IV Dexketoprofen Versus IV Paracetamol in Patients Presenting With Dysmenorrhea to the Emergency Department: A Randomized Controlled Trial

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Background: Dysmenorrhea is one of the most common acute pain disorders among women of reproductive age.

Aims: The present study aimed to compare the effects of intravenous dexketoprofen with intravenous paracetamol in patients presenting with primary dysmenorrhea to the emergency department.

Study Design: Randomized controlled trial.

Methods: Patients over 18 years old who presented with pelvic pain related to menstruation were eligible for the study. Study patients received 1 g paracetamol or 50 mg dexketoprofen in 100 ml normal saline as a 4 to 5 minute intravenous infusion. Pain intensity was measured using a visual analog scale at 15 and 30 minutes. Patients were randomized and assigned to either of the two study arms via sealed envelopes. The study drugs were identical in color, and thus both personnel and patients were blinded to the study drug. The dexketoprofen group comprised 49 patients, and the paracetamol group had 50 patients in the final analysis.

Results: The mean age of study subjects was 20.9±2.5 years, and the mean duration of pain was 1.9±1.7 (median: 1, interquartile range: 1 to 2) hours. Both dexketoprofen (median change: 33, 95% CI: 24 to 38) and paracetamol (median change: 21, 95% CI: 12 to 32) effectively reduced pain at 15 minutes, which was repeated at 30 minutes (median change: 63, 95% CI: 57 to 65 vs 55.5, 95% CI: 50 to 59, respectively). Pain improvement in the dexketoprofen group was better than in the paracetamol group at both 15 (median difference: 8; 95% CI: 0 to 16, p=0.048) and 30 (median difference: 6; 95% confidence interval: 1 to 12, p=0.028) minutes, which reached statistical significance but were not clinically significant.

Conclusion: Intravenous dexketoprofen has better visual analog scale scores at both 15 and 30 minutes compared with intravenous paracetamol but without clinical significance.

Keywords: Dysmenorrhea, dexketoprofen, paracetamol, emergency department, pain treatment

Dysmenorrhea is one of the most common acute pain disorders, affects about 40% to 70% of reproductive-age women, and is a frequent cause of time lost from work or school besides interfering with daily living (1,2). Dysmenorrhea is not uncommon, and in up to 20% of women its severity may influence their daily activities (3).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs used most commonly in the treatment of primary dysmenorrhea. The following NSAIDs are approved by the US Food and Drug Administration for the treatment of dysmenorrhea: diclofenac, ibuprofen, ketoprofen, meclofenamate, mefenamic acid, and naproxen. The use of NSAIDs is related to the findings that prostaglandins have a role in the pathogenesis of dysmenorrhea. Aspirin may not be as effective as these NSAIDs, and paracetamol as adjuvant therapy may be helpful for easing mild symptoms (1,4).

Randomized controlled trials showed that NSAIDs are effective options for easing primary dysmenorrhea. In a systematic review of 73 randomized trials, NSAIDs were significantly more effective than placebo (OR: 4.50, 95% CI: 3.85 to 5.27) or paracetamol (OR: 1.90, 95% CI: 1.05 to 3.44) (1). NSAIDs represent the mainstays of drug therapy. However, there are no randomized trial comparing the effectiveness of paracetamol with that of dexketoprofen as treatment options for patients who present to the emergency department (ED) seeking pain relief because of primary dysmenorrhea.

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Intravenous (IV) paracetamol has shown to be an effective treatment option for various painful conditions in the ED (5-7). The present study aimed to compare the effects of IV paracetamol with IV dexketoprofen in patients who presented with primary dysmenorrhea to the ED.

MATERIALS AND METHODS

Study setting and design

This prospective randomized, double-blind controlled study was conducted in the ED of a tertiary care hospital with an annual census of 75000 patients between December 15, 2014, and April 15, 2015. The central ethics committee approved the study (2014/70177). The clinicaltrial.gov ID is NCT02373514. The study was planned as a superiority trial with two intervention arms, IV dexketoprofen, and IV paracetamol. The funding of the study was provided by the authors.

Selection of participants

Patients over 18 years old who presented with pelvic pain related to menstruation were eligible to participate in the study. All consecutive patients who presented with dysmenorrhea as their chief complaint were enrolled in the study. The analyses focused on the severity of pain, rather than the duration of time it lasted. Patients who had signs of peritoneal irritation, received painkillers within the last six hours, were allergic to the study drugs, had history of renal and liver failure, alcohol or drug abuse. and those who did not provide informed consent were excluded from the study. Patients were enrolled in the study 24 hours/7 days a week. A senior resident determined the eligibility of patients. Diagnosis of dysmenorrhea was made by pelvic pain related to menstruation and the history of painful cycles as it resembled the current one. A normal physical examination without a remarkable pathology was also warranted for the diagnosis.

Interventions

Study patients received 1 g paracetamol (Perfalgan, Bristol Myers, Italy) or 50 mg dexketoprofen (Arveles, Ufsa, Turkey) in 100 mL normal saline administered as an IV infusion over 4 to 5 minutes. Study drugs were identical in color. Assignment of patients to one of the study arms was established on a 1:1 ratio according to eight computerized randomization blocks performed before the study by a person blinded to the study. Patients eligible for the study were assigned to one of the study arms by designating the numbers kept in an opaque envelope. A study nurse prepared the study drug and another nurse, unaware of the study drug, administered it to the patient. The physician, the nurse who administered the drug, and the patients were all blinded to the study drug.

Methods of measurement

A 100 mm visual analog scale (VAS) displaying the numbers as 0,10,20 … 100 (0: no pain; and 100 mm worst pain) was used to measure the intensity of the pain. Pain measurements of patients were carried out at baseline, 15, and 30 minutes after administration of the study drug. Patients were blinded to previous VAS scores. The need for rescue drug and adverse events was also recorded on the study form. Drug-related side effects attributed to either drug were evaluated in detail. Nausea was not accepted as a side effect if it existed before administration of the drug.

Outcome measures

The primary outcome measure was pain relief at 15 and 30 minutes after administration of the drug. Secondary outcome measures were the need for the rescue drug and adverse effects secondary to study drugs.

Statistical analysis

The study data were analyzed with MedCalc, Statistical Package for Social Sciences 18.0 (SPSS Inc.; Chicago, IL, USA) and Confidence Interval Analysis software. Numerical data were presented as mean ± standard deviation and median [interquartile range (IQR)], and frequency data were presented as rates. The study data were also expressed with 95% CI. The normality analysis was performed by a Kolmogorov-Smirnov test. Two group comparisons for numerical data were performed using a Mann-Whitney U test and a chi-square test for frequency data.

A power analysis recommended a sample of 37 patients in each group, for a 95% power and a standard deviation of 19 mm. All hypotheses were constructed as two-tailed, and an alpha critical value of .05 was accepted as significant. All analyses were performed according to the principle of intention to treat.

RESULTS

A total of 133 patients were eligible for the study. Thirty-three patients were excluded from the study for various

reasons, and one patient decided to withdraw from the study after 10 minutes of randomization and left the ED without rating VAS scores (Figure 1). Forty-nine patients in the dexketoprofen group and 50 patients in the paracetamol group were included in the final analysis.

The mean age of study subjects was 20.9±2.5, and the mean duration of pain was 1.9±1.7 (median: 1, IQR: 1 to 2) hours. There was no difference between study groups regarding age and duration of pain (Table 1).

Both dexketoprofen (median change: 33, 95% CI: 24 to 38) and paracetamol (median change: 21, 95% CI: 12 to 32) effectively reduced pain at 15 minutes (Figure 2, Table 2). This same effect was also observed at 30 minutes (median change: 63, 95% CI: 57 to 65) vs 55.5, 95% CI: 50 to 59; respectively) (Table 2, Figure 3). Pain improvement in the dexketoprofen group was better than in the paracetamol group at 15 (median difference: 8; 95% CI: 0 to 16) and 30 (median difference: 6; 95% CI: 1 to 12) minutes, which reached statistical significance but not clinical significance (Table 3).

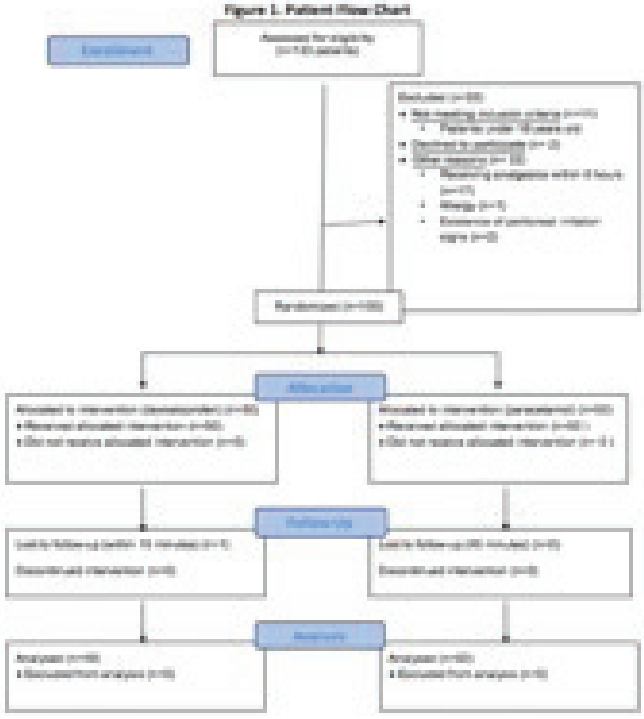

FIG. 1. Patient flow chart.

TABLE 1. Comparison of demographics and rescue drug need of study groups

Variable	Dexketoprofen group median (IQR)	Paracetamol group median (IQR)	p
Age	21 (19 to 22)	21 (19 to 23)	0.34
Duration of pain	1 (1 to 2.3)	1 (1 to 2)	0.76
Rescue drug need (%)	1 (2)	4 (8)	0.37

IQR: interquartile range

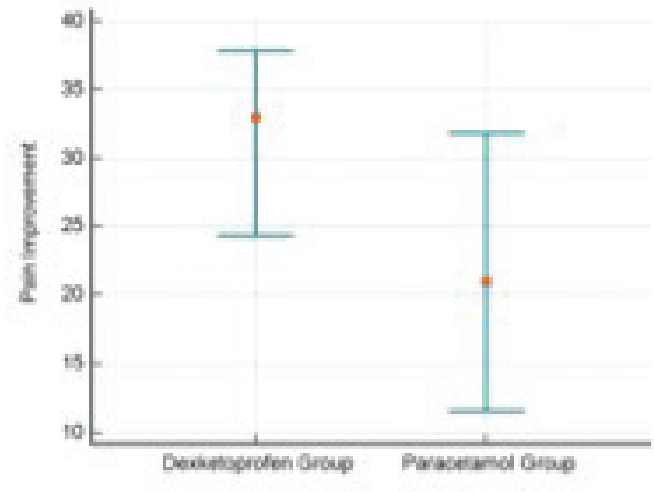

FIG. 2. Fifteen minutes pain improvement in each study group.

TABLE 2. Change in pain intensity at 15 and 30 minutes for each study arm

Variable	Dexketoprofen group	Paracetamol group
Visual analog scale		
Median with IQR		
Baseline	70 (65 to 82)	70.5 (62 to 81)
15 minutes	42 (32 to 53)	48 (38 to 61)
30 minutes	10 (6 to 17)	14.5 (8 to 27)
Change from baseline (VAS)		
Median differences with 95% CI		
15 minutes	33 (24 to 38)	21 (12 to 32)
30 minutes	63 (57 to 65)	55.5 (50 to 59)

VAS: visual analog scale; CI: confidence interval; IQR: interquartile range

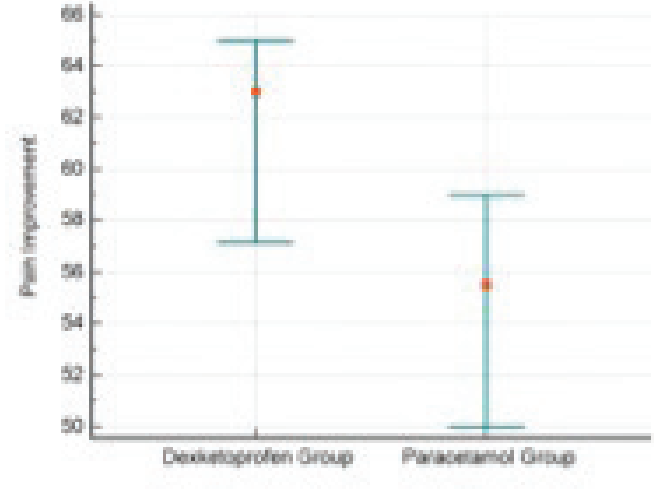

FIG. 3. Thirty minutes pain improvement in each study group.

TABLE 3. Comparison of pain improvements between two groups

Variable	Dexketoprofen vs Paracetamol median (95% CI)	p
Differences from baseline to 15 minutes	8 (0 to 16)	0.048
Differences from baseline to 30 minutes	6 (1 to 12)	0.028

CI: confidence interval

One patient (2%) in the dexketoprofen group and 4 patients (8%) in the paracetamol group needed rescue drug (p=0.37). One patient in the dexketoprofen group reported dry mouth, and there was one patient who had nausea and one patient with nausea and vomiting in the paracetamol group.

DISCUSSION

The present study showed that either IV dexketoprofen or IV paracetamol effectively enabled pain relief in patients who presented to the ED with primary dysmenorrhea. Despite better VAS scores with dexketoprofen at both 15 and 30 minutes when compared with those with paracetamol; this improvement did not reach clinical significance. Dexketoprofen was also associated with a reduced need for rescue drug but without statistical significance.

Dysmenorrhea, which manifests itself as severe cramping abdominal pain, is attributed mainly to high levels of prostaglandins in the body. The mechanism of action of NSAIDs is to decrease the production of prostaglandins by blocking the cyclooxygenase (COX) enzyme. Dexketoprofen is a nonselective NSAID with an aryl-propionic acid group containing the active S-enantiomer of racemic ketoprofen. Dexketoprofen is an NSAID with a relatively short half-life and rapid onset of action (8).

Paracetamol provides its analgesic effect through central anti-nociceptive actions, specifically by inhibiting COX-3, which is a variant of COX-1. Evidence suggests that paracetamol activates serotoninergic descending pathways that inhibit nociceptive signal transmission within the spinal cord. The most significant advantage of paracetamol is that it does not cause gastrointestinal bleeding or dyspepsia (9).

The current medical literature regarding dysmenorrhea consists of studies investigating oral forms of painkillers. We do not have sufficient data regarding the effects of parenteral painkillers in the ED. A Cochrane meta-analysis reported that NSAIDs achieve pain relief between 17% and 95% (mean: 67%) of women with an number of patients needed to treat value of 2.1 compared with placebo for three to five days although gastrointestinal side effects (nausea, vomiting, and/or diarrhea) were still a concern (10). However, it is important to note that paracetamol is the preferred choice among young women for dysmenorrhea worldwide (11). For example, 57% of young women in Hong Kong use paracetamol for dysmenorrhea, which may be related to its safe side effect profile (1).

Despite its antipyretic and analgesic effects, paracetamol has little or no effect on inflammatory pathways.The analgesic effect of paracetamol emerges partly through activation of supraspinal descending serotonergic pathways, but its primary site of action may still be selective with variable inhibition of prostaglandin production (12). IV paracetamol is a safe and effective drug for acute pain management even though its mechanism of action remains a controversial issue. Although most studies are interested in managing postoperative pain, IV paracetamol has been found to be as effective as opioids (5,6). IV paracetamol is believed to differ from both available IV opioids and NSAIDs by not being associated with adverse effects such as nausea, vomiting, and respiratory depression, seen after opioid use, or the platelet dysfunction, gastritis, and renal toxicity that are related to NSAIDs. In the present study, the incidence of side effects was also rare, an observation that might also be related to pain.

A retrospective analysis of patients who presented with dysmenorrhea to the ED by Ayan et al. reported that IV paracetamol produced better pain relief than intramuscular diclofenac sodium at 30 minutes (13). However, the study was a retrospective chart analysis rather than a randomized controlled trial.

It is unclear whether specific NSAIDs are more effective or safer than others. Although some studies have not reported differences in effectiveness, others stated that fenamates (mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamate, bromfenac) might have slightly better efficacy than phenylproprionic acid derivatives (ibuprofen, naproxen). Both fenamates and phenylproprionic acid derivatives inhibit prostaglandin synthesis, but fenamates also block prostaglandin action, which might be responsible for their enhanced effectiveness in some studies (1,14,15). A systematic analysis by Zhang et al. reported that ibuprofen was the NSAID with the most favorable risk-benefit ratio among other NSAIDs and aspirin (1). They also reported that paracetamol was less effective than NSAIDs but emphasized that this was only one study and further studies are needed.

Study limitations

This study has several limitations. First, it is a superiority trial, and we cannot conclude that the two drugs are equal.

One patient withdrew informed consent and left the ED without assigning a pain intensity on the VAS. There is no follow-up data of study patients indicating whether their pain recurred or they attended another medical facility due to dysmenorrhea.

In conclusion, IV dexketoprofen has better VAS scores at both 15 and 30 minutes compared with IV paracetamol but was not clinically significant.

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Conflict of Interest: No conflict of interest was declared by any of the authors.

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