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Original Contribution

Ketoprofen gel improves low back pain in addition to IV dexketoprofen: a randomized placebo-controlled trial☆,☆☆,★

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ABSTRACT

Objective: Oligoanalgesia is common in emergency departments (EDs), and pain management is of concern for ED physicians. The aim of this study was to reveal the effect of ketoprofen gel in patients presenting with mechanical low back pain to the ED.

Method: All the study patients received intravenous dexketoprofen additional to study drugs. After dexketoprofen, 2 g of 2.5% ketoprofen gel or placebo was administered to the site with pain and tenderness. Pain relief at 15 and 30 minutes was measured by visual analog scale scores. Rescue drug need and adverse effects were also recorded.

Results: A total of 140 patients were enrolled into the study. The mean age of the study patients was 35 ± 12, and 56% (n = 79) of them were male. The mean pain reduction at 30 minutes was 52 ± 18 for ketoprofen gel and 37 ± 17 for placebo, and ketoprofen gel was better than placebo at 30 minutes (mean difference, 16 mm; 95% confidence interval, 10-21). Ten patients (14%) in the placebo group and 2 patients (3%) in the ketoprofen gel group needed rescue drug ($P = .35$).

Conclusion: Ketoprofen gel improves pain in patients presenting with mechanical low back pain to ED at 30 minutes in addition to intravenous dexketoprofen when compared to placebo.

1. Introduction

Low back pain (LBP) is one of the leading presentations of patients seeking for pain relief in the emergency department (ED). Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, and skeletal muscle relaxants, commonly used as a combination agent, are the drugs used mostly in treatment of these patients [1].

Ketoprofen is a NSAID with analgesic, antipyretic, and anti-inflammatory effects. Although the oral form of ketoprofen has been used widely in musculoskeletal pain, NSAIDs have well-known adverse effects that are particularly related to long-term use. However, topical form of ketoprofen, which is thought to have no systemic effects, minimizes the risk of systemic adverse effects [2].

The present study aimed to reveal the effect of 2.5% topical ketoprofen (gel form) when added to intravenous (IV) dexketoprofen in patients presenting with mechanical LBP to the ED.

2. Material and method

2.1. Study design and setting

This prospective randomized, double-blind study was carried out in academic EDs of 3 tertiary care hospitals between June and December 2015. The local ethics committee approved the study. The clinicaltrial.gov ID is NCT02491879. The study was designed as an equivalence trial comparing the ketoprofen gel to placebo in addition to IV dexketoprofen.

2.2. Selection of participants

Patients between 18 and 65 years old presenting with mechanical LBP, which is defined as the pain located at the low back region and not radiating to sciatic nerve trace, were accepted to be eligible for the study. Patients were excluded if they had the following criteria: symptoms more 24 hours, visual analog scale (VAS) score of less than 40, positive Loseque test or pain radiating to sciatic nerve distribution, allergy

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to the study drugs, alcohol or drug addiction, pregnancy or lactation, and denied to give inform consent.

Patients were enrolled into the study consequently 24 hours/7 days a week. A senior resident decided the eligibility of the patients.

2.3. Interventions

All the study patients received 50 mg IV dexketoprofen (Fastjel, ARVELES). After IV dexketoprofen, 2 g of 2.5% ketoprofen gel or placebo was administered over the area with pain and tenderness according to the group which the patients being assigned. Placebo was identical to dexketoprofen gel in color, stiffness, and smell. Study drugs were implemented within an area of approximately 5 cm in diameter.

Patients were randomized according to the computerized blocks of 8. The study drugs were preserved in 50-mL syringe labeled as A or B. The only person aware of the representatives of A and B also prepared drugs and was not a part of patient enrollment and drug administration process. If a patient was eligible for the study, the study nursed took a number from an opaque bag displaying one of the letters A or B. In addition, the study drug was administered to the patient by the study nurse considering these numbers. Physicians, nurses, and patients were all blinded to the study drugs.

2.4. Methods of measurement

A 100-mm VAS (0, no pain, and 100 mm, the worst pain) with vertical lines intersecting multiples of 10 was used to measure the intensity of pain. Pain measurements of the patients were carried out at baseline, 15 and 30 minutes after the administration of the study drug. Patients were blinded to the previous VAS scores. Rescue drug needed and side effects also recorded to the study form.

2.5. Outcome measures

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

2.6. Statistical analysis

The study data were analyzed in SPSS software. Numeric variables were presented as mean ± SD; and frequent variables, as rates. Normality analysis was performed by Kolmogorov-Smirnov test, and improvements in pain score were depicted by mean and 95% confidence intervals (CIs). All variables depicting pain differences other than reduction of VAS at 15 minutes in placebo group was distributed normally. Two-group comparison for numeric variables was performed by the Student *t* test and χ^2 test with continuity correction for categorical variables. For a 17-mm SD and an equivalence limit of 10 mm with 90% power, at least 63 patients are needed apiece. All the analyses were performed according to the intention-to-treat principle. All the hypotheses were constructed as 2 tailed, and an α critical value of .05 was accepted as significant.

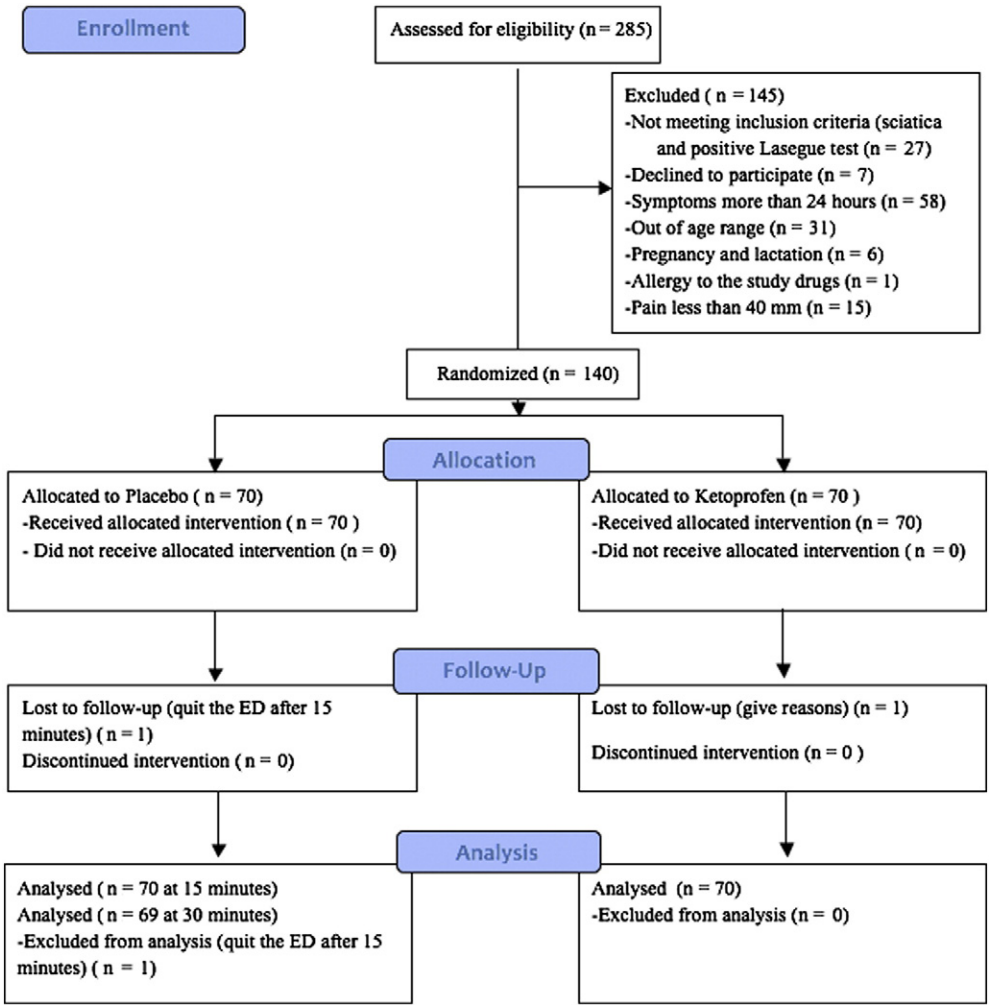

Fig. 1. Patient flow chart.

Table 1
Visual analog scale scores at various time points and change in pain intensity at 15 and 30 minutes for each study arm

Variable	Ketoprofen group	Placebo group
VAS, mean ± SD		
Baseline	74 ± 13	77 ± 14
15 min	47 ± 16	49 ± 20
30 min	21 ± 14	40 ± 20
Change from baseline (VAS), mean (95% CI)		
15 min	27 (24-30)	28 (25-31)
30 min	52 (48-57)	37 (33-41)

3. Results

A total 285 patients were eligible for the study, and 145 patients were excluded from the study for various reasons (Fig. 1). One hundred forty patients composed the population, but 1 patient in placebo group quit the ED after 15 minutes leading to the lack of 30th minute data. The mean age of the study patients was 35 ± 12, and 56% (n = 79) of them were male.

The mean pain reduction in ketoprofen (27 ± 13 mm) and placebo (28 ± 13) groups at 15 minutes was similar (Table 1). However, the mean pain reduction at 30 minutes was 52 ± 18 and 37 ± 17, respectively. (See Figure 2).

Although there was no difference considering the pain reduction at 15 minutes between 2 groups (mean difference, 0.5 mm; 95% CI, −4 to 5), ketoprofen gel was better than placebo at 30 minutes (mean difference, 16 mm; 95% CI, 10-21). (See Table 2).

Ten patients (14%) in the placebo group and 2 patients (3%) in the ketoprofen gel group needed rescue drug ($P = .35$). One patient in the placebo group stated nausea; and 1 patient in the ketoprofen gel group, vertigo.

4. Discussion

This study shows that the use of 2.5% topical ketoprofen gel additional to IV dexketoprofen is associated with a significant pain reduction at 30 minutes in patients presenting with LBP to the ED.

Topical application of NSAID gels is not a common choice for providing analgesia in EDs. Intravenous and intramuscular NSAIDs and opioids are the main agents being used for pain management. However, topical agents might be an option for ceasing pain because of their safer profile and topical analgesic effect on the peripheral nervous system. Studies have shown that topical NSAIDs penetrate the skin and distribute to the target tissues beneath the application site. The systemic absorption of topical agents is minimal resulting in less adverse events [3,4].

Patients with LBP commonly present to the ED. Although the IV and oral NSAIDs are effective choices for LBP, they might be associated with adverse effects such as ulceration and bleeding in gastrointestinal system, impairment of renal function, and hepatic failure. Several studies have reported that topical NSAIDs (ketoprofen gel or patch, ibuprofen gel or cream, and diclofenac gel or patch) effectively inhibit cyclooxygenase 2 at the tissue level while reducing pain and risk of systemic toxicity. Despite the aforementioned data, routine use of topical NSAIDs for ED patients is still controversial [5–7]. A current Cochrane meta-analysis by Derry et al [7] reported the effects of topical nonsteroidal anti-inflammatory agents in acute musculoskeletal pain including sprains, strains, or sports or overuse-type injuries. They included studies with dichotomized outcomes, defined as successful treatment, rather than outcomes in average. Seven trials studied topical ketoprofen with approximately 700 patients included into the meta-analysis, and the number of patients needed to treat for a successful treatment was reported as 3.9. When compared all the nonsteroidal anti-inflammatory topical agents to placebo for adverse effects by including more than 6000 patients, there was no difference either for local or systemic adverse effects [7].

Achieving a rapid pain relief is crucial in ED. However, the present study showed that topical ketoprofen is not superior to placebo at 15 minutes despite the 30-sminute efficiency. This finding may be indicating a slow onset of effectivity that needs to be clarified by further studies. Slow onset of action may hinder the use of an analgesic as a single agent.

One patient in each group reported adverse effects, nausea, and vertigo. However, these were most likely related to the pain or IV dexketoprofen rather than the topical ketoprofen.

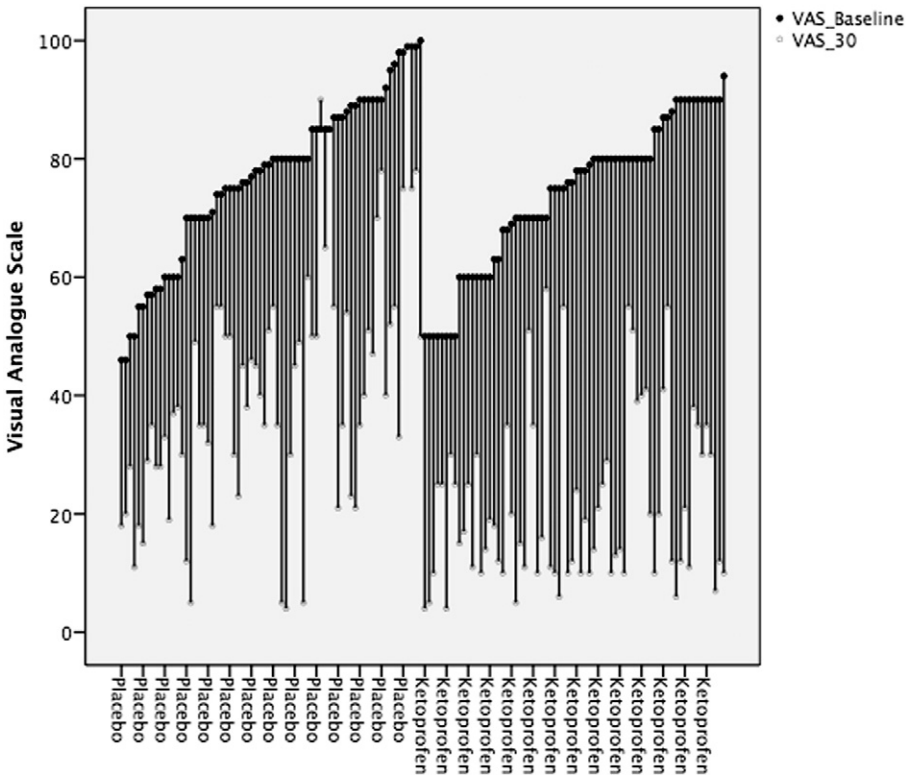

Fig. 2. Parallel line plot of study arms at baseline and 30 minutes.

Table 2
Comparison of pain improvements between 2 groups at 15 and 30 minutes

Variable	Placebo vs ketoprofen	*P*
Differences from baseline to 15 min, mean (95% CI)	0.5 (−4 to 5)	.8
Differences from baseline to 30 min, mean (95% CI)	16 (10-21)	.000

5. Limitation

There are several limitations to this study. Although the study was designed as an equivalence trial, the sample size is not so big that may lead the findings prone to random error. Pain scores after 30 minutes were not measured in the present study, and progress of the effect of topical ketoprofen is not known.

6. Conclusion

In conclusion, concomitant administration of topical ketoprofen gel and IV dexketoprofen is a simple, well-tolerated therapeutic and effective option with no serious local or systemic side effects for the treatment of LBP in ED.

Acknowledgment

The authors disclose that there is no conflict interest.

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