



Effect of Intravenous Acetaminophen and Flurbiprofen on Postoperative Pain after Lumbar Disc Surgery

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Authors' contributions

This work was carried out in collaboration among all authors. Authors M. Ono and YT carried out all parts of this study. Authors YK, AS, NO and M. Oji collected the clinical data. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Lumbar disc surgery is often associated with moderate to severe postoperative pain. Whether non-steroidal anti-inflammatory drugs or acetaminophen provides effective analgesia following lumbar disc surgery remains controversial. This study aimed to determine whether flurbiprofen produces analgesic effects equivalent to those of acetaminophen after lumbar disc surgery.

Study Design: Prospective, randomized, open-label, placebo-controlled trial

Place and Duration of Study: Department of Anesthesia, Nagasaki Rosai Hospital, Sasebo, Japan, between April 2018 and March 2019.

Methodology: We studied 76 patients who underwent elective lumbar disc surgery under general anesthesia. The patients were randomly allocated to one of three groups. Group A (n=25) received 1000 mg of acetaminophen intravenously every 6 h. Group F (n=25) received 50 mg of flurbiprofen intravenously every 6 h. Group C (n=26) received saline intravenously every 6 h as a placebo. Each drug was started before skin closure 18 h after surgery. All patients were anesthetized under total intravenous anesthesia with propofol and remifentanyl and received fentanyl before skin

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closure. Postoperative pain was evaluated using a numerical rating scale (NRS) at 0, 1, 3, 6, 12, 18, and 24 h postoperatively. The patients were administered diclofenac sodium or loxoprofen, as rescue analgesics, as needed.

Results: There were no significant differences in patient characteristics among the three groups. There were no significant differences in NRS scores among the three groups during the study period. However, rescue analgesics were administered significantly less frequently in group F than in groups A and C over 12 h and 24 h, respectively.

Conclusion: The results of this study showed that flurbiprofen might provide more effective analgesia than acetaminophen following lumbar disc surgery.

Keywords: Acetaminophen; flurbiprofen; lumbar disc surgery; postoperative pain.

ABBREVIATIONS

NRS : Numerical Rating Scale
PONV : Postoperative Nausea and Vomiting
NSAIDs : Nonsteroidal Anti-Inflammatory Drugs
TCI : Target-controlled Infusion
ANOVA : A Factorial Analysis of Variance
SD : Standard Deviation
ASA : American Society of Anesthesiologists
PCA : Patient Controlled Analgesia
COX : Cyclooxygenase

1. INTRODUCTION

Lumbar disc surgery is often associated with moderate to severe postoperative pain [1]. The benefits of well-controlled postoperative pain include reduced postoperative cardiopulmonary complications, hospital mortality, and length of hospital stay [2]. Although opioids are useful analgesic agents, their use is associated with side effects such as postoperative nausea and vomiting (PONV) and respiratory depression [1]. Moreover, postoperative pain is multifactorial in origin; it can arise from nociceptors and in response to inflammation. Thus, the current practice involves the use of a combination of multiple analgesics. Therefore, multimodal analgesia including non-opioid analgesics to reduce opioid consumption has become the mainstay of postoperative pain control in recent years.

However, whether non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen provides effective analgesia following lumbar disc surgery remains controversial [1,3]. Flurbiprofen is an injectable NSAID that is generally administered for postoperative analgesia in Japan [4]. Acetaminophen has fewer side effects, including gastrointestinal bleeding, ulceration, cardiovascular events, and renal dysfunction, than NSAIDs [5]. Acetaminophen reportedly provided analgesic effects comparable

to those for flurbiprofen after partial mastectomy [6]. However, few reports have compared the postoperative analgesic effects between flurbiprofen and acetaminophen after lumbar disc surgery.

This prospective, randomized, open-label, placebo-controlled study aimed to determine whether flurbiprofen produced analgesic effects equivalent to those of acetaminophen after lumbar disc surgery.

2. MATERIALS AND METHODS

2.1 Patients

The study protocol was approved by the Institutional Research and Ethics Committee of Nagasaki Rosai Hospital on February 8, 2017 (No. 29021). Written informed consent was obtained from all participants. After registration with the University Hospital Medical Information Network (ID: UMIN000032207), this prospective, randomized, open-label, placebo-controlled study was conducted at Nagasaki Rosai Hospital between April 2018 and March 2019.

2.2 Study Protocol

This study included a total of 76 patients with American Society of Anesthesiologists physical status 1 or 2, aged 20–80 years, weighing 50–80 kg, who underwent elective lumbar disc surgery (endoscopic discectomy or microscopic discectomy) 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 pre-anesthetic medication.

The patients were randomly allocated to one of three groups. Group A (n = 25) received 1000 mg of acetaminophen intravenously every 6 h. Group F (n=25) received 50 mg of flurbiprofen

intravenously every 6 h. Group C (n=26) received saline intravenously every 6 h as a control. Each drug was started before skin closure at 18 h after surgery. Randomization was performed by a responsible anesthesiologist using a sealed-envelope system.

2.3 Study Protocol

2.3.1 Anesthesia

The patients received a continuous infusion of remifentanyl 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 remifentanyl were titrated to maintain a bispectral index score between 40 and 60 after tracheal intubation. All patients received postoperative analgesia with fentanyl after a bolus administration of 250 µg fentanyl before skin closure.

The patients in group A received 1000 mg of acetaminophen (Acelio® Intravenous Injection 1000 mg, TERUMO, Tokyo, Japan) intravenously every 6 h; patients in group F received 50 mg of flurbiprofen axetil (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. Each drug was administered before skin closure and continued for 18 h after surgery. The patients were administered 50 mg diclofenac sodium suppository or 60 mg loxoprofen orally, as rescue analgesics after surgery when the patient requested analgesia. The nursing staff evaluated postoperative pain using a numerical rating scale (NRS; 10 points from 0 to 10) at 0, 1, 3, 6, 12, 18, and 24 h postoperatively. The NRS scores were evaluated immediately before analgesic drug injection at 6, 12 and 18 h.

2.4 Measurement

The primary outcome was the postoperative pain evaluated by the nursing staff using the NRS at 0, 1, 3, 6, 12, 18, and 24 h postoperatively. The secondary outcomes were the frequency of rescue analgesic use over 12 and 24 h, and the incidence of PONV during the 24 h after surgery.

2.5 Statistical Analysis

Values are expressed as medians (interquartile range). Intergroup comparisons were performed using Kruskal–Wallis, Mann–Whitney U, and chi-square tests. A factorial analysis of variance (ANOVA) with repeated measures was used to analyze the differences in NRS data among the time points and groups. Post hoc comparisons were performed using the Bonferroni/Dunn procedure, if appropriate. Statistical significance was defined as a p-value of <0.05.

The sample size was determined based on a previous study (SD, 2) [1], which indicated that a power of 90% would be required to detect a difference of 2 in NRS scores between the two groups at a 5% significance level, if each group contained 22 patients.

3. RESULTS

Table 1 shows the patient characteristics for each group. There were no significant differences among the three groups.

The repeated-measures ANOVA revealed no significant differences in NRS scores among the three groups during the study period (Fig. 1). The NRS scores at 1, 3, 6, 12, and 18 h postoperatively were higher than those at 0 h in Group C. The NRS scores at 1 and 3 h postoperatively were higher than those at 0 h in Group A. The NRS scores at 1, 3, 6, 12, 18, and 24 h were higher than those at 0 h in Group F.

Table 1. Patient characteristics

	Acetaminophen	Flurbiprofen	Control	P
Number	25	25	26	
Age (years)	46 (36, 69)	58 (39, 71)	49 (40, 62)	0.54
Height (cm)	164 (159, 174)	166 (161, 169)	168 (160, 173)	0.64
Weight (kg)	61 (55, 68)	63 (54, 68)	63 (54, 70)	0.84
ASA	2 (1, 2)	2 (1, 2)	2 (1, 2)	0.57
Female	9	9	9	0.99

Values are number or median (IQR)

ASA, American Society of Anesthesiologists physical status

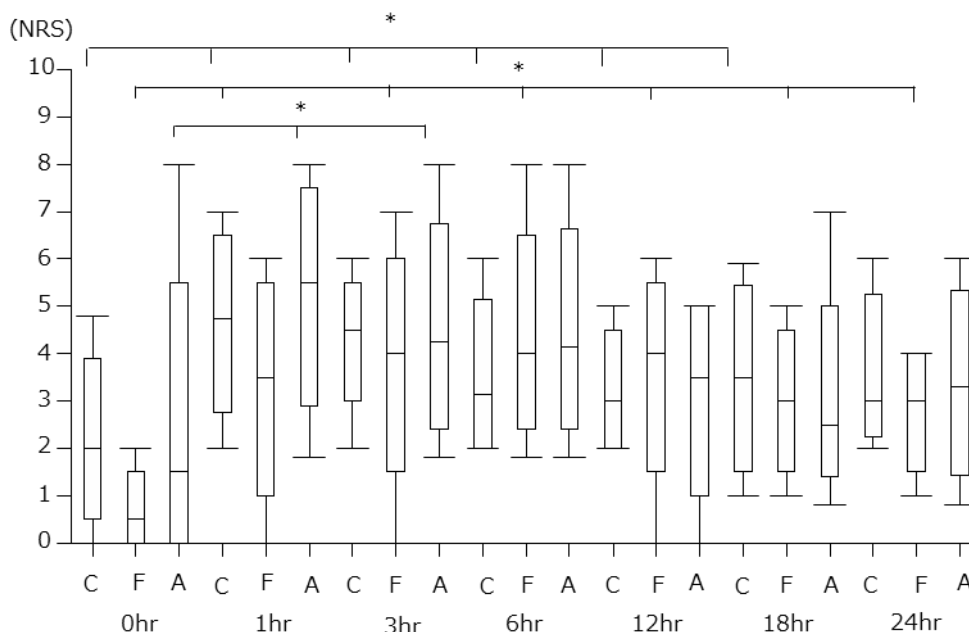


Fig.1. Numerical rating scale in group acetaminophen, flurbiprofen and placebo at each time point

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 2. Frequency of postoperative nausea and vomiting and rescue analgesics

	Acetaminophen	Flurbiprofen	Control	P
PONV (n)	2	2	3	0.88
Frequency of resques for 12 hrs	0 (0, 1)	0 (0, 0)*	0 (0, 1)	0.03
Frequency of resques for 24 hrs	1 (0, 2)	0 (0, 0)*	1 (0, 2)	0.04

Values are number or median (IQR). ;
 PONV, postoperative nausea and vomiting
 *p < 0.05 vs. other groups

The frequency of rescue analgesic use over 12 and 24 h in Group F was significantly lower than that in Groups C and A. 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.

4. DISCUSSION

Although there were no significant differences in NRS scores among the three groups, the frequencies of rescue analgesic use in group F were significantly lower than that in groups A and C during 12 and 24 h after surgery. The results showed that flurbiprofen might provide effective

analgesia compared to acetaminophen following lumbar disc surgery.

A previous study showed that acetaminophen produced an analgesic effect equivalent to that of flurbiprofen as the sole postoperative analgesia after partial mastectomy [6]. However, lumbar disc surgery is associated with moderate or severe postoperative pain [1]. Opioid-based patient-controlled analgesia (PCA) is a well-established therapy for postoperative pain control in patients undergoing spinal surgery [7,8]. Different nociceptive mechanisms are involved in the pathophysiology of postoperative pain; thus, multimodal analgesic techniques are used, with additive and synergistic effects. A combination of opioids and supplemental analgesics might reduce the amount of systemic opioids administered and lower the incidence of side

effects such as sedation, respiratory depression, nausea, and vomiting [1].

It remains controversial whether intravenous acetaminophen produces comparable analgesic effects to NSAIDs, except flurbiprofen, in patients undergoing spinal surgery [1,9,10]. Tunali et al. [1] demonstrated significantly lowered pain intensity during 24 h after lumbar disc surgery for dexketoprofen, but not acetaminophen, as a supplemental analgesic to morphine PCA; however, the two analgesics did not show morphine-sparing effects. In contrast, Kesimci et al. [9] demonstrated that dexketoprofen, but not acetaminophen, reduced morphine consumption, while the two analgesics showed similar pain scores. Dilmen et al. [3] reported that acetaminophen, but not lornoxicam (a type of NSAID), reduced pain intensity but that the two analgesics did not show morphine-sparing effects in patients undergoing lumbar disc surgery. In contrast, studies comparing acetaminophen and flurbiprofen showed comparable analgesic effects in lumbar spinal fusion surgery [10]. Acetaminophen and flurbiprofen did not show fentanyl-sparing effects in lumbar spinal fusion surgery. Moreover, perioperative intravenous acetaminophen did not reduce inpatient opioid prescription and opioid-related side effects in lumbar/lumbosacral spinal fusion [11]. Although the etiology of these discrepancies in analgesic and opioid-sparing effects between acetaminophen and NSAIDs is unknown, they may occur due to differences in morphine PCA administration, NSAIDs, or operative procedures.

Acetaminophen is a medication with antipyretic and analgesic effects that works via the central inhibition of the third isoform of the cyclooxygenase (COX) enzyme, which is mostly found in the cerebral cortex and heart [8]. Flurbiprofen is one of the most popular injectable NSAIDs administered after surgery in Japan. This medication blocks the production of prostaglandins by inhibiting COX-1 and COX-2. Svensson et al. [12] reported that flurbiprofen had almost equal selectivity for COX-1 and COX-2. However, 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 [13]. Thus, COX inhibitors may adversely affect bone remodeling. Some observational data suggest a possible association between high-dose NSAID use and nonunion in spinal fusion [14]. Although the evidence from the guidelines [5]

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.

A limitation of this study is that because the study was not blinded, bias by the nurses was possible. However, since more than 24 nurses were randomly involved in the care of each patient in the ward during the study period, the likelihood of bias was extremely low [15]. Moreover, two types of rescue analgesics were administered without objective assessment of pain intensity when patient requested. These potential biases will be equally divided among our study groups, therefore minimizing their effect.

5. CONCLUSION

The results of this study showed that flurbiprofen reduced the frequency of rescue analgesic use but not pain intensity. We concluded that flurbiprofen might provide effective analgesia compared to acetaminophen following lumbar disc surgery.

CONSENT

Written informed consent was obtained from all participants.

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.

REFERENCES

1. Tunali Y, Akçil EF, Ozlem KD, Ayse C. T, Koksall GM, Akbas S, et al. Efficacy of

- intravenous paracetamol and dexketoprofen on postoperative pain and morphine consumption after a lumbar disk surgery. *J Neurosurg Anesthesiol.* 2013; 25(2):143-7. [PMID: 23360885 DOI:10.1097/ANA.0b013e31827464af]
2. Xu B, Tu W, Wu Z, Ai F, Zhou D, Chen B, et al. Continuous wound infusion of ropivacaine for the control of pain after thoracolumbar spinal surgery: a randomized clinical trial. *Eur Spine J.* 2017;26(3):825-31. [PMID: 25935145 DOI: 10.1007/s00586-015-3979-x]
 3. Korkmaz Dilmen O, Tunali Y, Cakmakkaya OS, Yentur E, Tutuncu AC, Tureci E, et al. Efficacy of intravenous paracetamol, metamizol and lornoxicam on postoperative pain and morphine consumption after lumbar disc surgery. *Eur J Anaesthesiol.* 2010;27(5):428-32. [PMID: 20173643 DOI: 10.1097/EJA.0b013e32833731a4]
 4. Yamashita K, Fuskusaki M, Ando Y, Fujinaga A, Tanabe T, Terao Y, et al. Postoperative administration of intravenous flurbiprofen axetil reduces postoperative pain for spinal fusion surgery. *J Anesth.* 2006;20(2):92-5. [PMID: 16633764 DOI: 10.1007/s00540-006-0389-6]
 5. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' committee on regional anesthesia, exclusive committee, and administrative council. *J Pain.* 2016;17(1): 131-7. [PMID: 26827847 DOI: 10.1016/j.jpain.2015.12.008]
 6. Nonaka T, Hara M, Miyamoto C, Sugita M, Yamamoyo T. Comparison of the analgesic effect of intravenous acetaminophen with that of flurbiprofen axetil on post-breast surgery pain: a randomized controlled trial. *J Anesth.* 2016;30(3):405-9. [PMID: 26882922 DOI: 10.1007/s00540-016-2150-0]
 7. Song JW, Shim JK, Song Y, Yang SY, Park SJ, Kwak YL. Effect of ketamine as an adjunct to intravenous patient-controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. *Br J Anaeth.* 2013;111(4):630-5. [PMID: 23744819 DOI: 10.1093/bja/aet192]
 8. Kim EJ, Shim JK, Soh S, Song JW, Lee SR, Kwak YL. Patient-controlled analgesia with propacetamol-fentanyl mixture for prevention of postoperative nausea and vomiting in high-risk patients undergoing spine surgery: a randomized controlled trial. *J Neurosurg Anesthesiol.* 2016; 28 (4):316-22. [PMID: 26558356 DOI: 10.1097/ANA.0000000000000252]
 9. Keisimci E, Gümüř T, İzdeř S, řen P, Kanbak O. Comparison of efficacy of dexketoprofen versus paracetamol on postoperative pain and morphine consumption in laminectomy patients. *Agri.* 2011;23(4):153-9. [PMID: 22290679 DOI: 10.5505/agri.2011.86548]
 10. Urabe S, Terao Y, Tominaga S, Oji M, Fukusaki M, Hara T. A comparison of the effects between acetaminophen and flurbiprofen after lumbar spinal surgery. *Journal of Advances in Medicine and Medical Research.* 2018;28(11):1-7. [DOI: 10.9734/JAMMR/2018/v28i1130035]
 11. Morwald EE, Poeran J, Zubizarreta N, Cozowicz C, Mazumdar M, Memtsoudis SG. Intravenous acetaminophen does not reduce inpatient opioid prescription or opioid-related adverse events among patients undergoing spine surgery. *Anesth Analg.* 2018;127(5):1221-8. [PMID: 29596101 DOI: 10.1213/ANE.0000000000003344]
 12. Svensson CI, Yaksh TL. The spinal phospholipase-cyclooxygenase-prostanoid cascade in nociceptive processing. *Ann Rev Pharmacol Toxicol.* 2002; 42: 553-83. [PMID: 11807183 DOI:10.1146/annurev.pharmtox.42.092401.143905]
 13. Najafi HZ, Oshagh M, Salehi P, Babanouri M, Torkan S. Comparison of the effects of preemptive acetaminophen, ibuprofen, and meloxicam on pain after separator placement: a randomized clinical trial. *Prog Orthod.* 2015;16:34. [PMID: 26467790 DOI: 10.1186/s40510-015-0104-y]
 14. Lisowska B, Kosson D, Domaracka K. Lights and shadows of NSAIDs in bone healing: the role of prostaglandins in bone metabolism. *Drug Des Devel Ther.* 2018; 12: 1753-8. [PMID: 29950809]

- DOI: 10.2147/DDDT.S164562]
15. Saito M, Terao Y, Fukusaki M, Makita T, Shibata O, Sumikawa K. Sequential use of midazolam and propofol for long-term sedation in postoperative mechanically ventilated patients. *Anesth Analg.* 2003;96(3):834-8. [PMID: 12598270]

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