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A Comparison of the Effects between Acetaminophen and Flurbiprofen after Lumbar Spinal Fusion Surgery

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SU and YT carried out all parts of this study. Authors ST and MO collected the clinical data. Authors MF and TH revised the presentation and the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Introduction: Spinal fusion surgery is often associated with severe postoperative pain. This study aimed to determine whether intravenous acetaminophen produces equivalent analgesic effects to flurbiprofen under fentanyl patient-controlled analgesia (PCA) after one-level lumbar spinal fusion surgery.
Study Design: Rondomized controlled trial.
Place and Duration of Study: Department of Anesthesia, Nagasaki Rosai Hospital, Sasebo Japan, between October 2015 to March 2017.
Methodology: We studied 75 patients who underwent one-level lumbar spinal fusion surgery. Patients were randomly allocated to 1 of 3 groups: Group A (n = 25), which received 15 mg/kg acetaminophen intravenously every 6 hr. Group F (n = 25), which received 1 mg/kg flurbiprofen intravenously every 8 hr; and Group C (n = 25), which received saline every 6 hr as the control.

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Each drug was started from prior to skin closure to 24 hr after surgery. All patients received fentanyl at a fixed dose of 0.33 μg/kg/hr continuously after a bolus administration of 250 μg fentanyl. A bolus of 0.33 μg/kg of fentanyl was administered on demand by PCA (lockout interval 15 min). Postoperative pain was evaluated using a numerical rating scale (NRS) at 1, 2, 6, 12, 24 hr postoperatively and fentanyl consumption was recorded for 6 and 24 hr after surgery. The frequency of bolus fentanyl administration were also recorded.

Results: There were no significant differences in NRS scores among the 3 groups. Acetaminophen and flurbiprofen did not show opioid sparing-effects under fentanyl PCA. However, the frequency of fentanyl boluses were significantly less in group A than in group C.

Conclusions: Acetaminophen may produce equivalent analgesic effects to flurbiprofen after one-level lumbar spinal fusion surgery.

Keywords: Acetaminophen; flurbiprofen; spinal fusion surgery; fentanyl; postoperative pain.

ABBREVIATIONS

PCA : patient controlled analgesia;
NRS : numerical rating scale;
NSAIDs : nonsteroidal anti-inflammatory drugs;
PONV : postoperative nausea and vomiting;
ASA : American Society of Anesthesiologists;
TCI : target-controlled infusion;
ANOVA : A factorial analysis of variance;
COX : cyclooxygenase.

1. INTRODUCTION

In patients with moderate postoperative pain, intravenous acetaminophen produces comparable analgesic effects to nonsteroidal anti-inflammatory drugs (NSAIDs) [1]. However, it is controversial whether intravenous acetaminophen produces comparable analgesic effects to NSAIDs in patients undergoing spinal surgery [2,3]. Lumbar spinal fusion surgery is typically associated with severe postoperative pain [2]. Dexketoprofen, a newly developed NSAID, reduced morphine consumption after laminectomy, whereas acetaminophen did not reduce it [2]. On the other hand, acetaminophen provided effective analgesia when it was used as a supplemental analgesic to morphine patient-controlled analgesia (PCA) during the 24 hours following lumbar disc surgery, but lornoxicam, a kind of NSAID, did not provide it [3].

Acetaminophen has fewer side effects including gastrointestinal bleeding, ulceration, cardiovascular events, and renal dysfunction compared with NSAIDs [4]. Flurbiprofen is an injectable NSAID and is generally administered for postoperative analgesia in Japan [5]. There are few reports comparing postoperative additive analgesic effects to opioids after lumbar spinal fusion surgery and between flurbiprofen and acetaminophen. The benefits of well-controlled postoperative pain include reduced postoperative cardiopulmonary complications, hospital mortality, and length of hospital stay [6].

This prospective, randomized, open-label and placebo-controlled study aimed to determine whether acetaminophen produces equivalent analgesic effects to flurbiprofen under fentanyl PCA after one-level lumbar spinal fusion surgery.

2. MATERIALS AND METHODS

2.1 Patients

This prospective, randomized, open-label and placebo-controlled study was conducted in the Nagasaki Rosai Hospital from October 2015 to March 2017. The study protocol was approved by the Institutional Research and Ethics Committee ((No. 27004), and written informed consent was obtained from each participant. We studied 75 American Society of Anesthesiologists (ASA) physical status 1 or 2 patients aged 20 to 75 years who underwent elective one-level lumbar spinal fusion surgery for degenerative disorders under general anesthesia. 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.

2.2 Study Protocol

Patients were randomly allocated to 1 of 3 groups: Group A (n = 25), which received acetaminophen intravenously, Group F (n = 25) which received flurbiprofen intravenously, and Group C (n = 25), which received saline as the control. The randomization was done by the responsible anesthesiologist, using the sealed envelope system.

Patients received a continuous infusion at 0.5 μg/kg/min of remifentanil and propofol at 5 μg/mL for 2 min followed by 3 μg/mL of an effect-site concentration using a target-controlled infusion (TCI) system (TCI pump, TE-371, Terumo, Tokyo, Japan). Rocuronium, 0.8 mg/kg, was given to facilitate tracheal intubation after loss of consciousness. In order to maintain a bispectral index score of around 50 after tracheal intubation, the effect-site concentration of propofol and remifentanyl were titrated. All patients received postoperative analgesia with fentanyl at a fixed dose of 0.33 μg/kg/hr continuously by using a syringe pump (TERUFUSION® TE-332S; TERUMO, Tokyo, Japan) after bolus administration of 250 μg fentanyl after spinal stabilization (about 30 minutes before the end of surgery). Group A patients received 15 mg/kg of acetaminophen (Acelio® Intravenous Injection 1000 mg, TERUMO, Tokyo, Japan) intravenously every 6 hr, group F patients received 1 mg/kg of flurbiprofenaxetil (ROPION® Intravenous 50 mg, Kaken, Tokyo, Japan) intravenously every 8 hr and group C patients received 100 ml of saline intravenously every 6 hr as the control. Each drug was started from prior to skin closure and continued for 24 hr after surgery. If the patients suffered from postoperative pain, a bolus of 0.33 μg/kg of fentanyl was administered on demand by PCA (lockout interval 15 min). A bolus fentanyl administration dose was given by nursing staff. Postoperative pain was evaluated by nursing staff using a numerical rating scale (NRS) with rest from 0 to 10 at 1, 2, 6, 12, and 24 hr postoperatively. At the 6 and 12 hr time points, NRS scores were evaluated just before the analgesic drug injection was given. Fentanyl consumption was recorded at 6 and 24 hr after surgery. The cumulative frequencies of bolus fentanyl administration were recorded for 24 hr after surgery. The adverse effects including postoperative nausea and vomiting (PONV), pruritus and respiratory depression associated with acetaminophen or flurbiprofen or fentanyl PCA were evaluated by nursing staff during study period.

2.3 Statistical Analysis

Values are expressed as means ± standard deviation. A factorial analysis of variance (ANOVA) with repeated measures was used for analyzing the differences in data among the time points and among the groups. Post hoc comparisons were performed by using Tukey's method, if appropriate. Dichotomous variables were analyzed using the chi-square test. Statistical significance was defined as a *p* value of less than 0.05.

The sample size was determined based on a previous study (clinically relevant difference in NRS, 2) [3], which indicated that with 22 patients in each group, a power of 90% would be required to detect a difference of 2 in the NRS value between the 2 groups at a 5% significance level.

3. RESULTS

Seventy-five patients (44 men and 31 women) were included in the study. There were no significant differences among the three groups in patient characteristics (Table 1).

The ANOVA with repeated measures revealed that there were no significant differences in NRS scores with rest among the three groups during the study period (Fig. 1). The NRS scores with rest at 12 hr were lower than those at 1 and 2 hr in group C. The NRS scores with rest at 12 hr were lower than that at 1 hr in group A. The NRS scores with rest at 12 hr and 24 hr were lower than those at 0 or 1 hr in group F.

Table 1. Patient characteristics

Group	Control	Acetaminophen	Flurbiprofen	p
Patients (n)	25	25	25	
ASA Ⅰ/Ⅱ	3 (12) /22 (88)	3 (12) /22 (88)	5 (20) / 20 (80)	0.65
Male gender	13 (52)	18 (72)	13 (52)	0.25
Age (years)	66 ±11	62 ±10	62 ±9	0.29
Height (cm)	157 ±8	161 ±8	162 ±11	0.12
Weight (kg)	60 ±11	65 ±9	63 ±12	0.21
BMI (kg/m^2)	24.2 ±3.7	25.2 ±2.7	23.6 ±2.6	0.18
Smoker	11 (44)	16 (64)	12 (48)	0.33
Operative duration (min)	157 ±38	154 ±46	160 ±36	0.89
Operative blood loss (mL)	111 ± 79	103 ± 88	163 ± 227	0.31

Values are mean ± SD, number (percentage). ASA, American Society of Anesthesiologists physical status; BMI, body mass index; n, number;

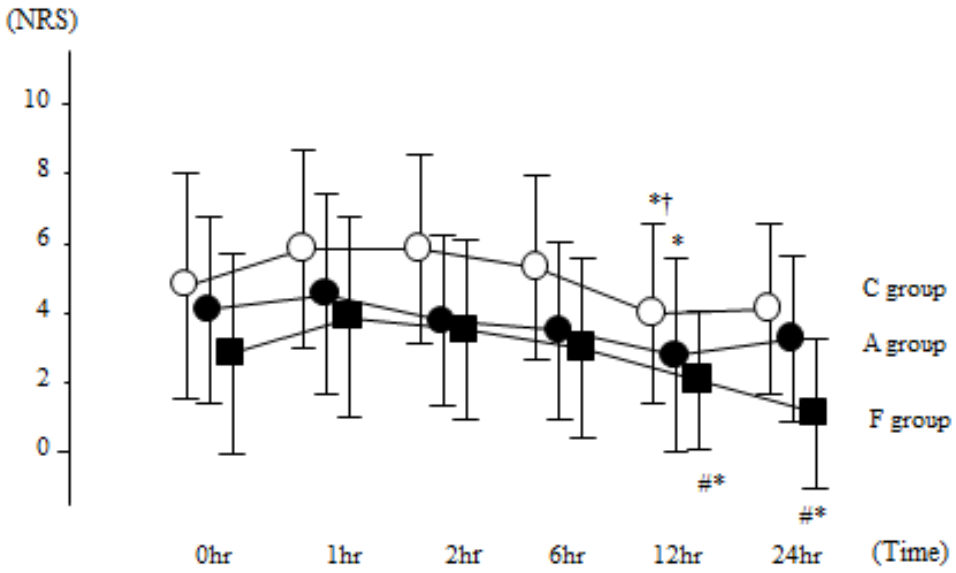

Fig. 1. NRS in group control (open circle) and acetaminophen (circle) and flurbiprofen (square) at each time point.

Values are expressed as mean ±S.D. NRS, numerical rating scale;
*# p<0.05 vs. values at 0hr; * p<0.05 vs. values at 1hr; †p<0.05 vs. values at 2hr;*

Table 2 shows the cumulative fentanyl consumption between the three groups for 6 hr and 24 hr after surgery. There were no significant differences in the cumulative fentanyl consumption among the three groups.

However, there were significant differences in the frequency of bolus fentanyl administration among the three groups. The frequency of bolus fentanyl administration in group A was significantly less than in group C (p = 0.04) (Table 3).

There were no significant differences in the incidence of PONV for 24 hours after surgery among the three groups (Table 4). No patient showed any adverse effects including pruritus and respiratory depression associated with acetaminophen or flurbiprofen or fentanyl PCA.

Table 2. The cumulative fentanyl consumption for 6 and 24 hours after surgery

Group	Control	Acetaminophen	Flurbiprofen	p
Fentanyl consumption for 6hr (μg/ kg)	3.3 ± 0.9	3.0 ± 1.3	3.2 ± 1.2	0.79
Fentanyl consumption for 24hr (μg/ kg)	9.8 ± 2.7	9.3 ± 1.3	9.4 ± 1.3	0.57

Values are mean ± SD.

Table 3. The frequencies of bolus fentanyl administration for 24 hours after surgery

Group	Control	Acetaminophen	Flurbiprofen
Frequencies of bolus fentanyl for 24hr (n)	5 ± 5	3 ± 2 *	3 ± 3

*Values are mean ± SD. * p<0.05 vs. control.*

Table 4. Incidence of postoperative nausea and vomiting for 24 hours after surgery

Group	Control	Acetaminophen	Flurbiprofen	p
Postoperative nausea and vomiting	7 (28)	6 (24)	6 (24)	0.93

Values are number (%).

4. DISCUSSION

This study showed that acetaminophen could produce equivalent analgesic effects to flurbiprofen with a fentanyl PCA after one-level lumbar spinal fusion surgery.

A previous study showed that acetaminophen produced an equivalent analgesic effect to flurbiprofen as a sole postoperative analgesic in post-partial mastectomy patients [1]. However, lumbar spinal fusion surgery is associated with severe postoperative pain [2]. Opioid-based PCA is a well-established therapy for postoperative pain control in patients undergoing spinal surgery [7]. Different nociceptive mechanisms involved in the pathophysiology of postoperative pain and multimodal analgesic techniques are used with additive and synergistic effects. A combination of opioids and supplemental analgesics might reduce the amount of systemic opioids and lower the incidence of side effects such as sedation, respiratory depression, nausea, and vomiting [2].

It is controversial whether intravenous acetaminophen produces comparable analgesic effects to NSAIDs except flurbiprofen in patients undergoing spinal surgery [2,3,8]. Tunali et al. [2] demonstrated that pain intensity during the 24 hours after lumbar disc surgery was significantly lowered by dexketoprofen, but not with acetaminophen, as a supplemental analgesic to morphine PCA, but the two analgesics did not show a morphine sparing effect. On the other hand, Kesimci et al. [8] demonstrated that dexketoprofen, but not acetaminophen, reduced morphine consumption, but two analgesics showed similar pain scores. Dilmen et al. [3] demonstrated that acetaminophen, but not lornoxicam (a kind of NSAID), reduced pain intensity, but the two analgesics did not show a morphine sparing effect in patients undergoing lumbar disc surgery. Although the etiology of these discrepancies in analgesic effects and opioid sparing effects is unknown, either the different manner of morphine PCA or the different NSAIDs would result in these discrepancies.

The fentanyl based PCA was set to run at a fixed dose of 0.33 μg/kg/hr continuously with a bolus dose of 0.33 μg/kg on demand (lockout interval 15 min) in this study. This setting is almost equal to the previous study [9]. The previous study [9] demonstrated that propacetamol, an acetaminophen prodrug, reduced pain intensity at rest, and reduced the use of additional use of rescue analgesics, but did not have a fentanyl sparing effect, in female patients undergoing posterior spinal fusion or laminectomy surgery. However, the discrepancies in pain intensity between propacetamol and control were only 10, on average, on 100 mm visual analog scale (VAS). Our results concerning acetaminophen were similar to this previous study [9].

Acetaminophen is a medication with antipyretic and analgesic effects which work via central inhibition of the third isoform of the cyclooxygenase (COX) enzyme, which is mostly found in the cerebral cortex and heart [9]. Flurbiprofen is one of most popular injectable NSAIDs after surgery in Japan. This medication blocks the production of prostaglandins through the inhibition of COX-1 and COX-2. Svensson et al. [10] reported that flurbiprofen had an 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. COX-2 is dominant in osteoblasts [11]. COX inhibitors may adversely affect bone remodeling. Some observational data suggest a possible association between high-dose NSAID use and nonunion in spinal fusion [12]. Although the evidence from the guidelines [4] recommending against the use of NSAIDs in patients who undergo spinal fusion is insufficient, we must consider alternatives to NSAIDs for postoperative pain control after spinal fusion surgery.

Admittedly, because the study was not blinded (open label), a theoretical bias by the nurses might have been present. However, since there were more than 24 nurses who could be randomly involved in the care of each patient during the study period on the ward, the likelihood of bias was extremely remote [13].

5. CONCLUSION

Although acetaminophen and flurbiprofen did not show an opioid sparing-effect or reduce the pain intensity under fentanyl PCA, they reduced the frequency of fentanyl boluses after one-level lumbar spinal fusion surgery. We concluded that acetaminophen produces equivalent analgesic effects to flurbiprofen after one-level lumbar spinal fusion surgery.

CONFERENCE DISCLAIMER

This manuscript was presented in a Conference.
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CONSENT

The study protocol was approved by the Nagasaki Rosai Hospital Institutional Research and Ethics Committee on 30 June 2015 (No. 27004). Written informed consent to publish was obtained from each participant.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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