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Intravenous Diclofenac Coupled with PCA Fentanyl for Pain Relief after Total Hip Replacement

J. Laitinen, M.D., L. Nuutinen, M.D., Ph.D.†*

Postoperative pain relief immediately after major surgery cannot be achieved with opioids alone in all patients without respiratory depression or other significant side effects. This investigation was conducted to determine whether the need for opioids and the incidence of side effects can be reduced while maintaining the quality of pain relief using a nonsteroidal antiinflammatory drug as an adjuvant to an opioid. The analgesic efficacy and safety of patient-controlled analgesia using fentanyl with and without intravenous diclofenac were compared after total hip replacement. Forty patients were randomly assigned to receive either diclofenac 75 mg as an initial intravenous loading dose followed by an infusion of 5 mg per hour or saline in a double-blind fashion. The amount of fentanyl administered was recorded. The patients assessed their pain intensity verbally and on a visual analogue scale at intervals of 4 h. The diclofenac group showed a significant reduction in the amount of fentanyl administered during the first 16 h postoperatively as compared to the placebo group (0.65 mg ± 0.2 *vs.* 1.08 mg ± 0.4 respectively, $P < 0.01$), and also reported less pain at 16 h (median score on visual analogue scale 0.75 *vs.* 2.4 respectively, $P < 0.05$)). There were no differences in side effects, postoperative blood loss, plasma activated partial thromboplastin time, or Ivy bleeding time between the groups. In conclusion, the addition of diclofenac led to a reduction in fentanyl requirement but did not have any other significant advantages in the treatment of pain following major orthopedic surgery. (Key words: Analgesia: patient-controlled analgesia. Analgesics: nonsteroidal antiinflammatory drugs; diclofenac. Pain: postoperative.)

THE WELL-RECOGNIZED SHORTCOMINGS of intramuscular opioids in the treatment of postoperative pain have resulted in the use of nonsteroidal antiinflammatory drugs (NSAIDs) and patient-controlled analgesia (PCA) as alternative modes of treatment.

A combination of analgesics acting by different mechanisms should result in additive or synergistic analgesia. Opioids act on specific receptors in the central nervous system, whereas NSAIDs act mainly in the periphery, interfering with prostaglandin synthesis.[1] If a NSAID reduces the opioid requirements after surgery, opioid-related side effects should be reduced and possibly even the quality of the analgesia improved. NSAIDs nevertheless have their own range of unwanted effects, these including upper gastrointestinal intolerance, prolonged bleeding time, and occasionally hypersensitivity.[2–4]

The analgesic effect of NSAIDs for the treatment of postoperative pain has been demonstrated repeatedly.[5–11] Most research into orthopedic postoperative pain nevertheless deals with pain that can be treated without opioids, *i.e.*, pain experienced immediately after minor orthopedic procedures[12,13] or for 1 or 2 days after major orthopedic surgery.[14–16] Only Serpell and Thomson have studied the effect of a NSAID on opioid requirements during the first 48 h after total hip replacement.[17] They demonstrated a reduction in the total consumption of morphine upon the administration of piroxicam as compared with a control group. The mean pain scores and the incidence of side effects at 48 h postoperatively were similar in both groups. Neither the consumption of morphine nor pain scores were recorded at 24 h. Until now there have been no data on the effect of intravenous or intramuscular diclofenac on opioid requirements immediately after major orthopedic surgery.

In this study, fentanyl usage, pain scores, and side effects were recorded and compared between patients receiving PCA fentanyl combined with intravenous diclofenac and patients receiving PCA fentanyl alone for pain relief during the first 16 h after major orthopedic surgery (total hip replacement).

Materials and Methods

Forty patients scheduled to undergo total hip replacement gave verbal consent for this double-blind, randomized, controlled trial, which was approved by the local ethics committee. Those with allergic reactions to NSAIDs, bronchial asthma, a history of gastrointestinal ulceration, bleeding disorders, renal insufficiency, or current anticoagulant medication were excluded. The patients were of ASA physical status 1–3. All received oral diazepam 10 mg 1 h before surgery. Subarachnoid isobaric 0.5% bupivacaine 3–4 ml (15–20 mg) was used to provide anesthesia during surgery. No analgesics were given either before or during spinal anesthesia.

Immediately after surgery the patients received, in a blinded fashion, solutions of either an intravenous loading dose of 75 mg of diclofenac over 60 min followed by an infusion of 5 mg/h for 15 h or an equal volume of saline.

* Staff Anesthesiologist.

† Associate Professor of Anesthesiology.

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Address reprint requests to Dr. Laitinen: Department of Anaesthesiology, Oulu University Central Hospital, Kajaanintie 52 A, SF 90220 Oulu, Finland.

TABLE 1. Patient Characteristics, Duration of the Operation, and Fentanyl Consumption

	Placebo (n = 18)	Diclofenac (n = 20)
Sex (M:F)	11:7	7:13
Age (yr)	62.8 ± 9.4 (42–74)	63.8 ± 7.8 (48–78)
Weight (kg)	73.3 ± 17.2 (49–105)	73.4 ± 17.5 (48–125)
Height (cm)	167.7 ± 6.1 (159–176)	164.5 ± 8.3 (149–183)
Duration of operation (min)	93 ± 20 (65–140)*	76 ± 22 (45–130)*
Total 16-h consumption of fentanyl (mg)	1.08 ± 0.4 (0.4–2.1)†	0.65 ± 0.2 (0.1–1.7)†

Mean ± SD; range in parentheses.
* $P < 0.05$.
† $P < 0.01$.

In addition, a patient-controlled analgesia device (Pharmacia Deltec CADD-PCA) was programmed to deliver 0.05-mg bolus doses of fentanyl intravenously (1 ml). The lockout interval was 5 min, and no more than 0.5 mg could be delivered in any 1-h period. The patients were instructed to take fentanyl whenever they felt they needed pain relief. The total number of fentanyl doses in 16 h was recorded.

The patients were asked to estimate their pain immediately upon arrival in the recovery room and every 4 h thereafter using a 10-cm visual analogue scale (VAS) and using a verbal score of no (0), mild (1), moderate (2) or severe (3) pain, and to classify their pain as either superficial or deep and as either sharp or aching. Side effects and respiratory rate were recorded. Droperidol 0.5 mg intravenously was administered to patients who vomited. Postoperative bleeding was assessed by measuring the blood recovered *via* the operative wound drains.

Ivy bleeding time and plasma activated partial thromboplastin time were determined preoperatively and at 3 h postoperatively. Demographic data, duration of operation, fentanyl consumption, and respiratory frequency (mean ± standard deviation) were analyzed using the unpaired Students's *t* test; the VAS and verbal pain scores (median and range) were analyzed using Wilcoxon's rank sums; and the incidence of side effects were analyzed using Fischer's exact test (two-tail) and chi-squared analysis. Linear regression was used to evaluate the association between the duration of the operation and the VAS scores. A P value of less than 0.05 was interpreted as an indication of statistical significance.

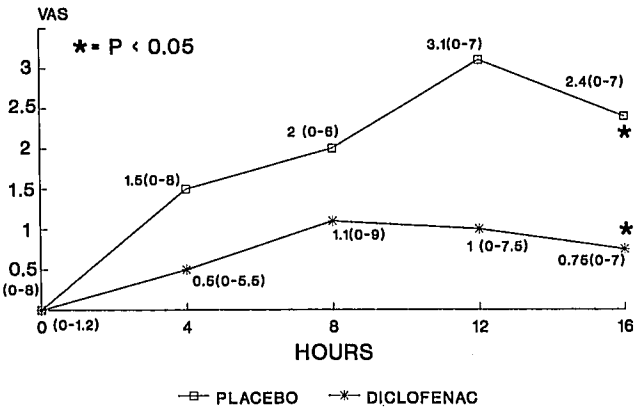

FIG. 1. Median (range) visual analogue scale (VAS) scores at 4-h intervals in both groups. The median score was lower in the diclofenac group at 16 h ($P < 0.05$).

Results

Patient characteristics and the durations of the operations are presented in table 1. Two patients in the placebo group were withdrawn from the trial as a result of programming errors, so that 38 patients were eventually studied, 18 of whom received saline and 20 diclofenac. The mean 16-h fentanyl consumption of the placebo group was significantly greater than that of the diclofenac group ($P < 0.01$) (table 1), and the VAS score at 16 h postoperatively also was higher ($P < 0.05$) (fig. 1). There were no differences in verbal pain scores between the groups (table 2). There were no significant differences between the two groups with respect to side effects (table 3). No patient in either group was noted to have a respiratory rate of less than 10 breaths per minute. There

TABLE 2. Median Verbal Pain Score at 4-h Intervals

	Placebo		Diclofenac	
Time (h)	Median	Range	Median	Range
0	0	0–1	0	0
4	1	0–2	1	0–1
8	1	0–2	1	0–2
12	1	0–3	1	0–2
16	1	0–3	1	0–2

Pain scores: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

TABLE 3. Side Effects during the First 16 h

Side Effect	Placebo (n = 18)	Diclofenac (n = 20)
Nausea		
Slight	2	2
Moderate	0	0
Severe	6	7
Vomiting	1	3
Urinary retention	2	3
Backache	4	3
Shivering	1	1
Restlessness	1	0
Sweating	1	0
Irritation at the infusion site	0	1
Muscle spasms	1	0
Number of patients with side effects	13	12

were no differences in postoperative blood loss, plasma activated partial thromboplastin time, or Ivy bleeding time between the groups (table 4).

Discussion

There is often a delay in administering an intramuscular opioid when patients report pain. It is impossible to maintain a constant blood concentration. Variable rates of absorption from intramuscular injection sites bring about variability in maximum blood concentrations and in times of their occurrence.[18] There also is great interpatient variability in minimum effective blood opioid concentrations for postoperative analgesia.[19] Theoretically, minimum effective blood opioid concentrations can be achieved and maintained by PCA despite interpatient variability, because each patient should be able to titrate an appropriate dose of opioids promptly to provide adequate analgesia.

The reduction of the mean postoperative fentanyl consumption by more than one third in the present diclofenac group should have the advantage of a diminished risk of respiratory depression. Two earlier reports mention that combination therapy with an opioid and a NSAID was associated with less respiratory depression,[2,3] and the present results contain no evidence of respiratory depression in either group of patients.

Although the VAS score appears to have been higher in the placebo group than in the diclofenac group throughout (*i.e.*, at 4, 8, 12, and 16 h), there is no statistical difference between the groups except at 16 h (fig. 1). The operations lasted longer in the placebo group than in the diclofenac group (table 1). Nevertheless, there was no correlation between the durations of the operations and the VAS scores ($r = -0.04$, 0.09, 0.04, 0.07, and 0.06 for 0, 4, 8, 12, and 16 h). This tendency to accept more pain in the placebo group than in the diclofenac group reflects an inability or unwillingness to demand analgesia frequently enough. If there is a (self-imposed) maximum demand rate that patients are reluctant to exceed, then the addition of a NSAID may improve the quality of analgesia achievable with a PCA opioid. The perioperative immobility and the loss of lumbar muscle tone during spinal anesthesia produce musculoskeletal discomfort in patients undergoing hip replacement, and NSAIDs may be able to alleviate such pain, which is probably less amenable to treatment with an opioid.

When the patients were asked to differentiate between superficial and deep pain and between sharp and aching pain, none of these components seemed to be specifically eliminated by diclofenac as compared with the placebo (table 5).

Diclofenac administered orally, intramuscularly, or rectally in single doses of 50–100 mg is an effective analgesic agent for the treatment of minor surgical pain.[20] By comparison, the dose of 75 mg intramuscularly twice per day led to morphine-sparing effects in the treatment of pain following abdominal surgery[3] and to reduced pain during the day after hip replacement.[10] The NSAIDs typically have a ceiling effect, and it is not known whether doses smaller than 75 mg produce a maximal analgesic effect on postoperative pain after major surgery.

Diclofenac infusion was started immediately after surgery in order to increase the plasma and tissue concentrations rapidly and thereby inhibit the synthesis and re-

TABLE 4. Ivy Bleeding Time and Plasma Activated Partial Thromboplastin Time

	Placebo (n = 18)	Diclofenac (n = 20)
Preoperative bleeding time (s)	264 ± 79 (120–360)	314 ± 79 (180–420)
3-h Postoperative bleeding time (s)	327 ± 198 (135–810)	348 ± 185 (120–870)
Preoperative P-APTT (s)	26 ± 4 (20–33)	25 ± 3 (18–29)
3-h Postoperative P-APTT (s)	25 ± 3 (19–32)	24 ± 3 (18–29)
Postoperative blood loss (ml)	1,080 ± 590 (420–2,650)	947 ± 579 (50–2,200)

Mean ± SD; range in parentheses.

P-APTT = plasma activated partial thromboplastin time.

TABLE 5. Subjective Classifications of Pain by Patients Receiving Diclofenac or a Placebo

	4-h		8-h		12-h		16-h	
Quality of Pain	Placebo	Diclofenac	Placebo	Diclofenac	Placebo	Diclofenac	Placebo	Diclofenac
Superficial/deep	8/6	11/3	7/7	6/8	8/6	6/7	9/5	8/4
Sharp/aching	3/11	6/8	1/13	3/11	2/12	4/10	1/13	2/10
Not able to differentiate	4	6	4	6	4	7/6	4	8

Numbers of patients.

lease of pain-mediating prostaglandins before the patients emerged from the perioperative analgesia. Prophylactic administration of a NSAID may prevent nociceptor sensitization and reduce postoperative pain by modifying the response of the central nervous system to subsequent painful stimuli.[21] This concept of prophylactic protection against surgical nociception was discussed originally by Wall[22] in another context, namely that of opiate premedication and/or regional anesthesia.

We administered the diclofenac intravenously. Campbell and Kendrick compared a single dose of intravenous diclofenac 1 mg/kg given before dental surgery with a single dose of intramuscular diclofenac 1 mg/kg, fentanyl, or a placebo[23] and observed significantly less pain in the intravenous diclofenac group 30 min after the operation.

The mean elimination half-life of diclofenac 50 mg after intravenous administration is about 1 h,[24] but it has a prolonged analgesic effect despite its short elimination half-life in plasma. Its uptake and retention by tissues is extensive, and its analgesic efficacy may be more closely related to tissue levels than to plasma levels. Following diclofenac 75 mg intramuscularly, synovial fluid concentrations increase to three to four times the plasma concentrations from 4 h on.[25]

After an intravenous loading dose of diclofenac 75 mg followed by continuous infusion of 5 mg/h, the plasma and tissue concentrations of the drug should be maintained at higher levels for a longer period than after a single dose or intermittent doses. The lower fentanyl requirement during the first 16 h postoperatively and the lower VAS score in the diclofenac group than in the placebo group at 16 h are compatible with the assumption of sustained plasma and tissue concentrations.

Potential disadvantages of NSAIDs are their effects on platelet function and on the gastrointestinal tract.[15] There were no differences in postoperative blood loss, bleeding time, or plasma activated partial thromboplastin time between the groups, nor any evidence of gastrointestinal irritation once patients with a history of gastrointestinal ulceration were excluded.

In conclusion, although the addition of diclofenac led to a reduction in the amount of fentanyl used, the incidence of side effects was unaltered as compared with the use of PCA fentanyl alone. The combination of drugs did not lead to significantly better analgesia than PCA fentanyl alone except at the end of the trial.

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