Comparison of i.m. and local infiltration of ketorolac with and without local anaesthetic

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Summary
We have studied postoperative analgesia in 32 patients undergoing outpatient repair of inguinal hernia. All patients received a standardized general anaesthetic of thiopentone followed by halothane or isoflurane in 70 % nitrous oxide and oxygen delivered by face mask or laryngeal mask with spontaneous ventilation. No patient received premedication, opioids or neuromuscular blockers. Before wound closure the surgeon infiltrated 20 ml of saline into the wound. The solution contained ketorolac 30 mg in saline, 0.25 % bupivacaine and ketorolac 30 mg, 0.25 % bupivacaine or saline (control group). The control group received ketorolac 60 mg i.m. at the same time. Pain scores were measured 2, 6 and 24 h after operation. Pain scores for all three active groups were significantly less (P < 0.05) than the control group at all times. There were no significant differences in pain scores at any time among the three study groups. Wound infiltration with ketorolac 30 mg in saline, 0.25 % bupivacaine or ketorolac 30 mg with 0.25 % bupivacaine provided equivalent analgesia. Wound infiltration with ketorolac 30 mg in saline provided analgesia superior to that of ketorolac 60 mg i.m. (Br. J. Anaesth. 1995; 75: 409–412)

Key words

The use of perioperative non-steroidal anti-inflammatory drugs (NSAID) has become popular in operations ranging from minor outpatient procedures to major inpatient surgery. In common with other NSAID, ketorolac has been advocated as an adjuvant agent to reduce postoperative pain and opioid analgesic requirements [1, 2]. Ketorolac is a NSAID that, through inhibition of prostaglandin synthesis, is said to have analgesic efficacy comparable with morphine 12 mg [3–5].

The explanation for the effectiveness of ketorolac stems at least in part from inhibition of peripheral production of eicosanoid mediators of pain and the tissue injury response. Therefore, we have investigated the possibility that ketorolac might have a more profound analgesic effect if present in high concentrations at the site of injury. We have compared the analgesic efficacy of wound infiltration with ketorolac and i.m. ketorolac. We also investigated if wound infiltration with ketorolac had an additional analgesic effect beyond that of local anaesthetics such that there would be benefit in combining them.

Patients and methods
With approval from the Institutional Human Studies Committee and patient informed consent, we studied 32 healthy patients, ASA I and II, undergoing elective inguinal hernia repair. Patients with significant hepatic, renal or cardiovascular disease, a history of bleeding abnormality, ulcer disease or sensitivity to NSAID were excluded. All surgery was performed by the same team of two surgeons.

Patients were assigned systematically to one of four groups according to the order of their entry into the study and allocated alternately to the following groups: (1) wound infiltration with ketorolac (Topdol, Teva Pharmaceuticals) 30 mg in 20 ml saline; (2) wound infiltration with 0.25 % bupivacaine 20 ml and ketorolac 30 mg; (3) wound infiltration with 0.25 % bupivacaine 20 ml; and (4) wound infiltration with saline 20 ml and ketorolac 60 mg i.m. (control group). Preliminary work [unpublished data] indicated the safety of both the combination of agents and local infiltration of ketorolac 30 mg.

No patient received premedication or any opioid at any time before or during operation. Anaesthesia was induced with thiopentone 3–4 mg kg⁻¹ and maintained with 70 % nitrous oxide in oxygen, with either halothane or isoflurane administered via either a face mask or laryngeal mask with spontaneous ventilation. No neuromuscular blockers were administered to any patient. Before closure of the wound the surgeon, who was blind to the contents of the study syringe, infiltrated the inguinal ring and the deep and subcutaneous edges of the wound. Patients in the control group received an i.m. injection of ketorolac 60 mg in the deltoid muscle immediately after infiltration.

After operation, patients who required additional treatment for pain were given dipyrone 1 g orally. The decision to administer this analgesic was left to the recovery room nurse caring for the patient. All nurses were blind to the study group. The intensity of postoperative pain at 2 h was measured in the

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recovery room using a 10-cm linear analogue scale administered by a separate blinded observer. The scale consisted of a horizontal line marked “no pain” at one end and “worst possible pain” at the other. The same observer used a verbal pain scale (pain score of 0–10 given by the patient where 0 was defined as “no pain” and 10 as “worst possible pain”) to assess pain scores by telephone interview at 6 and 24 h. Pain scores were measured at rest (supine), with activity (sitting up from supine) and with coughing. Patients were discharged home with additional dipyrone 500 mg and instructed to take 1–2 tablets every 4 h as necessary to relieve pain. Analgesic requirements were noted in the recovery area and home use was recorded at the 24-h telephone interview.

Pain scores were summarized (table 2) for each group at each time of measurement and for each of the three measurements (at rest, sitting, coughing). Pain scores were analysed using the Kruskal–Wallis test (Statview 4.02 Abacus Concepts, Berkeley, CA, USA). Further pairwise comparisons were examined with Mann–Whitney test using the Bonferroni correction for multiple comparisons. Analgesic requirements over 24 h were analysed using one-way analysis of variance (ANOVA) with Fisher’s protected least significant differences test. ASA status, sex and need for rescue analgesia in the recovery room were analysed by frequency table analysis. Group ages were analysed using the Kruskal–Wallis test. Differences were considered significant if \( P < 0.05 \).

**Results**

The study groups were comparable in number (eight patients each), age 62.5 (range 32–76), 59 (38–79), 57.3 (31–72) and 61.8 (39–71) yr, sex (groups 1 and 2 had one female each, groups 3 and 4 had no females) and ASA status (table 1).

Pain scores (table 2) were greatest at all times in group 4. The only significant differences between group pain scores were those between group 4 and the other three groups. Pain scores in group 4 differed significantly from those in the three other groups at all times on all three levels of activity assessed. There were no significant differences in pain scores between groups 1, 2 and 3 at any time or at any activity level.

Dipyrone was administered in the recovery room to five of eight patients in group 1, six of eight patients in groups 2 and 3 and to all patients in group 4 (ns). Mean 24 h requirements for dipyrone for the four groups were, respectively, 2.24 (SEM 0.27) g, 2.18 (0.26) g, 1.92 (0.31) g and 3.23 (0.17) g. Only the control group required significantly more analgesic than the three other groups, which did not differ significantly from each other.

There were no problems either during or after operation in terms of wound haemostasis secondary to the use of ketorolac. Late follow-up in the surgical clinic revealed no complications, including wound haematoma, delayed healing or infection.

**Discussion**

Surgical injury unleashes a complex chain of events caused by both direct mechanical and thermal damage to nerve endings. The primary phase nociceptive discharge can establish a hyperexcitable state at the level of the spinal cord [6]. At the same time, in peripheral tissues, a secondary phase injury response develops which creates a state of peripheral hypersensitivity. This peripheral response is caused by release of algogenic chemical mediators (substance P, histamine, bradykinin, prostaglandins, leukotrienes, serotonin) from nerve and damaged tissue. Substantial evidence points to an important role for the products of arachidonic acid metabolism in the local promotion of pain, inflammation and hyperalgesia [7]. NSAID, through inhibition of cyclooxygenase mediated production of prostaglandins and thromboxanes, may inhibit the injury response in the tissue [8].

NSAID, however, are no longer believed to act exclusively in the periphery. Some workers argue for a dominant role of prostaglandin inhibition in the CNS [9, 10]. Ferreira, Lorenzetti and Corrêa [11] suggested a peripheral–central synergistic action that varies depending on the particular NSAID and on the presence or absence of an inflammatory process. Arachidonic acid metabolites may also play an important role in the systemic response to surgery [12]. Thus, in addition to analgesic effects both centrally and peripherally, NSAID may also moderate the systemic aspects of the injury response.

There is much current interest in combined analgesia therapy or “balanced analgesia” [12], in particular the combined use of NSAID with opioids. Ketonolac, a potent analgesic, has an opioid sparing effect [13, 14]. Our purpose in this study was to examine if local administration of ketorolac would be more effective than systemic and if there might be an additional analgesic effect with local anaesthetic. Combination regimens of NSAID and regional anaesthesia have not been studied extensively. As conduction block does not affect the peripheral tissue response, analgesia after dissipation of a block might be enhanced by pre-emptive treatment of the local secondary phase response [15]. Mogensen and colleagues [16] showed no benefit of the addition of rectal piroxicam to extradural infusion of bupivacaine and morphine after major abdominal surgery. However, it is possible that the extradural infusion was sufficiently effective that the pain could not be reduced further.

The results of this study showed that through the...
first 24 h after operation there were significant differences in pain scores and analgesic use between the control group who received ketorolac 60 mg i.m. and the ketorolac group who received wound infiltration with only 30 mg. Although we did not measure drug concentrations, we believe it is probable that greater systemic concentrations were achieved in the former group. Differing absorption between the i.m. and wound infiltration routes probably did not affect the results, as the first measurement of pain was made long after the expected peak concentration [17]. We conclude that the high tissue concentrations of ketorolac reached at the site of surgery yielded more effective analgesia than that afforded by the larger i.m. dose. Lower pain scores in the wound infiltration group suggest the local effect of ketorolac exceeded the systemic effect. The analgesic advantage of wound infiltration with ketorolac persisted throughout the first 24 h after surgery in spite of greater analgesic use by the control group.

We failed to show any difference between the analgesic efficacy of wound infiltration with bupivacaine or ketorolac, or any additional benefit from their combination. Given their different mechanisms of action, one might have expected otherwise, but an unknown drug interaction might explain the lack of additional analgesia. It is known that amide local anaesthetics have potent and long-lasting anti-inflammatory properties [18, 19]. This could at least partially explain the lack of additional analgesia from adding ketorolac to the local anaesthetic. The converse possibility, that ketorolac has local anaesthetic properties, is unlikely.

The failure to demonstrate significant differences between groups 1, 2 and 3 deserves comment as to why there were only eight patients per group, the failure to discern real differences may stem from the small group sizes. We conducted a post hoc power analysis imposing several basic assumptions. First, we considered that a significant clinical difference between any two techniques would be reflected by a difference of 2.0 mm in the mean linear analogue pain scores between groups. Second, we used a pooled average SD from all data in the study and assumed a common SD for two theoretical groups. Using a two-sided significance level of 5 % (P = 0.05) we found that eight patients per group yielded a power of 80–90 %.

Our model may have been influenced by administering the drugs near the end of surgery. There is evidence of increased postoperative pain when a regional anaesthetic is given at the end of surgery as opposed to the beginning [20]. Therefore, we cannot necessarily extrapolate these findings to the pre-operative administration of a local anaesthetic and ketorolac. Tverskoy and colleagues [21] used 0.25 % bupivacaine 40 ml for regional analgesia, before incision for herniorrhaphy. Their patients had lower postoperative pain scores than our group 3 (wound infiltration with bupivacaine). They concluded that peripheral block is more effective than central block in preventing a hyperexcitable state and emphasized the importance of pre-emptively inhibiting peripheral sensitization.

It is appropriate that we comment on the use of dipyrone. The literature and international opinion is sharply divided on the safety of the drug and an international effort at systematic evaluation was without a definitive conclusion [22]. Dipyrone remains the most popular non-prescription analgesic in Israel. Further, the choice of this second NSAID as the rescue medication was based on both clinical experience regarding its effectiveness in combination with ketorolac and maintaining continuity of analgesic medication with a familiar agent.

The choice of ketorolac doses, 30 mg and 60 mg, was based on recommended doses at the time this work was done. While these are doses commonly found in the literature, it should be noted that in the UK the recommended dose has been reduced to 10 mg.

References


