Original Article

Comparison of the Efficacy and Safety of Different Doses of Propacetamol for Postoperative Pain Control after Breast Surgery

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Abstract:

Intravenous propacetamol has been shown to be effective for postoperative pain control. However, the recommendations regarding propacetamol doses for pain control are vague. The present study was performed to compare the efficacy and safety of propacetamol at a dose of 1 g or 2 g. After breast-conserving surgery, patients received 1 g or 2 g intravenous propacetamol. Treatment efficacy for pain control was assessed using a 100 mm visual analog scale at 15, 30, 45, and 60 minutes and 4 hours after surgery, and global evaluation was assessed by a 4-point categorical scale at the end of the 4-hour study period. Safety was monitored through adverse event reporting. Patients were allowed rescue analgesia, and the timing of requests was recorded. A total of 111 patients were enrolled in the study. There were no differences in efficacy variables, including visual analog scale, the 4-point categorical scale, and requests for rescue analgesia, between propacetamol doses of 1 g and 2 g. Adverse events were similar in the two groups. Intravenous propacetamol at a dose of 2 g is not superior to the lower dose of 1 g with regard to postoperative analgesia or the incidence of side effects in breast-conserving surgery.

Postoperative pain control is an important component of postsurgical management. Opioids and nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for postoperative pain management. However, opioids are known to induce a wide range of adverse events, such as nausea, vomiting, dizziness, pruritus, sedation, and respiratory depression; and NSAIDs may be associated with increased operative site bleeding, gastrointestinal injury, and renal toxicity,

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which may limit the dose that can be administered (Harirforoosh, Asghar, & Jamali, 2013; Hassanein, Abdelrahim, Said, Hussein, & Abuseif, 2013; Misurac, et al., 2013; White, 2002). Therefore, there is increasing interest in the use of other classes of analgesics. Acetaminophen (AAP) or paracetamol has a well-established safety and analgesic profile. AAP has been formally recommended by the American Society of Anesthesiologists for first-line use as one of the possible components of multimodal analgesic regimens for postoperative pain management, as it has few contraindications and lacks significant drug interactions (American Society of Anesthesiologists Task Force on Acute Pain, 2004). Propacetamol hydrochloride is a prodrug of paracetamol, which is completely and rapidly hydrolyzed by nonspecific plasma esterases to paracetamol and diethylglycine. Intravenous administration of 2 g propacetamol, equivalent to 1 g AAP, has been effective for postoperative pain control, including breast surgery (Faiz, et al., 2014; Kampe, et al., 2006; McNicol, et al., 2011; Ohnesorge, et al., 2009). However, the label recommends a dose of 1-2 g propacetamol administration every 4–6 hours in adults, which is very vague, and no references are provided regarding these recommendations.

The present study was performed to compare the analgesic efficacy and safety of intravenous propacetamol below the recommended dosage (1 g and 2 g) in patients after breast-conserving surgery.

METHODS

The study was approved by the Institutional Review Board (H-1303-040-474) of Seoul National University Hospital, Korea and registered at http://cris.nih.go.kr/cris (KCT0000807). Written informed consent was obtained from the patients, and the study was conducted in a prospective, blind and randomized manner.

Study Population

We enrolled patients of the American Society of Anesthesiologists Physical Status I or II, aged 19-80 years, who were scheduled for breast-conserving surgery. Patients were excluded according to the following criteria: (1) expression disorder; (2) significant liver or coagulation disease; (3) history of drug abuse; (4) hypersensitivity to propacetamol; (5) neurological or psychiatric disorders; (6) bilateral surgery; and (7) other combined operations. No pre- or intraoperative opioid administration was permitted.

Anesthetic Technique

The patients arrived in the operating room without premedication. After establishing noninvasive patient monitoring, such as pulse oximetry, electrocardiography, and noninvasive blood pressure, anesthesia was induced by the attending anesthesiologist who was blind to the study group. General anesthesia was induced using 5 mg/kg thiopental sodium and 0.6 mg/kg rocuronium for intubation. Anesthesia was maintained with desflurane with 50% oxygen in air, adjusting the desflurane concentration according to heart rate and blood pressure. After surgery, the patients were administered propacetamol according to the group allocation, and were transferred to the postanesthesia care unit (PACU).

Efficacy Evaluation

Pain intensity was assessed using a visual analog scale (VAS; 0 = no pain, 100 = worst possible pain) at 15, 30, 45, 60 minutes, and 4 hours (T_{15min}, T_{30min}, T_{45min}, T_{60min}, and T_{4h}, respectively) after surgery. Assessment was done by PACU nurses who were blinded to the dose of drug in PACU and researchers who were blinded to the study groups at ward. In addition, the sum of the pain intensity over the 4-hour period was recorded. The patients received training from the study observer on the use of the pain VAS before surgery. The global evaluation was rated by patients at the end of the 4-hour study period (T_{4h}) on a 4-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = excellent) (Moller, et al., 2005). If patients experienced insufficient pain relief at any time later than 30 minutes after administration of the study drug, rescue analgesia was provided as intravenous ketorolac (30 mg), and the time of the request was recorded. Safety was assessed by reporting adverse events and the occurrence of gastrointestinal symptoms (nausea, vomiting, gastralgia) throughout the study period. Adverse events were also assessed by infusion site examination and measurement of vital signs.

Statistics

A sample size of 60 patients per group was calculated based on a comparison of the acetaminophen 1 g and 2 g groups with power = 0.8, and α error = 0.05 for the weighted sum of pain intensity differences over a 6-hour period with a 10% dropout rate (Moller, et al., 2005).

All values were calculated as means ± standard deviation (SD) and compared among subjects. Demographics, number of patients requiring rescue analgesia, and adverse events were analyzed using the chi-square test. For pain intensity score of VAS and global evaluation scale, repeated ANOVA, and ANOVA tests were used. SPSS Version 21.0 (IBM Corp., Armonk, NY) was used for statistical analyses. In all analyses, $p < .05$ was taken to indicate statistical significance.