, and a score of 7 ~ 10 with an intramuscular injection of pethidine (50 mg) combined with promethazine hydrochloride (25 mg). The postoperative ward analgesia plan was determined by the operating surgeon. Pain scores were routinely recorded upon admission, before discharge, and every 4 hours after

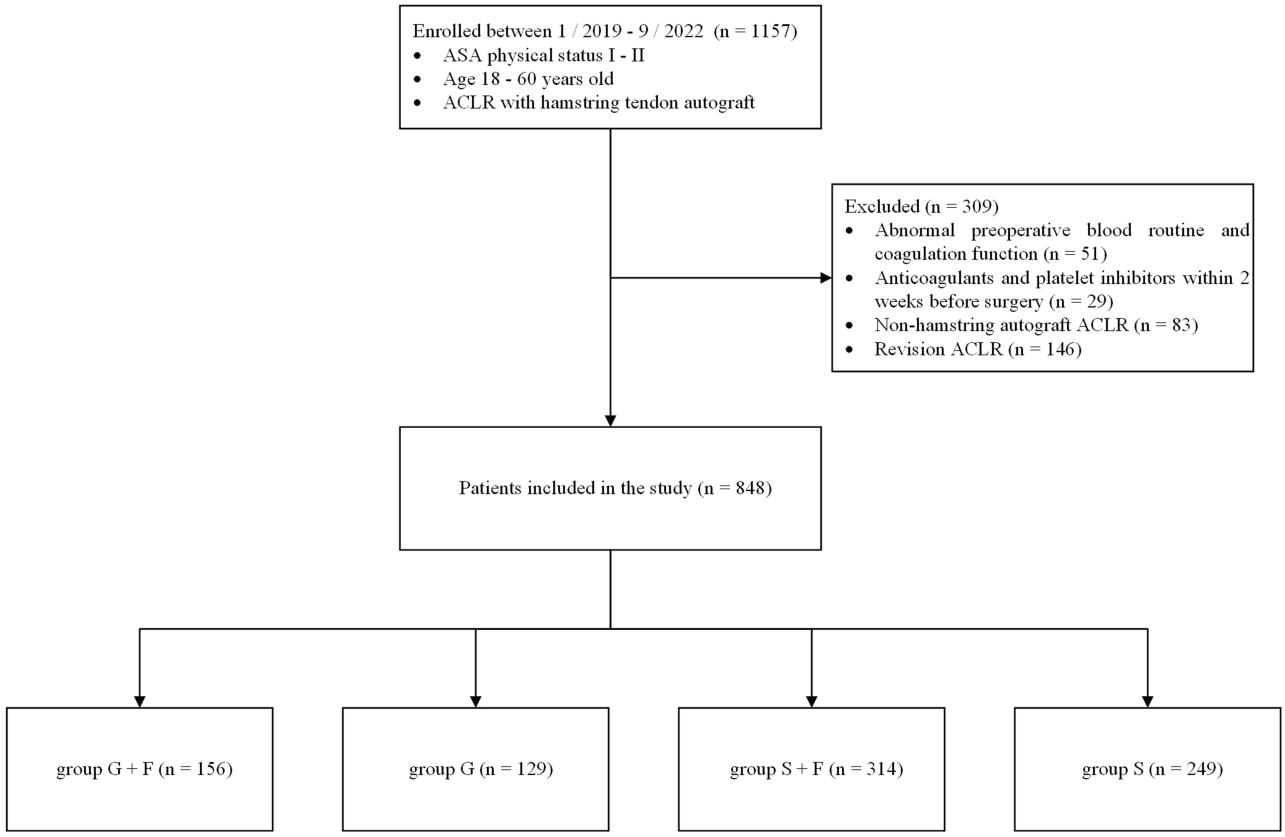

Figure 1 Patient inclusion flow diagram.
Abbreviations: ACLR, arthroscopic anterior cruciate ligament reconstruction; ASA, American Society of Anesthesiologists; G + F, general anesthesia combined with femoral nerve block; G, general anesthesia; S + F, spinal anesthesia combined with femoral nerve block; S, spinal anesthesia.

surgery. If a patient experienced postoperative breakthrough pain, an additional score was recorded following analgesic intervention on the ward.

Data were extracted from electronic medical records and subsequently exported to a database for analysis. Data collected included the type of anesthesia (general or spinal), use of a single-shot FNB, time to first analgesic request, and pain scores. Pain was assessed at three time points: upon admission to the sports medicine ward (first recorded score), and at 12 and 24 hours postoperatively.

Statistical Analysis

This study employed a retrospective cohort design. Data analysis was conducted using IBM SPSS Statistics (version 26.0). Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, while categorical variables are described as frequencies (percentages). Preliminary comparisons of baseline characteristics and the primary outcome among groups were performed using the chi-square test (for categorical variables) or one-way analysis of variance (for continuous variables). To adjust for potential confounders of the primary outcome, a multivariable logistic regression model was constructed, which included as covariates those variables showing statistically significant intergroup differences. The model was fitted using maximum likelihood estimation. The statistical significance of independent variables was assessed with the Wald χ^2-test, and association strengths are expressed as odds ratios with their 95% confidence intervals. All tests were two-sided, with a significance level set at $P < 0.05$.

Results

Baseline Participant Characteristics

The baseline characteristics of the four groups ultimately included in this study are summarized by group in Table 1.

Table 1 Demographic Characteristics of Different Groups

Variables	Group G + F (n = 156)	Group G (n = 129)	Group S + F (n = 314)	Group S (n = 249)	95% CI	*P*-value
Age (years)	36.71 ± 10.43	33.27 ± 9.87	34.10 ± 9.51	32.91 ± 9.74	33.45–34.76	0.001*
Gender (F/M)	90/66	62/67	85/229	59/190	/	< 0.001*
Height	169.58 ± 9.74	171.99 ± 9.81	173.76 ± 8.36	173.76 ± 8.04	171.98–173.18	< 0.001*
Weight	72.71 ± 14.59	74.91 ± 14.95	75.83 ± 13.42	76.29 ± 13.78	74.30 −76.19	0.068
BMI (kg/m^2)	25.16 ± 3.91	25.22 ± 3.95	25.15 ± 3.62	25.15 ± 3.51	24.91–25.41	0.998
ASA (I/II)	99/57	95/34	202/112	222/27	/	< 0.001*
Postoperative NSAIDs Administration in the ward (N/Y)	26/130	17/112	100/214	16/233	/	< 0.001*
Length of hospital stay (days)	4.88 ± 1.61	4.78 ± 1.45	4.40 ± 1.17	4.74 ± 1.73	1.19–1.36	0.002*

Note: *Indicates *P*-value less than *0.05*.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval.

Time for the First Analgesic Request

Regarding the time to first analgesic request following ACLR, a significant difference was observed among the groups ($p < 0.001$). When comparing Group G + F to Group G and Group S + F to Group S, both latter groups demonstrated a shorter interval before their first postoperative analgesic request ($p < 0.001$). However, the time to first analgesic request did not differ significantly between Group S+F and Group G+F ($p = 0.676$) (Figure 2).

Risk Factors for Postoperative Breakthrough Pain During Hospitalization

The incidence of the breakthrough pain during hospitalization was not associated with age, height, weight, BMI, length of hospital stay or ASA classification ($p > 0.05$). There was a statistically significant difference in the incidence of breakthrough pain during hospitalization between females and males ($p < 0.05$). The incidence of postoperative breakthrough pain was significantly associated with postoperative NSAIDs administration in the ward ($p < 0.001$). Compared to Group S, the incidence of postoperative breakthrough pain was significantly higher in both Group G and Group S+F (both $p < 0.001$). Group G+F and Group S did not differ significantly in the incidence of postoperative breakthrough pain (Table 2).

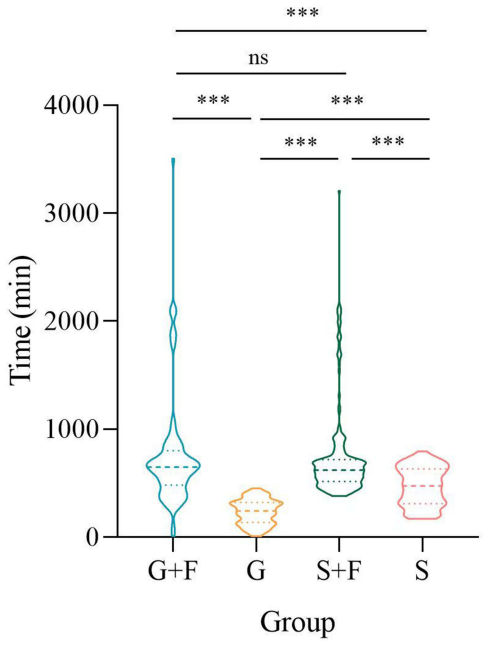

Figure 2 Time to the first postoperative analgesic request across different groups. G + F, general anesthesia combined with femoral nerve block, n = 81; G, general anesthesia, n = 114; S + F, spinal anesthesia combined with femoral nerve block, n = 208; S, spinal anesthesia, n = 104. Error bars show the mean ± SD, ***Indicates P < 0.001.
Abbreviation: ns, no significance.

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Table 2 Multinomial Logistic Analysis on Postoperative Breakthrough Pain during Hospitalization

Variables	OR	95% CI	*P*-value
Continuous Variables			
Age	0.984	0.967–1.001	0.066
Height	1.057	0.936–1.193	0.375
Weight	0.956	0.835–1.093	0.507
BMI	1.173	0.786–1.752	0.435
Length of hospital stay	0.976	0.882–1.080	0.638
Categorical Variables			
Gender/(Female as reference)			
Male	0.502	0.307–0.821	0.006*
Postoperative NSAIDs administration in the ward (NO administration as reference)			
Administration in the ward	0.286	0.182–0.451	< 0.001*
ASA (I as reference)			
Grade II	1.143	0.801–1.631	0.463
Type of Anesthesia (SA [group S as reference])			
GA + FNB (group G + F)	1.177	0.756–1.833	0.470
GA (group G)	8.064	4.508–14.423	< 0.001*
SA + FNB (group S + F)	2.060	1.416–2.995	< 0.001*

Note: *Indicates *P*-value less than *0.05*.
Abbreviations: BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; ASA, American Society of Anesthesiologists; GA, general anesthesia; FNB, femoral nerve block; SA, spinal anesthesia.

Postoperative Breakthrough Pain at 12 h and 24 h

Multivariable logistic regression analysis indicated that postoperative breakthrough pain at 12 and 24 hours was not associated with gender, age, height, weight, BMI, or ASA classification ($p > 0.05$). The risk of postoperative breakthrough pain at both 12 and 24 hours differed significantly between Group G and Group S ($p < 0.001$). Additionally, Group S+F had a significantly lower risk of postoperative breakthrough pain than Group S at both 12 hours ($p = 0.016$) and 24 hours ($p < 0.001$). Furthermore, a longer hospital stay was significantly associated with a higher incidence of postoperative breakthrough pain at both 12 hours ($p = 0.001$) and 24 hours ($p = 0.006$) (Tables 3 and 4).

Table 3 Multinomial Logistic Analysis on Breakthrough Pain at 12 Hours Postoperatively

Variables	OR	95% CI	*P*-value
Continuous Variables			
Age	0.995	0.979–1.012	0.569
Height	1.026	0.913–1.152	0.670
Weight	0.776	0.863–1.116	0.776
BMI	1.081	0.737–1.586	0.691
Length of hospital stay	1.186	1.069–1.315	0.001*
Categorical Variables			
Gender/(Female as reference)			
Male	0.841	0.524–1.349	0.472
Postoperative NSAIDs administration in the ward (NO administration as reference)			
Administration in the ward	0.846	0.575–1.245	0.395
ASA (Grade I as reference)			
Grade II	1.211	0.858–1.709	0.276
Type of Anesthesia [SA (group S as reference)]			
GA + FNB (group G + F)	0.867	0.555–1.356	0.533
GA (group G)	11.869	6.461–21.805	<0.001*
SA + FNB (group S + F)	1.576	1.089–2.282	0.016*

Note: *Indicates *P*-value less than *0.05*.
Abbreviations: BMI, body mass index; NSAIDs, nonsteroidal anti - inflammatory drugs; ASA, American Society of Anesthesiologists; GA, general anesthesia; FNB, femoral nerve block; SA, spinal anesthesia.

Table 4 Multinomial Logistic Analysis on Breakthrough Pain at 24 Hours Postoperatively

Variables	OR	95% CI	*P*-value
Continuous Variables			
Age	0.992	0.976–1.009	0.348
Height	1.010	0.899–1.134	0.869
Weight	0.984	0.866–1.119	0.805
BMI	1.086	0.741–1.593	0.671
Length of hospital stay	1.156	1.043–1.281	0.006*
Categorical Variables			
Gender/(Female as reference)			
Male	0.982	0.613–1.574	0.939
Postoperative NSAIDs administration in the ward (NO administration as reference)			
Administration in the ward	0.973	0.660–1.434	0.888
ASA (Grade I as reference)			
Grade II	1.125	0.796–1.590	0.504
Type of Anesthesia [SA (group S as reference)]			
Group G + F	1.174	0.759–1.816	0.472
Group G	10.826	5.898–19.871	< 0.001*
Group S + F	2.290	1.580–3.318	< 0.001*

Note: *Indicates *P*-value less than *0.05*.
Abbreviations: BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; ASA, American Society of Anesthesiologists; GA, general anesthesia; FNB, femoral nerve block; SA, spinal anesthesia.

Discussion

Our findings confirm that a FNB effectively prolongs the time to the first postoperative analgesic request, regardless of whether general anesthesia or neuraxial anesthesia is chosen. On multivariate regression analysis, both regular ward-based NSAID administration and male sex were independently associated with a lower incidence of postoperative breakthrough pain during hospitalization.

The duration of postoperative pain varies, typically persisting for 24 to 72 hours.[12] Surgical trauma from ACLR directly damages mechanoreceptors in the joint capsule, ligaments, and muscles, leading to a sudden reduction in normal proprioceptive afferent input to the central nervous system. A longer interval from injury to surgery is associated with a more pronounced reduction in the number of mechanoreceptors within the stump.[13,14] A deficit in proprioceptive input can induce functional reorganization and sensitization in the spinal cord and somatosensory cortex. Central sensitization amplifies nociceptive processing, resulting in a pain perception abnormality in which patients perceive normal joint movement or mild pressure as pain, clinically known as mechanical hyperalgesia.[15] Thus, this neuroplastic mechanism underlies the severe postoperative pain commonly observed after ACLR. Our findings indicate that compared to general anesthesia or neuraxial anesthesia alone, the combination of neuraxial anesthesia with a FNB or general anesthesia with an FNB significantly prolongs the time to the first request for postoperative analgesia. The FNB non-selectively inhibits the conduction of all afferent fiber types, including mechanoreceptive and nociceptive fibers.[16] This creates a transient, complete sensory deprivation, resulting in a "pain-free and sensation-free" state. Our findings are consistent with several studies on nerve block analgesia in other surgical contexts.[17–19]

Furthermore, based on an analysis of the incidence and associated risk factors of postoperative breakthrough pain, we selected indicators showing statistically significant differences. For this purpose, we employed multivariate logistic regression analysis to identify independent risk factors influencing breakthrough pain following ACLR. Our study identified a sex-related difference in the incidence of postoperative breakthrough pain during hospitalization, with female patients demonstrating a higher incidence than males. The risk of postoperative breakthrough pain occurrence in males is only 50.2% of that in females. Previous research has also demonstrated that men and women differ in their experience of pain: women typically exhibit higher pain sensitivity and lower pain thresholds. Hormonal differences—particularly involving estrogen and progesterone—also influence pain perception.[20–22] Consequently, this finding highlights the necessity of implementing enhanced analgesic strategies for female patients to improve pain management outcomes. Our analysis further revealed that the occurrence of postoperative breakthrough

pain was not correlated with patient age, BMI, length of hospital stay, or ASA physical status. However, some studies have explicitly indicated that younger age is an independent risk factor for moderate to severe postoperative pain.[23–25] Given that most ACLR patients are young adults and our study cohort was limited to ages 18 ~ 60, we observed no differential impact of age on postoperative breakthrough pain. Furthermore, our analysis found that, compared with no NSAID use, routine NSAID administration in the ward was associated with a 28.6% risk of postoperative breakthrough pain. This suggests that protocolized analgesic administration in the ward can significantly reduce breakthrough pain in patients. Consequently, this strategy must be given high priority by the attending surgeon. Furthermore, our analysis revealed that the timing of initial postoperative breakthrough pain was significantly influenced by the choice of anesthetic technique. Patients who underwent general anesthesia alone had an 8.06 times higher risk of postoperative breakthrough pain than those who received spinal anesthesia alone. This result suggests that for patients opting for general anesthesia to undergo ACLR, who are at an increased risk of postoperative breakthrough pain, anesthesiologists should provide adequate multimodal analgesia to reduce its incidence.

No association was found between patient age, BMI, or gender and the risk of breakthrough pain at 12 or 24 hours after surgery. However, the choice of anesthetic method had a significant effect. Compared with patients receiving spinal anesthesia alone, those undergoing general anesthesia alone showed 11.87-fold and 10.83-fold higher incidences of breakthrough pain at 12 and 24 hours postoperatively, respectively. We recommend that anesthesiologists administer a combined single-injection FNB for patients undergoing ACLR under general anesthesia to reduce breakthrough pain within the first 12 and 24 hours postoperatively. Moreover, the incidence of breakthrough pain was 1.58 times higher at 12 hours and 2.29 times higher at 24 hours postoperatively in patients receiving spinal anesthesia combined with FNB compared to those receiving spinal anesthesia alone. As the FNB wears off, the previously blocked normal nociceptive and proprioceptive signals are restored simultaneously. At this point, a central nervous system that has already been sensitized is suddenly flooded with a surge of amplified nociceptive signals and mismatched proprioceptive inputs. This may trigger a transient afferent signal storm, which manifests clinically as severe "rebound pain".[26,27] Our conclusion is supported by existing literature reporting comparable rebound pain after the resolution of peripheral nerve blocks.[28–30] These studies suggest that certain risk factors for rebound pain include young age, female sex, and orthopedic surgery. Furthermore, these studies also found that intravenous administration of dexamethasone during surgery can effectively reduce the incidence of rebound pain. By identifying these risk factors, we can develop targeted pain management strategies for specific populations and surgical procedures that are at higher risk of rebound pain. Furthermore, our study found that longer hospital stays are associated with a greater likelihood of experiencing pain at 12 and 24 hours postoperatively. This finding suggests that an increased incidence of postoperative pain is associated with prolonged hospital stay.

Conclusion

Patients undergoing ACLR who received FNB demonstrated a prolonged duration to first analgesic request. Risk factors for breakthrough pain during hospitalization following ACLR included patient sex, scheduled postoperative NSAID administration, and the analgesic modalities.

Data Sharing Statement

All the authors agreed to share the individual deidentified participant data, and the data are available from the corresponding authors, Zhengqian Li (zhengqianli@hsc.pku.edu.cn) and Hong Zeng (z_hong0326@163.com), upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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