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Efficacy of Intravenous Ketoprofen for Pre-Emptive Analgesia

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Abstract:

AIM: To determine whether intravenous ketoprofen is effective as pre-emptive analgesia for breast surgery. DESIGN: Randomised, controlled, double blind study. PATIENTS AND METHODS: 50 patients undergoing breast surgery under general anaesthesia randomised to receive either 100 mg intravenous ketoprofen 30 minutes before (Group I), or immediately after surgical incision (Group II). Postoperatively, pain scores (Visual Analogue Scale, VAS) and time to rescue analgesic were recorded by an independent, blinded observer. The study was terminated when rescue analgesic was required (VAS ≥ 4 or demand for analgesic). STATISTICAL ANALYSIS: Continuous variables were analysed by the unpaired ‘t’ test, discrete variables with the chi square test, and survival curves by the log-rank test. RESULTS: Pain scores were significantly lower in Group I till 10 hours after surgery. The number of patients requiring analgesia at 4, 6, 8 and 10 hours was significantly lower in group I (0% vs. 47% [P<0.0001], 0% vs. 44% [P<0.003], 0% vs. 80% [P<0.0001], 0% vs. 100% [P<0.0001] respectively). The mean time for rescue analgesic was 15.47 ± 2.87 hours in group I versus 4.22 ± 2.55 hours in group II (P<0.0001). CONCLUSION: Pre-emptive analgesia with Intravenous ketoprofen (100mg) produces better postoperative pain-relief in patients undergoing breast surgery. (J Postgrad Med 2002;48:109-112)

Key Words: Analgesia, intravenous, pre-emptive, NSAIDs, ketoprofen.

Post-operative analgesia is an important consideration in patients undergoing surgery. Analgesics administered before an initial noxious stimulus such as skin incision i.e. pre-emptive analgesia maybe more effective than the same dose given afterwards.1,2

Pre-operative noxious inputs can contribute to both peripheral and central sensitisation modulating post-operative pain and they can be targets for pre-emptive analgesia.3 Various agents including non-steroidal anti-inflammatory drugs (NSAIDs) have been used in an effort to pre-empt post-operative pain.4,5,6 NSAIDs are widely used for mild to moderate pain, they have a well-recognised opioid sparing role and are effective when administered pre, peri and post operatively.7,8,9,10

Ketoprofen is one of the few NSAIDs available for intravenous administration in India. It belongs to the group of phenyl-propionic acid derivatives. The distribution half-life of ketoprofen after intravenous administration is 0.34±0.19 hours, while its elimination half-life is 2.05±0.58 hours. The volume of central compartment is 5.58±1.67 l, volume of the tissue compartment is 5.14±2.12 l and the plasma clearance is 5.10±1.14 l/hour. Ketoprofen is metabolised in the liver and is excreted by the kidney. It does not interact with commonly used anaesthetics and opioids.11

Ketoprofen has been used for postoperative analgesia in several studies.12,13,14,15 However, its efficacy for pre-emptive analgesia has not been reported.

We therefore undertook a prospective, randomised, double blind, controlled study to determine whether pre-emptive intravenous ketoprofen resulted in superior postoperative pain relief after breast surgery.

Patients and Methods

After obtaining a written informed consent, 50 patients of ASA Grade I or II who were scheduled for elective breast surgery such as lumpectomy, simple mastectomy and modified radical mastectomy were included in the study. Patients less than 18 years or more than 65 years of age, those with a history of allergy to any NSAID, renal dysfunction, asthma, coagulopathy and peptic ulcer disease were excluded from the study.

All patients were instructed in the Visual Analog Scale (VAS 0 = no pain to VAS 10 = worst pain). The patients were randomised into two groups using a computer-generated table of random numbers. Patients in Group I received 100 mg ketoprofen diluted in 100 ml normal saline as an intravenous (IV) infusion before surgical incision over a period of 15 minutes in the preoperative room. This infusion was completed 30 minutes before the surgical incision was taken. 100ml plain normal saline was infused over 15 minutes immediately after surgical incision in this group. Patients in group II received plain normal saline 100ml as an...
infusion over 15 minutes in the preoperative room. This infusion was completed 30 minutes before skin incision. An IV infusion of ketoprofen 100 mg diluted with 100 ml normal saline was started immediately after surgical incision and infused over a period of 15 minutes in this group. All patients received intramuscular midazolam (0.07 mg/kg) for premedication. General anaesthesia was induced with IV Fentanyl (2 mcg/kg), IV Propofol (2 mg/kg). A Laryngeal Mask Airway (LMA) was introduced and anaesthesia was maintained by controlled ventilation using vecuronium, nitrous oxide mixed with oxygen and isoflurane.

An anaesthetist, blinded to the study, monitored the heart rate and mean arterial pressure intra-operatively. Residual neuromuscular blockade was reversed at the end of the surgery with intravenous neostigmine (0.05mg/kg) and glycopyrrolate (0.01mg/kg). The LMA was removed and patients were shifted to the recovery room.

Postoperatively in the recovery room the VAS, postoperative nausea vomiting (PONV) score (1-no nausea, 2-mild nausea, 3-moderate nausea, 4-severe nausea and 5-severe nausea and vomiting) and need for rescue analgesic were recorded by an independent observer who was unaware of the patients’ group. The parameters were recorded immediately on admission to the recovery room and thereafter every 5 minutes for 15 minutes, then every 15 minutes for 2 hours and then every 30 minutes. Rescue analgesic (IV tramadol 100mg) was given when the patient had a VAS pain score >4, or earlier if they demanded an analgesic, irrespective of the pain score. The study was terminated either with the administration of the rescue analgesic or at the end of 24 hours of observation, whichever was earlier.

Continuous variables were analysed by the unpaired ‘t’ test, discrete variables with the chi square test and survival curves by the log-rank test.

Results
Both groups of patients were similar with respect to age, weight and duration of surgery. (Table 1)

The mean pain score (VAS) was significantly lower in Group I at all time intervals till 10 hours after surgery (Table 2). The time for rescue analgesic (mean ± SD) was 15.47 ± 2.87 hours in group I versus 4.22 ± 2.55 hours in group II (P < 0.0001).

The number of patients requiring analgesia at 2, 4, 6, 8 and 10 hours was significantly lower in group I as compared to group II (0% vs. 46% [P< 0.0001], 0% vs. 47% [P< 0.0001], 0% vs. 44% [P< 0.003], 0% vs. 80% [P< 0.0001] and 0% vs. 100% [P< 0.0001] respectively).

The VAS (mean ± SD) when rescue was given was 4.25 ± 2.07 in group I and 5.04 ± 3.06 in group II (P < 0.0001). All patients in group II required an analgesic before 10 hours, whereas twelve patients (48%) in group I did not require the rescue analgesic for up to 20 hours (Figure). However, all patients received a rescue analgesic within 24 hours of surgery.

In group I, 20 (80%) patients did not have nausea or vomiting, while 5 (20%) patients had mild nausea. No patient had moderate to severe PONV. Whereas in group II, 14 (56%) patients had severe nausea and vomiting and 11(44%) patients had moderate nausea. This difference i.e. patients with none to mild PONV versus moderate to severe PONV was highly significant (P < 0.00001). No patient had excessive bleeding requiring blood transfusion, re-exploration or postoperative haematoma formation.

Discussion
Surgical trauma generates powerful nociceptive impulses that are generated by the procedure itself and by the action of proteolytic and inflammatory agents that are released following tissue injury. This release of inflammatory mediators and subsequent oedema may result in pain for several hours.\textsuperscript{6} Pain can be viewed as the end product of a passive transmission system that transmits a peripheral signal through the spinal cord up to the pain centre in the brain. In addition, the transmission of noxious afferent inputs from the periphery (example – brought about by incision and intra-operative events) to the spinal cord induces a prolonged state of central neural sensitisation or hyper excitability that amplifies subsequent inputs from the wound and leads to post-operative
Pre-emptive analgesia reduces nociception and stress during surgery, prevents establishment of central sensitisation, resulting in reduced pain intensity and lower analgesic requirements even after the analgesic effect of the (pre-emptive) agents have worn off. NSAIDS have analgesic effects, which have been attributed to their peripheral anti-inflammatory actions in inhibiting the synthesis of prostaglandins through the inactivation of cyclooxygenase. This peripheral receptor action of the NSAIDs can thus indirectly inhibit central neural sensitisation and consequently reduce the amplification of pain.

While the role of pre-emptive analgesia has a sound theoretical basis, the results of some studies that administered NSAIDs to pre-empt post-operative pain have not been encouraging. However, a few studies have shown pre-emptive analgesia to be effective in post-operative pain.

It is difficult to account for the differences in results of these conflicting studies. The various routes of administration included oral, rectal, intramuscular and intravenous. And a variety of NSAIDs such as acetic acids, oxicams, and paracetamol that differ in their pharmacokinetics and in the extent of their anti-inflammatory, analgesic and anti-pyretic actions have been used. Moreover, these studies were conducted on various surgeries where the degree of pain ranged from mild to excruciating.

Our study was the first one to have evaluated ketoprofen for pre-emptive analgesia. Unlike other studies, the route of administration, type and duration of surgery and use of drugs during anaesthesia were controlled across both the groups. We found out that the pain scores, time to first rescue analgesic requirement and the number of patients requiring rescue analgesic were significantly reduced in the pre-emptive group as compared to the post-incision group. Also, no patient in the pre-emptive group demanded analgesia till 20 hours post-operatively. While the post-operative renal function tests and coagulation profile were not carried out in our study, other studies have proven the safety of the drug including its usage in children.

Hence, we believe that pre-emptive analgesia with intravenous Ketoprofen (100mg) is an effective, simple and safe strategy for postoperative pain relief after superficial breast surgery. Its use should be evaluated for postoperative analgesia following other types of surgery.
References