J Anesth (2009) 23:500–503
DOI 10.1007/s00540-009-0799-3

Journal of
Anesthesia

Postoperative analgesic effect of preoperative intravenous flurbiprofen in arthroscopic rotator cuff repair

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Abstract
Purpose. This study was carried out to evaluate the postoperative analgesic effects of preoperative intravenous flurbiprofen in patients undergoing arthroscopic rotator cuff repair under general anesthesia.
Methods. We studied 44 patients who underwent an elective arthroscopic rotator cuff repair in a prospective, randomized, and double-blind fashion. The patients were divided into two groups. Group A ($n = 22$) received lipid emulsion 0.1 ml·kg^{-1} as a placebo, and group B ($n = 22$) received flurbiprofen 1 mg·kg^{-1} before the surgery. Intralipid or flurbiprofen was given intravenously 5 min before the surgery. General anesthesia was maintained with sevoflurane and nitrous oxide, and 10 ml of 0.75% ropivacaine was administered intraarticularly at the end of the surgery. Postoperative analgesia was supplied with intravenous 0.1 mg buprenorphine according to the patient's demand. The effectiveness of flurbiprofen's analgesic effect was measured by a visual analog scale (VAS) and by the amount of buprenorphine consumption at 0.5, 1, 2, 4, 6, 12, and 24 h after the surgery. Time to the first analgesic was also recorded.
Results. VAS in group B was significantly ($P < 0.01$) lower than that in group A during the first 6 h postoperatively. The amount of buprenorphine consumption in group B was also significantly ($P < 0.01$) less than that in group A within the first 2 h postoperatively. The time to first analgesic request in group B was significantly ($P < 0.01$) longer than that in group A.
Conclusion. These results show that preoperative intravenous flurbiprofen facilitates the analgesic effect in the early postoperative period after arthroscopic rotator cuff repair.

Key words Postoperative analgesia · Intraarticular injection · Ropivacaine · Flurbiprofen

Introduction

It is known that an arthroscopic rotator cuff repair is often associated with sustained moderate to severe postoperative pain [1]. Postoperative pain after shoulder surgery is characterized by musculoskeletal pain related to soft tissue and muscle dissection and to manipulations and removal at the operation site. The intraarticular administration of local anesthetics (LAs) for orthopedic surgery has been shown to alleviate the postoperative pain through an action upon peripheral nerve endings [2,3]. Although intraarticular ropivacaine injection for arthroscopic rotator cuff repair has recently been reported to provide better postoperative analgesia than bupivacaine injection in the late postoperative period [1], the analgesia obtained is often inadequate.

It has been recommended that nonsteroidal anti-inflammatory drugs (NSAIDs) be used in a multimodal analgesic approach for the management of postoperative pain [4–7]. Flurbiprofen inhibits the cyclooxygenase (COX) enzymes nonselectively, and decreases peripheral and central prostaglandin (PG) production. Moreover, it has been reported that the preoperative administration of flurbiprofen reduced postoperative pain after minimally invasive surgery [8–10].

Therefore, we hypothesized that multimodal analgesia with a combination of intravenous flurbiprofen and intraarticular ropivacaine could produce better postoperative analgesia than intraarticular ropivacaine alone, because the two drugs have different pharmacokinetics and different sites of action.

This study was carried out to evaluate whether the combination of preoperative intravenous flurbiprofen and postoperative intraarticular ropivacaine could reduce postoperative pain compared to intraarticular ropivacaine alone in patients undergoing arthroscopic rotator cuff repair under general anesthesia.

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Received: April 10, 2008 / Accepted: May 28, 2009

Patients and methods

With the approval of the Institutional Review Board and written informed consent from each patient, we studied 44 patients with American Society of Anesthesiologists physical status I-II who were scheduled for arthroscopic rotator cuff repair. Excluded were patients aged less than 16 or more than 75 years; those with a history of allergy to any NSAID or fentanyl; and those with renal dysfunction, coagulopathy, peptic ulcer disease, opioid usage within the preceding 12 h, hypertension, or ischemic heart disease. The use of NSAIDs and/or steroids had been discontinued 24 h and 1 week prior to the study, respectively. Each patient was preoperatively instructed to use a ruler with a visual analog scale (VAS) for the evaluation of postoperative pain. A 100-mm horizontal VAS with end descriptors of "no pain" and "pain as bad as it could be" was used. The study was performed in a prospective, randomized, placebo-controlled, and double-blind fashion by three investigators, as follows. Each test solution was prepared in a 100-ml bag of saline by the first investigator, who was responsible for subject grouping. The second investigator, who did not know the type of test solution being used, performed the intravenous injection. The postoperative pain (VAS) was measured by the third investigator, who was blinded to the type of test solution used.

After the induction of anesthesia with 1.5 $mg \cdot kg^{-1}$ propofol and 5 $\mu g \cdot kg^{-1}$ fentanyl, and tracheal intubation with 0.1 $mg \cdot kg^{-1}$ vecuronium, anesthesia was maintained with sevoflurane 1.5%–2.5 % and N_2O 60% in oxygen, and additional vecuronium was administered as needed. No further opioids were given during the operation. The depth of anesthesia was monitored with the bispectral index (BIS) to ensure similar anesthetic depth in all patients.

By the use of a table of random numbers, the patients were randomly allocated to one of two equally sized groups. Group A (n = 22) received 0.1 $ml \cdot kg^{-1}$ lipid emulsion (10%; Intralipid; Terumo, Tokyo, Japan), in which the ingredients are the same as those of the flurbiprofen solvent, as a placebo, given intravenously 5 min before surgery. Group B (n = 22) received 1 $mg \cdot kg^{-1}$ flurbiprofen, given intravenously 5 min before surgery. The placebo and flurbiprofen were mixed with 100 ml saline and given over a period of 15 min. The two kinds of solution were similar in appearance.

The surgeon administered 10 ml of 0.75% ropivacaine intraarticularly at the end of the procedure. To prevent rapid effusion of the solution, the intraarticular injection was performed after skin closure and through a different site from the portals used during the procedure.

Postoperative pain (VAS) was assessed at 0.5, 1, 2, 4, 6, 12, and 24 h after the surgery. Because the shoulder was fixed with a triangular bandage so as not to move during 24 h postoperatively the pain score was assessed on bed rest, but not during movement. Postoperative analgesia was provided with intravenous 0.1 mg buprenorphine according to the patient's demand. The time to the first analgesic (the time from the end of surgery to the first rescue analgesic request) was also recorded.

A statistical comparison was made between group A and group B. Categorical data were compared by using the χ^2 test, and continuous data were compared by using the two-tailed Student's t-test. Interval variables are expressed as means ± SD. Ordinal variables (VAS and analgesic consumption) are presented as medians (ranges). The Mann-Whitney U-test was used for the evaluation of differences between the groups, followed by Wilcoxon's rank sum test where necessary. A statistical application, Stat View Version 5 (SAS Institute, Cary, NC, USA), was used for statistical analysis. $P < 0.05$ was regarded as significant.

Results

The demographic data for both groups were similar (Table 1). VAS in group B was significantly lower than that in group A within the first 6 h postoperatively (Table 2). There was no significant difference in VAS between the two groups at 12 h or later. Buprenorphine consumption in group B was also significantly lower than that in group A within the first 2 h postoperatively (Table 3). The time to the first analgesic (the time from the end of surgery to the first rescue analgesic request) in group B (368 ± 295 min) was significantly ($P = 0.0027$) longer than that in group A (110 ± 167 min). There was no significant difference in the number of patients who reported not using opioid analgesics within the 24-h postoperative period between group A (3/22; 14%) and group B (6/22; 27%).

Table 1. Demographic data

	Group A (n = 22)	Group B (n = 22)
Sex (M/F)	18/4	20/2
Age (years)	49 ± 18	57 ± 10
Height (cm)	164 ± 6	163 ± 5
Weight (kg)	63 ± 9	61 ± 10
ASA (I/II)	16/6	18/4
Operation time (min)	117 ± 20	110 ± 28

Data are presented as means ± SD. There were no significant differences in demographic data between the two groups
ASA, American Society of Anesthesiologists

Table 2. Postoperative pain

	Postoperative time (h)						
	0.5	1	2	4	6	12	24
Group A	70 (30–100)	60 (40–100)	60 (20–80)	50 (10–90)	38 (20–80)	30 (0–90)	30 (0–80)
Group B	35 (0–70)	25 (0–70)	15 (0–70)	12 (0–70)	20 (0–70)	25 (0–80)	30 (0–75)
P value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0008*	0.4146	0.9528

* $P < 0.01$ was regarded as significant
The postoperative pain (visual analog scale; VAS) in group B was significantly lower than that in group A during the first 6 h postoperatively. Data are presented as medians (ranges)

Table 3. Analgesic consumption

	Postoperative time (h)		
	Within 2 h	2–6 h	6–24 h
Group A (mg)	0.1 (0–0.2)	0 (0–0.1)	0 (0–0.1)
Group B (mg)	0 (0–0.1)	0 (0–0.1)	0.1 (0–0.2)
P value	0.0002*	0.2216	0.2865

* $P < 0.01$ was regarded as significant
Buprenorphine consumption in group B was significantly lower than that in group A within the first 2 h postoperatively, but not in the subsequent period. Data are presented as medians (ranges)

Discussion

The present study shows that preoperative intravenous flurbiprofen combined with intraarticular ropivacaine injection reduces postoperative pain intensity and supplemental analgesic consumption, and prolongs the time to first analgesic request in the early postoperative period after arthroscopic rotator cuff repair.

A recent metaanalysis has shown that either preemptive NSAIDs or LA infiltration was effective and clinically useful in reducing supplemental analgesic consumption and prolonging the time to the first analgesic request, but the effect of these drugs on postoperative pain intensity did not reach levels of statistical significance [11].

Peripheral tissue injury and inflammation would be involved in the mechanisms of postoperative pain after shoulder surgery. Intraarticular ropivacaine blocks peripheral afferents from acting on voltage-dependent Na+ channels and has a more extended action and slower clearance than bupivacaine, due to its potency of vasoconstriction, its greater molecular weight, and its lower lipid solubility [12–14]. Rodola et al. [1] demonstrated that ropivacaine provided better postoperative pain relief and led to less use of postoperative analgesics than bupivacaine in the first 6–24 h after shoulder surgery, suggesting a long-lasting satisfactory level of analgesia with intraarticular ropivacaine.

In the present study, there were significant differences in VAS and buprenorphine consumption between the two groups in the early but not late (>6 h) postoperative period. We recently reported that preoperative flurbiprofen prevented increases in peripheral prostaglandin E2 (at the operation site), resulting in the reduction of early postoperative pain [15]. Similarly, in the present study, the preoperative flurbiprofen likely reduced the early postoperative pain.

In the periphery, initial PG release is probably due to COX-1 [16], because COX-2 would become a major enzyme for PG production only after gene expression, which would take 2–8 h [17]. Preoperative flurbiprofen inhibits COX-1 and COX-2 nonselectively [18], resulting in reduced peripheral PG release initially.

It has also been demonstrated that, in the rat, free flurbiprofen rapidly crosses the blood-brain barrier, although plasma protein binding limits the brain uptake [19]. Intravenous flurbiprofen may penetrate to the central nervous system, resulting in the partial suppression of central PG production. Thus, preoperative flurbiprofen may be suited to attenuate early postoperative pain, possibly through a preemptive mechanism.

Intravenous flurbiprofen would provide a short-term effect because the terminal half-life of flurbiprofen elimination is fast [7]. It is possible that the combination of preoperative intravenous flurbiprofen and intraarticular ropivacaine would act on each pain pathway, resulting in a decrease of postoperative pain, produced additively and chronopharmacologically.

In conclusion, in patients undergoing arthroscopic rotator cuff repair who received intraarticular ropivacaine for basal analgesia, those who also received preoperative intravenous flurbiprofen showed better postoperative analgesia and less analgesic consumption in the early postoperative period than those who received intraarticular ropivacaine alone.

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