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Original Article

Efficacy measurement of ketorolac in reducing the severity of headache

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Abstract

Objective: One of nonsteroidal anti-inflammatory drugs (NSAIDs) named as ketorolac is frequently used to relieve acute pain. Current study was conducted with the aim of ketorolac efficacy measurement as a pain killer agent for controlling the primary headache in emergency departments.

Methods: In this study, we enrolled 50 patients with primary headache who received 60 mg ketorolac intravenously as a slow infusion in about 10 minutes. Pain scores were evaluated with visual analog scale (VAS) on arrival and also 1 hour and 2 hours after ketorolac infusion. Statistical analysis was performed on collected data by using Wilcoxon and Mann-Whitney tests to assess the differences in VAS pain scores.

Results: Decreasing the VAS more than 3 points from the arrival until 1 hour ($P<0.001$), and more than 5 points from the arrival until 2 hours after ketorolac administration ($P<0.001$) were seen. Those with history of analgesic use before admission in emergency department in comparison with the others did not accompany with more decline in pain score after 1 hour ($P=0.34$) or 2 hours ($P=0.92$).

Conclusion: It seems that ketorolac is assured, safe and well tolerated agent for pain control in patients presented with primary headache to the emergency departments. Based on the results achieved in this study, ketorolac illustrates its perceptible effects within 1 hour after administration that even more prominent after 2 hours.

Keywords: Ketorolac, Headache, Pain management, Emergency medicine

Introduction

Headache is an omniscient illness with a lifetime prevalence rate reaching 90% (1). There are several types of headaches, so that 150 diagnostic headache categories have been defined. Most patients arriving in the emergency department (ED), suffering from severe headache require a rapid and an effective release from their symptoms (2, 3). There are frequent guidelines for management of acute headaches that generally recommended several different agents, such as dihydroergotamine, triptans, phenothiazines, opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) (4-6). Ketorolac is one of NSAIDs which has been tested several times in randomized clinical trials and recommended as an effective agent for patients with pain (7-11). However the search is still on. Ketorolac accepted as an alternative to non-steroidal analgesics and also opioid in controlling moderate to severe pain (12). About 2 decades before, it was thought that although ketorolac has a considerable analgesic effect, but has restriction for application as a fast pain abortive in the ED (13). Some other believed that this drug could be considered as a useful adjuvant, or alternative for opioids in subjects with moderate to severe pain (14, 15). Thinking that different types of headaches involve the same inflammatory component in their pathophysiology, ketorolac is expected to be effective. This agent is an efficient non-narcotic pain killer with intermediate anti-inflammatory effect. Therefore consider as a preferable option for pain management of different type of primary headache cases admitted to the ED (16-19). Current study was conducted with the aim of ketorolac efficacy measurement as a non-narcotic anti-inflammatory pain killer agent for controlling the primary headache in of patients presented to the ED with all types of primary headaches.

Methods

Patients with any kind of primary headache admitted to the ED of Shohadaye Tajrish hospital in Tehran, Iran were

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participated in this study.

All patients in 18-60 years old age range with complaint of moderate to severe headache (pain score>5) that indicated for intravenous treatment were included.

Patients with positive history for any of the following items were excluded: breast feeding, pregnancy, active peptic ulcer disease, coagulopathy, inflammatory bowel disease, renal failure or hepatic failure.

The pain scores were recorded on arrival based on visual analog scale (VAS) and those with the score more than 5 received 60 mg ketorolac intravenously as a slow infusion in about 10 minutes. All were considered for any possible side effects including irritability, itching, pain on injection, hypertension, tachycardia, nausea and/or vomiting. If any happened then process had to be stop. One and 2 hours after injection of medication to the patients, they were asked about their pain scores again. Decreasing more than 3 scores in pain scale was considered as proper response.

SPSS version 22 was used for performing the statistical analysis. For describing continuous variables mean, median, interquartile range, and standard deviation were used. For analyzing the differences in registered pain scores, Mann-Whitney U and Wilcoxon tests were used. For describing categorical variables, frequency and percentage were used. $P \leq 0.05$ was considered as meaningful level.

Results

Fifty patients with the mean age of 30.14±11.4 years old were involved. From the participants, 22 patients (44%) were male and 28 patients (56%) were female. It should be mentioned that 28 (56%) patients did not use any kind of analgesic before arrival to the ED. From other 22 patients (44%) who had already taken other medication, almost all of them had used acetaminophen or different type of NSAIDs. The mean ± standard deviation period from taking other medication to ketorolac administration was 2.77 ± 1.9 hours. The VAS median reduced significantly from 8.0 ± 2.0 to 5.0 ± 4.0 after 1 hour and to 3.0 ± 2.0 after 2 hours (Figure 1).

Significant VAS drop (>3 points, >35%) was reported from baseline until 1 hour after ketorolac administration (Wilcoxon test Z = –6.1; $P < 0.001$). One hour later, more decline (>6 points, >60%) was seen (Wilcoxon test Z = –6.1; $P < 0.001$). There was also a statistical significant difference between VAS at 1 hour and 2 hours after drug administration (Wilcoxon test Z = –4.2; $P < 0.001$).

To assess the possible effect of medication use before arrival to the ED, enrolled patients were divided into 2 groups according to taking previous medication or not. Statistical analysis did not reveal significant difference between the groups. The P values related to comparison of VAS between two groups at baseline, 1 hour and 2 hours after ketorolac administration were 0.51, 0.62, and 0.69, respectively. There was also no significant statistical difference between the groups in terms of VAS reducing 1 hour ($P = 0.34$) and 2 hours ($P = 0.92$) after ketorolac administration (Figure 2).

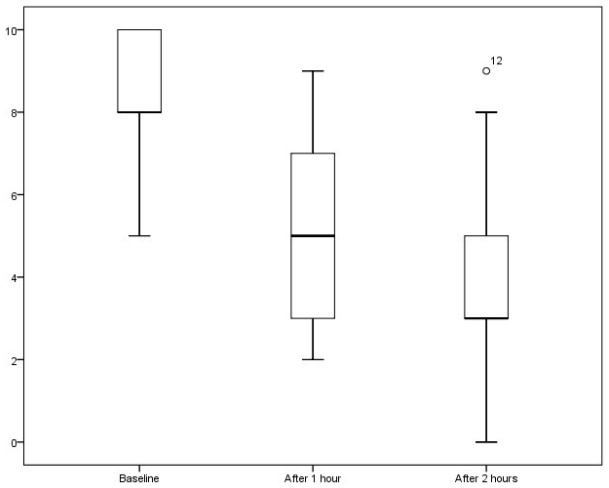

Figure 1. Minimum, maximum, median and interquartile range of visual analogue scale at baseline, 1 hour and 2 hours after ketorolac intravenous infusion.

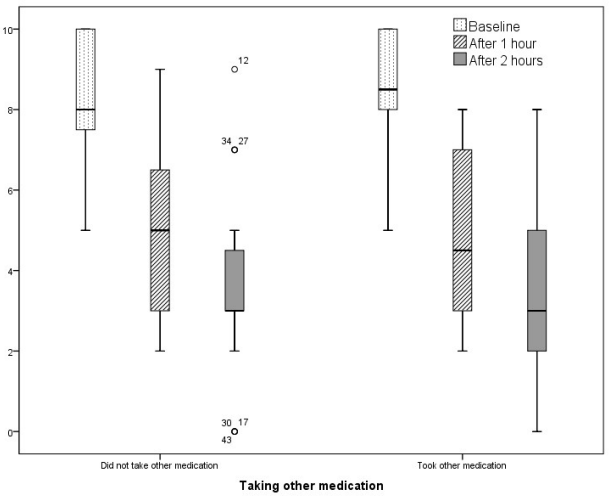

Figure 2. Minimum, maximum, median and interquartile range of visual analogue scale at baseline, one hour and two hours after ketorolac intravenous infusion for patients who took analgesic before arrival and those who did not.

Discussion

Based on findings of the current study, significant decreasing of pain score was seen from baseline to 1 hour and 2 hours after ketorolac administration. This improvement was obtained in almost all cases except two patients whose VAS did not improve well even after 2 hours. The intravenous ketorolac accompanied with significant success rate so that lead to more than 3 points decline in VAS after one hour and more than 5 points after 2 hours.

All patients were observed for about 6 hours after drug administration for possible short time side effects and also replace of headache. Fortunately, there was no case of such complications, which can confirm the safety and effec-

tiveness of intravenous ketorolac in the enrolled patients. According the rigorous intended inclusion and exclusion criteria for selecting patients in this study, results should be interpreted with caution.

Parenteral ketorolac is frequently used for abortive treatment of moderate to severe headache. As a NSAID, ketorolac mechanism of action is inhibition of prostaglandin synthesis by non-selective inhibition of cyclooxygenase enzyme.

Ketorolac were used in several studies, so supporting and opposing comments has been proposed. In a pilot study, 60 mg intramuscular ketorolac was administered to twelve patients with headache crisis. All patients showed statistically significant improvement on their McGill pain questionnaire and authors recommended this drug as a possible useful agent in the treatment of such patients (20).

Intravenous ketorolac was compared with nasal sumatriptan in a prospective double-blind study that performed on patients with complaint of migraine headache. Authors reported that although both drugs significantly reduced the pain, but intravenous ketorolac was more effective than nasal sumatriptan in this regard (21).

In a controlled trial, intramuscular ketorolac was compared with meperidine plus promethazine, and also normal saline as a placebo in tension headache. The authors reported that ketorolac was superior to placebo at 0.5 and 1 hour and superior to meperidine at 2 hours (22). Interestingly, these authors had conducted the same study on acute headache crises 2 years earlier and had reported that using all three options could lead to significant pain control, but the amount did not differ among them (23).

In a non-interventional non-randomized survey on pain management, intramuscular ketorolac and oral ibuprofen were compared. The authors of the mentioned study concluded that both option produced similar pain relief in dealing with acute pain in ED. They believed that ketorolac did not have certain superiority than ibuprofen for this aim (24).

In another study which performed on patients presenting with migraine headache, it was shown that one dose injection of ketorolac can lead to significant decrease in headache symptoms after 1 hour in most participants (25).

In a randomized trial for comparing the effectiveness of intravenous ketorolac, metoclopramide, and valproate sodium for management of acute migraine headache, it was concluded that ketorolac was superior to valproate sodium but less efficacious than metoclopramide (26).

Intravenous ketorolac was also compared with intravenous diphenhydramine plus metoclopramide for treatment of some primary headaches. The study concluded that for adults who presented to an ED with non-migraine, non-cluster primary headaches, intravenous diphenhydramine plus metoclopramide have better efficacy than intravenous ketorolac (27).

Using a standard measuring tool like VAS and the precise selection of patients can be considered as the strengths in this study. On the other hand, short time follow up period is one of the limitations. Considering a control group, escalating doses, larger population, and describing non-responders patients to ketorolac are recommended for future research.

Conclusion

It seems that ketorolac is assured, safe and well tolerated agent for pain control in patients presented with primary headache to the EDs. Based on the results achieved in this study, ketorolac illustrates its perceptible effects within 1 hour after administration that even more prominent after 2 hours.

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Ethical issues

This study was done with respect of Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. All eligible patients were enrolled only after signing the informed consent. Study protocol was assessed and approved by the ethical committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. This study is a fundamental part of a clinical trial registered at Iranian Registry of Clinical Trials (code: IRCT2013120315640N1).

Authors' contributions

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. This study was a part of Dr. Sadegh Hasani's thesis as general physician course at Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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