Pain treatment in patients with acute pancreatitis: A randomized controlled trial

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas in which adjacent tissues and remote organ systems may also be involved. The chief symptom is abdominal pain that is usually associated with severe nausea and vomiting lasting for several days. Severe abdominal pain is mostly reported in the epigastric region or right upper quadrant and in some patients, radiates to the back. It is particularly difficult to establish a diagnosis in the elderly (1-3). The entity generally causes severe and persistent pain, and thus, necessitates effective treatment (4).

Effective treatment of pain is warranted in the management and this does not hamper diagnosis or treatment. An agreement has not yet been reached as to which analgesics are useful in treating pain in patients with AP (4). Opioids are considered an appropriate choice in this context. These drugs are known to decrease the need for supplementary analgesia. Opioids are commonly used to manage pain in patients with AP, although there are some unclear points with regard to their clinical effectiveness and safety (1,4). In contrast, intravenous paracetamol is a cyclooxygenase inhibitor that has been documented to have comparable effectiveness with opioids in the last decades in an emergency setting and in various acute pain patterns (5,6).

In this study, the analgesic effectiveness of tramadol, a synthetic opioid, was compared with paracetamol and dexketoprofen in adult patients with acute pancreatitis in the emergency department.

MATERIALS AND METHODS

Study setting and design

This prospective, randomized, controlled study was conducted in ED of a tertiary care hospital with an annual census of 324,000 adult patients between January
The study enrolled all consecutive adult patients who were referred to ED with acute abdominal pain and were diagnosed with AP after laboratory examination and computed tomography results had been obtained. All patients underwent standard diagnostic and therapeutic procedures that were predetermined in the study protocol. Exclusion criteria were as follows:

- Those with symptoms for >24 h.
- VAS values <40/100 mm
- Ongoing treatment with NSAID (has taken the drug within 24 h)
- Comorbidities such as diabetes mellitus, congestive heart failure, chronic liver failure/cirrhosis, and chronic renal failure
- Those with a history of allergy to paracetamol, dexketoprofen, and/or tramadol
- Those with a history of trauma
- Those who declined to participate in the study

Interventions

All patients were randomized in a 1:1:1 ratio. Random number table was used to allocate patients to either of the three treatment arms. Computerized six randomization blocks were prepared and scheduled by a person blinded to the study. Treatment allocation assignments and numbers were contained in sealed envelopes. Study drugs were identical in color and appearance, enabling the patients’ blindness to the intervention. Study patients were intravenously administered 1000 mg paracetamol (Parol, Atabay, Istanbul, Turkey), 50 mg dexketoprofen trometamol (Arveles, IE Ulagay-Menarini; Istanbul, Turkey), or 1 mg/kg tramadol (Contramal, Abdi Ibrahim, Istanbul, Turkey) in 100 mL normal saline with a 4-5 min infusion. Patients were blinded to the study; thus, the study was conducted in a single-blinded manner. Patients with inadequate pain relief at 30 min were administered morphine sulfate as a rescue drug.

Methods of measurement

A 100-mm visual analog scale (VAS) displaying numbers between 0 and 100 (0 mm, no pain and 100 mm, worst pain) was used to measure pain intensity. Pain measurements of the patients were conducted at baseline (just before administering the drug) and 30 min after the treatment intervention. Patients were blinded to previous VAS scores. Patients were also asked if they required any additional drug at the end of the study. Adverse effects, such as allergic reaction, nausea and vomiting, dyspepsia, and others reported by study subjects, were also recorded in the study form.

Outcome measures

The primary outcome measure was pain relief at 30 min after administering the drug. The secondary outcome measures were the requirement for a rescue drug and adverse effects secondary to study drugs.

Statistical analysis

Study data were analyzed with SPSS, MedCalc, and Confidence Interval Analysis Software (SPSS Inc.; Chicago, IL, USA). Numerical variables were presented as median (interquartile range) and frequent variables as rates. Normality analysis was performed using the Kolmogorov–Smirnov Test. Three-group comparison was conducted using Kruskal–Wallis test. The study data were also presented with respect to confidence intervals. All the hypotheses were constructed as two-tailed, and the alpha critical value was accepted as 0.05.

RESULTS

Of the 116 patients diagnosed with AP, 26 were excluded from the study because of different reasons. Ninety patients (30 in paracetamol group, 30 in dexketoprofen group, and 30 in tramadol group) were enrolled and were included in the final analysis (Figure 1).

The subjects had a mean age of 53.5±13.3 years and 58.9% (n=53) were male. Furthermore, 73.3% (n=66) of patients had documented gallstones and biliary etiology for pancreatitis. The demographical and clinical characteristics of subjects are listed in Table 1.

The subjects were divided into the following three groups: paracetamol, dexketoprofen, and tramadol groups. Mean VAS scores of the three groups at baseline and 30 min were similar. Similarly, the changes in pain scores from baseline to 30 min did not differ among the groups (Table 2).

The changes in pain scores were calculated by subtracting the median scores at baseline and 30 min as pairs. According to the comparison of pain improvements, there were no differences among the groups (dexketoprofen vs. paracetamol, paracetamol vs. tramadol, and dexketoprofen vs. tramadol) (Table 3). In addition, the trends of scores between baseline and 30 min are shown for each group in Figure 2.

Six (20%) patients in the dexketoprofen group, four (13.3%) in the paracetamol group, and three (10%) in the tramadol group required the administration of a rescue drug. Nausea and vomiting were reported by two patients in the dexketoprofen group and by one in the paracetamol group. Furthermore, two patients had nausea and vomiting and one had a short hypotensive episode in the tramadol group.

DISCUSSION

Although not very common in ED, AP almost always necessitates pain treatment. The choice of analgesic is currently not straightforward. This study compared tramadol, which is an opioid that is being more extensively and increasingly (year by year) used in treating severe pain in an acute setting, with two different cyclooxygenase inhibitors with discrete mechanisms.
of action. Findings suggested that there is no significant difference among the treatment arms with regard to analgesic efficacy and the requirement for rescue medication.

Opioids are commonly used in the management of pain caused by AP in ED. These drugs were somewhat avoided because of the fear that they may mask the manifestation and clinical course of the disease, which is currently known to be obsolete because many well-designed studies have demonstrated that they are safe and effective measures in pain treatment. Widespread use of computed tomography also rendered the clinical decision-making very effective and expedient, thereby enabling judicious use of analgesics.

Opioids were also claimed to increase pain because of their spasmogenic effect, which may in turn increase intraluminal pressure in the sphincter of Oddi. However, no clear evidence is obtained from controlled clinical trials that would support this theory (1,7). There is no finding in the literature indicating the superiority of one specific opioid drug to another in pain treatment of patients with AP. Tramadol, an atypical opioid, is a narcotic analgesic and has scarce data in the literature regarding its clinical use.

It works through a combined mechanism of weak l– receptor binding (opioid activity) and the inhibition of serotonin and norepinephrine uptake (nonopioid activity). This dual mechanism of action is considered to underlie its effectiveness in some pain patterns that are poorly responsive to conventional opioids. Tramadol is associated with some adverse events, such as nausea and vomiting (most common), dizziness, headache, hypotension, seizures, and respiratory depression (8). Nausea

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**Figure 1.** Patient flow chart.
and vomiting were the most common side effects that were reported in all groups, although it is difficult to claim that these were caused by the drugs themselves as these complaints are usually associated with AP.

Intravenous paracetamol is a drug extensively used and researched in the ED to treat almost all kinds of pain patterns, including colicky pain caused by hollow viscera and musculo-skeletal pain, and was proven to be effective in an acute setting (5,9,10). Moreover, this study also supports that paracetamol induces efficient analgesia in patients with AP. It should also be noted that a high-dose paracetamol has been accused in triggering drug-induced AP in the literature (11,12).

Dexketoprofen trometamol is an outstanding NSAID as it has high potency and has a rapid absorption rate, short time to peak blood levels, and earlier onset of analgesic efficacy in acute pain treatment. Studies have demonstrated that dexketoprofen reduces pain by decreasing the consumption of rescue opioid administration, and thus, opioid-related side effects after various operations (13). This study failed to demonstrate its superiority over tramadol with respect to efficacy. Recently, some reports have been demonstrated that the combination of dexketoprofen and tramadol was used in treating acute pain patterns with more remarkable results (14).

Limitations
A number of factors prohibited a double-blind design in this study. In addition, study subjects had many different AP etiologies, which may also have had an impact on different pain responses to the interventions. Broader well-designed studies may minimize such difficulties in pain management research in AP.

In conclusion, intravenous paracetamol, dexketoprofen, and tramadol are not superior to each other in the management of pain caused by nontraumatic AP.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Bezmialem Vakif University (2015).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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