J Anesth (2006) 20:92–95
DOI 10.1007/s00540-006-0389-6

Journal of
Anesthesia

Preoperative administration of intravenous flurbiprofen axetil reduces postoperative pain for spinal fusion surgery

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Abstract
Purpose. The aim of the study was to investigate postoperative analgesia and the opioid-sparing effect of the preoperative administration of intravenous flurbiprofen axetil in patients undergoing spinal fusion surgery.
Methods. Thirty-six patients were randomly allocated into one of three groups. Group A received preoperative flurbiprofen axetil, 1 mg·kg^{-1}. Group B received postoperative flurbiprofen axetil, 1 mg·kg^{-1}. Group C received a placebo. All groups were given a standardized anesthesia and intravenous morphine via a patient-controlled analgesia device for postoperative analgesia. The pain score was evaluated by a visual analog scale (VAS) at 0 (T_0), 1 (T_1), 2 (T_2), 6 (T_3), 12 (T_4), and 24 (T_5) h after surgery, and the morphine requirement was recorded during the study period.
Results. VAS in group A was significantly lower than that in group B at T_0 and T_1. VAS in group A was significantly lower than that in group C throughout the time course after surgery. Postoperative morphine consumption in group A was significantly lower than that in groups B and C at T_0 to T_3.
Conclusion. As compared with postoperative administration, preoperative administration of intravenous flurbiprofen axetil provides better postoperative analgesia and an opioid-sparing effect in patients undergoing spinal fusion surgery under general anesthesia.

Key words Flurbiprofen axetil · Postoperative pain · Opioid-sparing effect

Introduction

It is known that spinal fusion surgery is often associated with severe postoperative pain. Postoperative pain after spinal posterior fusion surgery is usually controlled by systemic opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) because epidural analgesia is not indicated.

Address correspondence to: K. Yamashita
Received: October 13, 2005 / Accepted: January 19, 2006

Although NSAIDs show an opioid-sparing effect [1–4], whether NSAIDs have a preemptive analgesic effect is controversial [5–7]. Reuben and Connelly [1] reported that the preoperative administration of celecoxib or rofecoxib, cyclooxygenase (COX)-2 selective inhibitors, showed a postoperative analgesic effect and an opioid-sparing effect after spinal stabilization surgery.

Flurbiprofen axetil (FA) is an injectable nonselective COX inhibitor. It has been reported that preoperative administration of FA reduces postoperative pain after hysterectomy [8], pulpectomy [9], laparoscopic cholecystectomy [10], and pediatric strabismus surgery [11]. However, there are few reports on whether preoperative FA can reduce postoperative pain and the postoperative opioid requirement after major spinal surgery.

This study was carried out to evaluate whether preoperative administration of intravenous FA can provide postoperative analgesia and reduce postoperative opioid consumption in patients undergoing spinal posterior fusion surgery under general anesthesia.

Materials and methods

With the approval of the Institutional Human Ethics Committee and written informed consent from each patient, we studied 36 patients with American Society of Anesthesiologists physical status I–II who were scheduled for spinal fusion surgery, that is, posterolateral fusion–pedicle screw fixation (PLF-PSF) of one vertebral space between L_4/L_5 or L_5/S_1. Excluded were patients aged less than 30 or more than 75 years and those with a history of allergy to any NSAIDs or opioids, coagulopathy, renal dysfunction, or peptic ulcer disease. NSAIDs and steroids were discontinued 24 h and 1 week prior to surgery, respectively.

After the induction of anesthesia with 5 mg·kg^{-1} thiamylal and 2 μg·kg^{-1} fentanyl, and tracheal intubation

facilitated with 0.1 mg·kg^{-1} vecuronium, anesthesia was maintained with sevoflurane, 1.5%–2.5% end-tidal, and N_2O 60% in oxygen, and additional vecuronium was administered as needed. Percutaneous oxygen saturation was maintained at 98% or more, and end-tidal carbon dioxide tension was maintained at 35 mmHg during surgery. The depth of anesthesia was maintained with the bispectral index at a score of 40–50 to ensure similar anesthetic depth in all patients. Acetated Ringer's solution was infused at a rate of 6 to 8 ml·kg^{-1}·h^{-1} during surgery. The subjects were randomly assigned into one of three groups. Group A (n = 12) received intravenous FA, 1 mg·kg^{-1} [9], before surgery. Group B (n = 12) received intravenous FA, 1 mg·kg^{-1}, after surgery. Group C (n = 12) received intravenous lipid emulsion (Intralipid, Terumo, Tokyo, Japan), 0.1 ml·kg^{-1}, as a placebo before surgery.

After spinal stabilization, morphine, 0.1 mg·kg^{-1}, was intravenously administered to all patients. Postoperative morphine was administered with a patient-controlled analgesia (PCA) pump (DIB PCA system Soft Shell Type OD-349; Hakko Medical, Tokyo, Japan; increment dose, 3 ml; lockout interval, 30 min).

The study was performed by three investigators in a double-blinded manner as follows: Each solution was prepared in a syringe by the first investigator, who was responsible for subject grouping. The second investigator, who did not know the type of test solution, performed the intravenous injection. The third investigator, who was blinded to the type of test solution, evaluated postoperative morphine consumption by measuring the weight of the pump using a precision electronic balance (model CB-X; Ishida, Kyoto, Japan). Each patient was instructed to evaluate pain while at rest using a visual analog scale (VAS) ruler. A 100-mm horizontal VAS with end descriptors of "no pain" and "pain as bad as it could be" was used.

VAS was measured at 0 (T_0), 1 (T_1), 2 (T_2), 6 (T_3), 12 (T_4), and 24 (T_5) h after surgery by a trained nurse blinded to the study drug. Morphine consumption was recorded during the study period.

Data are expressed as means ± SD. Demographic data (age, height, and weight), operation time, and blood loss were analyzed with the Kruskal-Wallis test. Pain score, nausea score, and morphine doses were also analyzed with the Kruskal-Wallis test. If a significant result was obtained, a Mann-Whitney U test was performed. Significance was determined at $P < 0.05$.

Results

The demographic data of the three groups were similar (Table 1). VAS data are presented in Fig. 1. VAS in group A was significantly lower than that in group B at T_0 and T_1. VAS in group A was significantly lower than that in group C throughout the time course after surgery. Although VAS in group B was significantly lower than that in group C at T_0 and T_1, no significant difference of VAS was found between groups B and C from T_2 to T_5.

Postoperative morphine consumption in group A was significantly lower than that in groups B and C at T_0 to T_3, while there were no significant differences among the three groups at T_3 to T_5 (Fig. 2).

No patient showed any adverse effect associated with FA.

Table 1. Demographic data

Groups (n)	Age (years)	Height (cm)	Weight (kg)	Operation time (min)
A (12)	60 ± 9	162 ± 10	63 ± 9	207 ± 53
B (12)	64 ± 13	154 ± 10	54 ± 10	168 ± 78
C (12)	61 ± 15	162 ± 10	64 ± 12	190 ± 40

Values are means ± SD
A, preoperative administration of flurbiprofen; B, postoperative administration of flurbiprofen; C, no administration of flurbiprofen

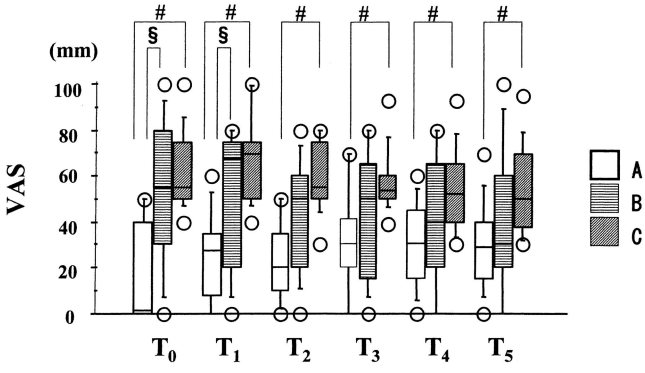

Fig. 1. Time course in visual analog scale of postoperative pain in three groups. Values are expressed as medians (*middle line* in the *box*) with the 25th–75th percentiles. *Capped lines* indicate 10th–90th percentiles of the data. Open circles indicate the values over 90th percentiles or under 10th percentiles. #$P < 0.05$ vs no administration of flurbiprofen. §$P < 0.05$ vs postoperative administration of flurbiprofen. *VAS*, visual analog scale; *A*, preoperative administration of flurbiprofen; *B*, postoperative administration of flurbiprofen; *C*, no administration of flurbiprofen; T_0, immediately after the end of surgery; T_1, 1 h after surgery; T_2, 2 h after surgery; T_3, 6 h after surgery; T_4, 12 h after surgery; T_5, 24 h after surgery

Discussion

The present results show that preoperative FA provides better immediate postoperative analgesia and results in less morphine consumption during the early postopera-

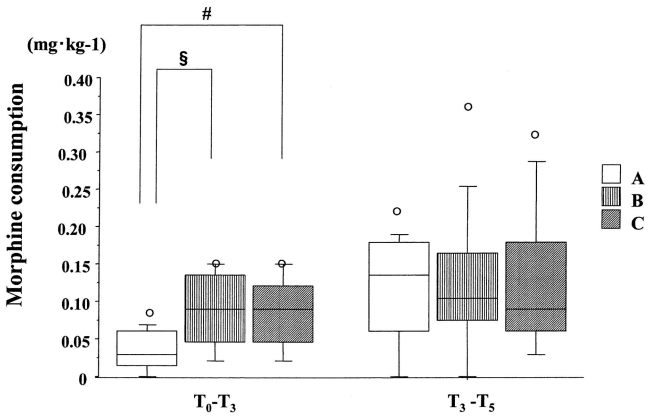

Fig. 2. Time course of morphine consumption during the postoperative period in three groups. Values are expressed as medians (*middle line* in the *box*) with the 25th–75th percentiles. *Capped lines* indicate 10th–90th percentiles of the data. Open circles indicate the values over 90th percentiles or under 10th percentiles. # $P < 0.05$ vs no administration of flurbiprofen. § $P < 0.05$ vs postoperative administration of flurbiprofen

tive period than postoperative FA in patients undergoing spinal fusion surgery.

Nakayama et al. [8] reported that preoperative FA reduced the need for late postoperative analgesia (15, 24, 48, 72 h postoperatively) compared with postoperative FA after abdominal hysterectomy, and suggested that the effect was due to a possible preemptive analgesic effect. However, its mechanism was not discussed in detail.

In the present study, the dose of FA was adopted on the basis of values reported in the literature [8,9]. We administered FA about 30 min before surgery in group A, because the analgesic effect of FA would begin 30 min after administration, with an elimination half-life of 6 h. The COX selectivity of FA is not known in detail, but Svensson and Yaksh [12] reported that FA had an almost equal selectivity for COX-1 and COX-2.

Tissue damage leads to the release of multiple mediators [including prostaglandins (PGs)] of nociceptor activity [13,14]. Released PGs lower the activation threshold for sensor neurons, and increase both the size of the receptive field and the types of stimuli that will activate these neurons [13,14]. The analgesic properties of NSAIDs can be attributed to their inhibition of COX and the subsequent decrease in PGs in the periphery [13,14]. Inhibition of peripheral PG production is important for decreasing nociceptive transmission to the central nervous system [14]. In the periphery, the initial PG release is probably due to COX-1 [14], because COX-2 becomes a major enzyme for PG production after gene expression, which takes 2–8 h [12]. Consequently, a COX-1 selective inhibitor might suppress peripheral PG production better than a COX-2 selective inhibitor [14].

NSAIDs also inhibit PG production in the spinal cord [12,15]. Svensson and Yaksh [12] reported that intrathecal phospholipase A_2 and COX-2 inhibitors, but not COX-1 inhibitors, attenuated the pain generated by peripheral injury/inflammation by direct activation of spinal glutamine and substance P receptors resulting from peripheral injury/inflammation. On the other hand, Zhu et al. [16] reported that intrathecal administration of COX-1 inhibitors may be useful for treating postoperative pain. Norman et al. [17] showed that the administration of ketorolac before tourniquet (TQ) inflation provided better postoperative analgesia than its administration after TQ inflation, and suggested that peripheral sensitization plays an important role in immediate postoperative pain.

In the present study, the mechanism of immediate postoperative analgesia in preoperative FA was attributed to peripheral and central effects. Preadministration of FA might reduce or delay the development of peripheral inflammation resulting from the inhibition of PG production during spinal surgery. The immediate postoperative analgesia might be due to inhibition of peripheral sensitization, in which PGs play important roles.

Preoperative FA also might reduce central sensitization. The action of PGs, especially PGE_2, in the dorsal root ganglia is important in the production of the hyperalgesia associated with central sensitization [14]. Zhu et al. [16] reported that COX-1 plays an important role in spinal cord pain processing and sensitization after surgery. The ability of NSAIDs to penetrate into cerebrospinal fluid (CSF) in sufficient quantity to prevent PG production depends on drug properties and timing, and may be affected by preexisting inflammation [14]. Ketoprofen, which is a propionate like FA, can cross the blood–brain barrier [18]. The ability of FA to penetrate into CSF is not well known. However, FA might be expected to easily penetrate into CSF and inhibit central sensitization during spinal surgery because FA is a fat emulsion drug.

In the present study, PLF-PSF causes tissue damage in the lumbar vertebra and might easily produce severe pain associated with somatic nerve injury during the immediate postoperative period, comparable to other procedures, such as hysterectomy, pulpectomy, laparoscopic cholecystectomy, or strabismus surgery. Thus, preoperative administration of FA might reduce immediate postoperative somatic pain more than later postoperative inflammatory pain.

In conclusion, preoperative administration of intravenous FA provides better immediate postoperative analgesia and opioid-sparing effects during the early postoperative period than postoperative FA in patients undergoing spinal fusion surgery under general anesthesia.

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