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Original Article

Analgesic efficacy of tramadol/acetaminophen and propoxyphene/acetaminophen for relief of postoperative wound pain

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ABSTRACT

Background/purpose: Weak opioid combined with acetaminophen (APAP) has been proven to provide better analgesic efficacy and cause fewer complications than either drug alone. However, there are questions about whether different opioids, tramadol and propoxyphene, provide similar efficacy or safety. Thus, we investigated Ultracet (37.5 mg tramadol/325 mg APAP) and Depain-X (65 mg propoxyphene/650 mg APAP). The primary aims of this study were to compare the analgesic efficacy and adverse effects of single-dose oral Ultracet versus Depain-X in acute postoperative pain.

Materials and methods: This was a randomized, open-label, active-controlled parallel study on patients with postsurgical pain. Sixty patients who sustained moderate postsurgical pain (visual analog scale^{3}3 cm) after undergoing implantation of venous access were randomized to two groups to receive either Ultracetor Depain-X for postoperative analgesia. Assessment items included pain intensity and pain relief ratings at the first 4 hours, and adverse events.

Results: There were initially 107 patients who were enrolled in this trial, but up to 45 (42.1%) of them were withdrawn during the study. In these 62 patients who complied with treatment (Ultracet: Depain-X = 29: 33), pain relief scale indicated that Ultracet could provide a better analgesic effect than Depain-X provided at1 hour ($p < 0.05$). At 4 hours, the pain score in the Ultracet group was significantly lower than that in the Depain-X group ($p < 0.05$). Adverse events, such as drowsiness, dizziness, and skin itching did not differ in both groups.

Conclusion: Among patients with mild to moderate postoperative wound pain, single-dose Ultracet can provide slightly better analgesic efficacy than Depain-X in terms of onset and duration. Depain-X is no longer marketed in Europe, America, Taiwan and other countries, therefore, Ultracet can serve as a good substitute for treating postoperative pain.

1. Introduction

Clinical evidence has shown that acetaminophen (APAP) combined with weak opioids (codeine, propoxyphene or tramadol) can serve as a first-line analgesic for postoperative pain.[1,2,3,4] Combination of these two sorts of analgesic agents with complementary mechanisms of action may enhance analgesia and at the same time reduce the risk of adverse events.[5] These combination drugs can provide a safe and effective analgesic option for ambulatory surgery.

Propoxyphene is another weak opioid that is structurally similar to methadone. The analgesic efficacy of propoxyphene is one-half to two-thirds as potent as codeine, meaning that 90–120 mg propoxyphene provides pain relief equal to that of 60 mg codeine. Propoxyphene (65 mg) plus 650 mg APAP (Depain-X) has a similar analgesic efficacy to that of 100 mg tramadol but with a lower incidence of adverse effects. [6] Thus, Depain-X is a good analgesic for moderate to severe postsurgical pain.

Tramadol has recently been recommended as first-line analgesic for postsurgical pain because it causes less respiratory depression, cardiac depression, dizziness and drowsiness than morphine does.[7] Use of a combination of 37.5 mg tramadol and 325 mg APAP (Ultracet) allows reduction of tramadol dose, causes a lower incidence of adverse effects, and provides a better analgesic effect. [7] In recent years, most of the therapeutic trials of Ultracet were

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conducted with the dental pain model (pain after removal of impacted third molars), which is a useful clinical model for evaluation of oral analgesics for treatment of acute pain. The results had proven that Ultracet could provide greater relief of dental pain with faster onset and longer duration than either of its constituent agents as monotherapy.[8,9,10] Although this dental pain model is successful, determination of the safety and effectiveness of this new analgesic in other postsurgical pain models warrants investigation.

The objective of these studies was to determine the therapeutic profile (efficacy, onset, duration, and safety) of single-dose Ultracet (tramadol/APAP) and Depain-X (propoxyphene/APAP) for the treatment of postoperative pain after implantation of an intravenous access device (IVAD).

2. Patients and methods

2.1. Patients

This randomized, open-label, active-controlled study had an enrollment of 107 patients aged between 18 and 75 years with an American Society of Anesthesiologists (ASA) physical status I or II. They underwent implantation of and IVAD under total intravenous general anesthesia. The study protocol was approved by the Committee for Human Investigation of National Taiwan University Hospital, and informed consent was obtained from each patient. Patients who had a history of drug abuse, psychiatric disorders, dementia, sleep apnea, or known contraindication to opioids and acetaminophen were excluded. We also excluded pregnant or lactating women, and patients who took tramadol or propoxyphene within 30 days of the proposed operation, or those who used sedatives, antiemetics or antipruritics within 24 hours of the operation.

Patients were allocated randomly into one of the two treatment groups (Ultracet or Depain-X) using a computer-generated randomized number table. Patients were considered to have completed the study if they had received at least one treatment dose and assessments of pain intensity with a 10-cm visual analog scale (VAS), pain relief ratings, and sustained adverse event 4 hours after taking study medication.

2.2. Treatment and assessment

All patients underwent implantation of the same type of port(PORT-A-CATH II Implantable Venous Access Systems; Deltec, Kennett Square, PA, USA), which was made possible with the implantable infusion port introducer kit (Arrow Inc. Mt holly, NY, USA), and through percutaneous infraclavicular landmark, the subclavian vein was accessed. Anesthesia was induced with midazolam and fentanyl, and maintained with propofol infusion. No local anesthesia was performed.

Following the surgical procedure, the subjects with VAS pain score ≥ 3 were administered one tablet of the study drug. The patients were not allowed to take any acetaminophen-containing agent, apart from the study medication for the first 4 hours postoperatively. Four hours after surgery, the patients were allowed to receive supplemental analgesic medication. Those who received supplemental pain medication were considered to withdraw from the study.

Pain intensity was evaluated with a 10-cm VAS at baseline (before the single dose) and at 30 minutes, 1 hour and 4 hours after the single dose of the study medication. Additionally, at 30minutes, 1 hour and 4 hours after the single dose of study drug, the patients were asked to rate the degree of pain relief compared with the pain experienced before taking the single dose of study medication using a six-point scale[11] (4 = complete; 3 = a lot; 2 = moderate; 1 = slight; 0 = none; −1 = worse). Adverse events were also assessed at these time points.

2.3. Statistical methods

Patient characteristics were presented as means ± standard deviation for continuous variables and proportions for categorical variables. The comparison between two groups was tested by Wilcoxon rank-sum test for continuous variables and by χ^2 test for categorical variables. The primary set of analysis data was an intent-to-treat population, that is, having completed post randomization efficacy assessment and taken the study medication. The efficacy variables were the VAS changes from baseline after administration of the single-dose study medication. The changes in VAS for each time point were presented by each group and analyzed by signed-rank test. The comparison between Ultracet and Depain-X was tested by Wilcoxon rank-sum test. The incidence of adverse events was analyzed by χ^2 test and Fisher's exact test. All statistical tests of the efficacy parameters were conducted at the two-sided, 5% significance level. No interim analysis was conducted.

3. Results

3.1. Demographic and baseline pain characteristics

Among the 107 patients who were enrolled, 45 (42.06%) withdrew from the study at their own desire (Fig. 1). Of the patients who withdrew, 21 (38.89%) belonged to the Depain-X group of 54 and 24 (45.28%) belonged to Ultracet group of 53. The withdrawal rate in the two groups did not differ ($p = 0.5029$). The number of intent-to-treat (ITT) patients was 62, and the number in the Depain-X and Ultracet treatments groups was 33 and 29, respectively. The ITT population was defined as the randomized patients who received at least one treatment dose and a baseline pain assessment (VAS value). The number of per-protocol (PP) patients was 57, and the number in the Depain-X and Ultracet treatment groups was 32 and 25, respectively. One patient in the Depain-X group and four in the Ultracet group had protocol deviation in randomization. The PP population was defined as the randomized patients who completed the study without any major deviation.

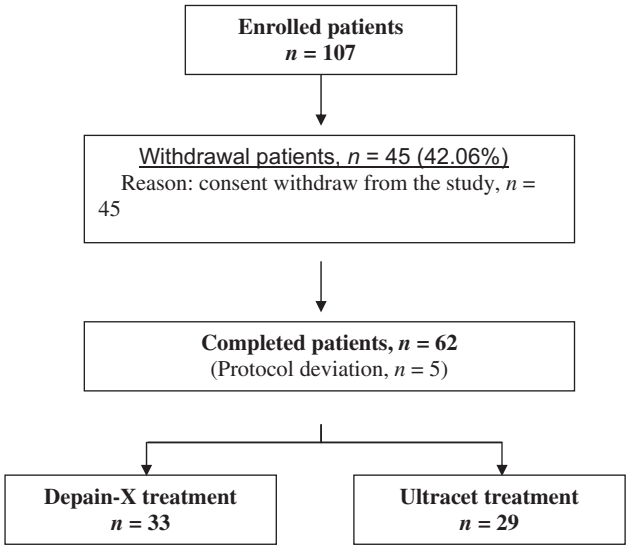

Fig. 1. Disposition of patients.