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Comparison of The Effect of Intravenous Acetaminophen and Flurbiprofen on Postoperative Pain After Total Knee Arthroplasty: A Randomized Controlled Trials

Yusuke Kasai[1], Yoshiaki Terao[1]*, Ayako Shimazaki[1], Maki Ono[1], Natsuko Oji[1], Makito Oji[1], Tetsuya Hara[2]

[1]Department of Anesthesia, Nagasaki Rosai Hospital, 2-12-5 Setogoe, Sasebo 857-0134, Japan
[2]Department of Anesthesiology, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

***Correspondence:** Yoshiaki Terao, Department of Anesthesia, Nagasaki Rosai Hospital, 2-12-5 Setogoe, Sasebo 857-0134, Japan. Tel: +81-956- 49-2197; Fax: +81-956-49-2358; E-mail: yoterao@nagasakih.johas.go.jp

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Abstract

Introduction: Femoral nerve block and local infiltration anesthesia are effective in ameliorating early postoperative pain after total knee arthroplasty. However, patients can experience rebound pain after the cessation of femoral nerve block and local infiltration anesthesia. This prospective, randomized, open-label, and placebo-controlled study aimed to determine whether acetaminophen and flurbiprofen were effective analgesic adjuvants to femoral nerve block and local infiltration anesthesia after total knee arthroplasty.

Methods: This study was conducted from October 2017 to April 2019 with 75 patients who underwent total knee arthroplasty under general anesthesia. All patients were administered total intravenous anesthesia with propofol and remifentanil and received ultrasound-guided femoral nerve block with 0.25% levobupivacaine (30 mL) before surgery and local infiltration anesthesia with 0.25% levobupivacaine (30 mL) before cementing the components. Patients were randomly allocated to one of three groups: group A (n=25), which received intravenous acetaminophen 1000 mg before the end of surgery, and 6, 12, 18, and 24 h after surgery; group F (n= 25), which received flurbiprofen 50 mg; and group C (n=25), which received saline. Patients were administered diclofenac sodium, loxoprofen, or pentazocine as rescue analgesics, if needed. Postoperative pain was evaluated by the nursing staff using a numerical rating scale 0, 1, 3, 6, 12, and 24 h postoperatively.

Results: There were no significant differences in numerical rating scale of the three groups. The frequency of rescue analgesic administration was significantly lower in groups A and F than in group C.

Conclusions: Intravenous acetaminophen and flurbiprofen were equivalent and effective adjuvants to femoral nerve block and local infiltration anesthesia after total knee arthroplasty.

Trial Registration: UMIN Clinical Trials Registry database reference number: UMIN000029487. This study was registered on October 10, 2017. https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000033687

Keywords: Acetaminophen; Flurbiprofen; Total knee arthroplasty; Femoral nerve block; Local inilitration anesthesia.

ABBREVIATIONS

TKA: total knee arthroplasty; FNB: femoral nerve block; LIA: local infiltration anesthesia; PONV: postoperative nausea and vomiting; NSAID: nonsteroidal anti-inflammatory drug; A: acetaminophen; F: flurbiprofen; C: control; TCI: target-controlled infusion; NRS: numerical rating scale; ANOVA: A factorial analysis of variance; COX: cyclooxygenase; SNB: sciatic nerve block;

INTRODUCTION

Proper postoperative analgesia is thought to improve the postoperative prognosis by preventing pain-related complications [1]. Acute pain after total knee arthroplasty (TKA) has a substantial effect on functional recovery and patient satisfaction. Multimodal analgesia, including the femoral nerve block (FNB) and local infiltration anesthesia (LIA), is known to be effective for

the amelioration of early postoperative pain after TKA [2,3]. However, patients experience rebound pain after the effects of FNB and LIA are diminished [4].

Although opioids are extremely useful analgesic agents, their use is associated with side-effects, such as postoperative nausea and vomiting (PONV), and respiratory depression [5]. Moreover, postoperative pain is multifactorial in origin: it can arise from nociceptors and in response to inflammation, and the current practice involves the combination of multiple analgesics. Therefore, multimodal analgesia that combines non-opioid analgesics and peripheral nerve blocks to reduce opioid consumption has become the mainstay of postoperative pain control in recent years. Flurbiprofen is an injectable nonsteroidal anti-inflammatory drug (NSAID), which is generally administered to achieve postoperative analgesia in Japan [6]. The analgesic effect of intravenous acetaminophen is comparable to that of NSAIDs in patients with moderate postoperative pain [7]. However, few studies have compared the postoperative analgesic effects of flurbiprofen and acetaminophen after TKA.

This prospective, randomized, open-label, and placebo-controlled study aimed to determine whether acetaminophen and flurbiprofen were effective analgesic adjuvants to the FNB and LIA after TKA.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Ethics Committee, and written informed consent was obtained from each patient. This open-label randomized clinical trial included 75 patients with an American Society of Anesthesiologists physical status of 1 or 2, weighing 50–70 kg, who underwent TKA under general anesthesia at Nagasaki Rosai Hospital between October 2017 and April 2019. The exclusion criteria included liver and renal dysfunction, and a medical history of peptic ulcers and asthma. None of the patients received any pre-anesthetic medication.

Study Protocol

Patients were randomly allocated to one of three groups: group A (n = 25), which received intravenous acetaminophen, group F (n = 25), which received flurbiprofen intravenously, and group C (n = 25), which received saline as the control. Randomization was performed by the responsible anesthesiologist using the sealed-envelope system.

Patients received a continuous infusion of remifentanil 0.5 μg/kg/min and propofol 5 μg/mL for 2 min followed by 3 μg/mL to achieve the desired effect-site concentration using a target-controlled infusion system (TCI pump, TE-371, Terumo, Tokyo, Japan). Rocuronium (0.8 mg/kg) was administered to facilitate tracheal intubation after loss of consciousness. The effect-site concentrations of propofol and remifentanil were titrated to maintain the bispectral index score between 40 and 60 after tracheal intubation. All patients received ultrasound guided FNB with 0.25% levobupivacaine 30 mL before surgery and LIA with 0.25% levobupivacaine 30 mL into the posterior capsule of the knee before cementing the components. All patients received a bolus administration of fentanyl 250 μg after cementing the components (approximately 30 min before the end of surgery). Patients in group A received acetaminophen 1000 mg (Acelio® Intravenous Injection 1000 mg, TERUMO, Tokyo, Japan) intravenously every 6 h, patients in group F received flurbiprofen axetil 50 mg (ROPION® Intravenous 50 mg, Kaken, Tokyo, Japan) intravenously every 6 h, and those in group C received 100 mL of saline intravenously every 6 h (as the control). The administration of each drug was started prior to skin closure and continued for 24 h after surgery. Patients were administered diclofenac sodium 50 mg, loxoprofen 30 mg, or pentazocine 15 mg as rescue analgesics after surgery, if needed. The nursing staff evaluated the postoperative pain using a numerical rating scale (NRS; 10 points from 0 to 10) 1, 2, 6, 12, and 24 h postoperatively. NRS scores were evaluated just before analgesic drug injection.

Measurements

The primary outcome was the postoperative pain evaluated by the nursing staff using the NRS 0, 1, 3, 6, 12, and 24 h postoperatively. The frequency of rescue analgesic use and incidence of PONV during 24 h after TKA were the secondary outcomes.

Statistical Analysis

The results were expressed as the median (interquartile range). A two-factorial analysis of variance (ANOVA) was performed to analyze the interaction between time and the 3 groups' NRS scores. A post-hoc comparison was performed between the groups at each time-point and among the repeated measures in each group using the Dunn procedure, wherever appropriate. Continuous data were analyzed using the Kruskal–Wallis and Mann–Whitney U tests. Dichotomous variables were analyzed using the chi-squared test, and p-values < 0.05 were considered statistically significant.

The sample size was determined on the basis of a previous study (SD, 2) [3], which indicated that a power of 90% would be required to detect a difference of 2 in the NRS scores between the two groups at a 5% significance level, if each group contained 22 patients.

RESULTS

Table 1 shows the demographic parameters of each group of patients. No significant differences were observed in the demographic parameters, except height, among the 3 groups.

The repeated-measures ANOVA revealed no significant differences between the NRS scores of the three groups during the study period (Figure 1). The NRS scores 1, 3, 6, and 12 h postoperatively were higher than those at 0 h in group A. The NRS scores 1, 3, 6, and 12 h postoperatively were higher than those at 0 h in group C. The NRS scores at 12 and 24 h were higher than those at 0 h in group F.

The frequency of rescue analgesic use in groups A and F was significantly lower than that in group C. Table 2 depicts the incidence of PONV. There were no significant differences in the incidence of PONV among the three groups.

No patient showed any adverse effects associated with acetaminophen or flurbiprofen.

DISCUSSION

This study showed that the combination of FNB and LIA with acetaminophen or flurbiprofen did not reduce the NRS scores but could reduce the frequency of rescue analgesic use. This study showed that intravenous acetaminophen and flurbiprofen were equivalent and effective adjuvants to FNB and LIA after TKA.

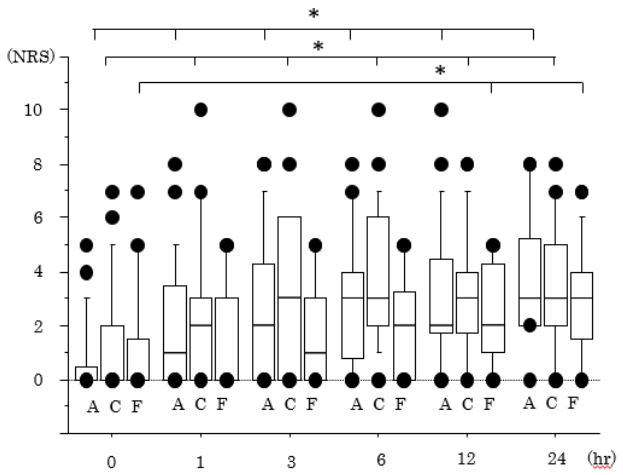

Figure1: Numerical rating scale in group acetaminophen, flurbiprofen and placebo at each time point. Values are expressed as median (line inside the boxes), IQR (boxes), and 10-90percentiles (whiskers). A, acetaminophen group; F, flurbiprofen group; C, control group; NRS, numerical rating scale; *p < 0.05 vs. 0hr values.

Table 1: Patients characteristics.

	Acetaminophen	Flurbiprofen	Control	p
Patients (n)	25	25	25	
Age (years)	77 (69,80)	76 (70,81)	76 (71,79)	0.99
Height (cm)	154 (151,159)	148 (145,155)*	153 (150,155)	0.02
Weight (kg)	62 (60,65)	59 (54,65)	58 (52,65)	0.32
BMI (kg/m^2)	25.6 (23.8,27.8)	26.4 (24.3,29.1)	24.8 (22.8,27.4)	0.28
Male gender	13	3	5	0.37
Anesthetic time (min)	152 (143,165)	147 (133,163)	148 (139,157)	0.34
Operative time (min)	95 (89,106)	86 (78,100)	92 (82,106)	0.15
Operative blood loss (g)	10 (5,11)	10 (5,13)	10 (5,16)	0.81
Values are median (IQR) or number. BMI, body mass index; n, number.				

Table 2: Postoperative valuables.

	Acetaminophen	Flurbiprofen	Control	p
PONV (n)	14	11	12	0.69
Rescue analgesics for 12 hr (n)	0 (0,0)*	0 (0,0)*	1 (0,1)	<0.01
Rescue analgesics for 24 hr (n)	0 (0,1)*	0 (0,0)*	1 (1,2)	<0.01
Values are median (IQR) or number. PONV, postoperative nausea and vomiting;				
*<0.05, vs. control group.				

Acetaminophen is a pharmacological agent with antipyretic and analgesic effects that are mediated via the central inhibition of the third isoform of the cyclooxygenase (COX) enzyme, which is mainly found in the cerebral cortex and heart [8]. Flurbiprofen blocks the production of prostaglandins through the inhibition of COX-1 and COX-2. Svensson et al. [9] reported that flurbiprofen demonstrated almost equal selectivity for COX-1 and COX-2. The inhibition of COX-1 is responsible for the adverse effects of NSAIDs, such as gastric ulceration and bleeding disorders. However, guidelines recommend that clinicians should incorporate acetaminophen and/or NSAIDs into the multimodal analgesia regimen for postoperative pain in patients without contraindications for their use [10]. A previous study showed that acetaminophen produced an analgesic effect equivalent to that of flurbiprofen as a sole postoperative analgesic in patients who underwent partial mastectomy [6]. However, TKA is associated with severe postoperative pain. It is controversial whether the analgesic effect produced by intravenous acetaminophen acted as an adjunct to periarticular multidrug injection in patients undergoing TKA [11,12].

The efficacy of the FNB in providing postoperative analgesia after TKA has been established [2]. Moreover, several studies have also attested to the efficacy of LIA [2,3]. However, the efficacy of the combination of flurbiprofen or acetaminophen with FNB and LIA after TKA has not been reported. This study found that although the combination of FNB and LIA with acetaminophen or flurbiprofen could not reduce the NRS scores, it could reduce the frequency of rescue analgesic use.

Although the FNB is already the standard protocol for postoperative analgesia after TKA, several patients complain of posterior knee pain despite its administration [3]. It is currently used in combination with the sciatic nerve block (SNB) or LIA. Meta-analyses performed on the comparison between the SNB and LIA [13-15] reported that the analgesic effect was slightly better with the SNB. However, the SNB prolonged the time and cost required to administer the nerve block along with the risk of peripheral neuropathy compared to LIA. There is a 1.3–2.2% chance of peroneal neuropathy after TKA [13]. Peroneal nerve damage may not be identified immediately after surgery if the FNB and SNB are used together, which prompted the selection of LIA in this study.

Admittedly, the lack of a blinding procedure in this study could have resulted in the introduction of a theoretical bias by the nursing staff. However, more than 24 nurses stationed in the ward were randomly involved in the care of each patient during the study period. Thus, the probability of theoretical bias was extremely remote [16].

CONCLUSION

The administration of intravenous acetaminophen or flurbiprofen as adjuvants to FNB and LIA after TKA reduced the frequency of rescue analgesic use but did not improve the NRS scores. Intravenous acetaminophen and flurbiprofen were equivalent analgesic adjuvants to FNB and LIA after TKA.

DECLARATION

Ethics Approval and Consent to Participate

The study protocol was approved by the Nagasaki Rosai Hospital Institutional Research and Ethics Committee on 15 September 2017 (No. 29009). Written informed consent was obtained from each participant.

Consent for Publication

Not applicable.

Availability of Data and Material

Please contact author for data requests.

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Author's Contribution

YK and YT carried out all parts of this study. AS, MO, NO and MO collected the clinical data. TH revised the presentation and the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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