

Comparison the Efficacy of Intranasal Ketamine Versus Intravenous Ketorolac on Acute Non-traumatic Headaches: A Randomized Double-Blind Clinical Trial

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Abstract

Introduction: Non-traumatic headaches are one of the most common causes of referral to hospital emergency. This study aimed to compare the efficacy of intranasal ketamine and intravenous ketorolac on acute non-traumatic headaches.

Methods: This randomized and double-blind clinical trial in 2019 years. 140 people were randomly divided into intranasal ketamine (A) and intravenous ketorolac (B). Group (A) received ketamine intranasal (0.75 mg/kg, max 75mg), and group B received intravenous ketorolac (30 mg). Headache severity was measured on arrival, 30, 60, and 120 minutes after intervention with Visual Analogue Scale (VAS). The side effects were recorded an hour after the intervention.

Result: The mean difference of pain intensity 30, 60, and 120 minutes after the intervention between the two groups were statistically significant ($p < 0.001$). In the first 30 minutes, significant changes were observed in the VAS levels of the two groups. These changes were more and significant in the intranasal ketamine group ($p < 0.001$). Side effects such as fatigue, dizziness, public discomfort, nausea, increased heart rate, and hypertension were significantly higher in the ketamine group ($p < 0.05$).

Conclusion: Intranasal ketamine and intravenous ketorolac both effectively reduced headaches. However, more analgesic effects of intranasal ketamine in a short time can be considered as a selective approach to reducing headaches.

Trial registration: IRCT20180108038276N3, Registered 29 September 2019.

Introduction

Headache is one of the most common complaints of patients referring to outpatient clinics and emergency departments (1). About 50% of the world's population encounters headaches; this has led to the WHO's concerns. In patients referred to the emergency department (ED), the prevalence of non-traumatic headaches is 0.5% to 5.4%, which is considered a big diagnostic challenge (3). The treatment methods used to treat and control headaches are varied and include pharmacological and non-pharmacological treatments. Among pharmacological treatments can be noted to use narcotics and acetaminophen (4, 5). Due to the special limitations that sometimes have with narcotic use (e.g., respiratory problems, nausea, and vomiting), today, newer drugs are being used that effectively reduce pain and have fewer side effects (6). Ketamine is one of the most commonly used medications to control pain in the emergency room and is injected into intramuscular, intravenous, and intranasal forms (7, 8). Ketamine, in addition to a significant reduction in pain, it has also been introduced as an effective remedy for headache control (9, 10). Ketorolac is another common drug used in an emergency for headaches management and is used in intramuscular, intravenous, or oral forms (11, 12). Numerous studies have been performed to evaluate these drugs' effectiveness, but so far, no recommended drug in this regard has been selected (9, 13–17).

Given that so far, no study has been done to compare the efficacy of intranasal ketamine and intravenous ketorolac on the severity of headache, and also, to provide effective and useful evidence in decision making for better and practical intervention to headache management, the present study was designed to compare the efficacy of intranasal ketamine and intravenous ketorolac on acute non-traumatic headaches.

Materials And Methods

Study Design

The present study was a randomized, double-blind clinical trial with parallel design and a 1:1 allocation ratio in the intranasal ketamine and intravenous ketorolac groups. The study was conducted based on the CONSORT guidelines.

Sample and sampling method

The study population included all patients with non - traumatic acute headaches referred to Imam Reza Hospital based in Kermanshah, Iran. The sample size is calculated according to Meredith et al.s' and Zitek et al.s' studies with the confidence level of 95% and the test power of 80% (17, 18). The number of samples required in each group was 35 subjects. In order to increase the reliability and ensure sufficient study power, 70 subjects were assigned to each group. Thus, 140 subjects in total were considered in the study. Among these samples, 70 were considered for the ketamine intranasal intervention group and 70 for the intravenous ketorolac intervention group. The inclusion criteria were primary (Migraine, tension, and cluster)(19), being in the 18–65 age group, with self-reported severity of 4 or greater on a Visual Analogue Scale (VAS) (0–10), and willingness to participate in the study. Exclusion criteria were weight < 45 kg or > 115 kg, vital sign abnormalities including heart rate < 50 beats/min or > 150 beats/min, systolic blood pressure < 80 or > 200 mm Hg, oxygen saturation < 92%, or respiratory rate < 8 or > 30 breaths/min, patient with a history of alcohol abuse, intracranial hypertension, ischemic heart disease, human immunodeficiency virus or immunosuppression, a renal disease requiring dialysis, liver disease, poorly controlled thyroid disease, active bleeding, or current use of anticoagulants (20). Also, patients with Functional neurological disorder (FND), headache with an impaired level of consciousness, headaches with comorbidity, pregnant and lactating women were excluded from our study.

Measurement instrument

The study instrument included a questionnaire consisting of 3 parts. The first part was related to the demographic information (including age, sex, history of drug sensitivity, and history of headache). In the second part, the heart rate, blood pressure, fatigue, dizziness, general discomfort, and nausea were recorded one hour after the intervention. The third section was devoted to recording patients' pain scales based on VAS before prescribing the drug, 30 minutes, 60 minutes, and 120 minutes after receiving the drug. Visual Analogue Scale (VAS) is the same pain ruler with a horizontal line graded from 0 to 10 (21). VAS is the most widely used and easiest means of measuring the pain in the world, whose validity and

reliability, both English and Persian versions, have been reviewed and approved in previous studies(22,23). 0 non-pain, 1-3 mild pain, 4-6 moderate pain, 9-7 severe pain, and 10 indicate the most severe pain according to this tool (24,25).

Intervention

Approval was first obtained from the Ethical Review Committee of Kermanshah University of Medical Sciences (KUMS), and then sampling was conducted. After taking a history and physical examination of patients by the emergency medicine resident and evaluation them in terms of inclusion and exclusion criteria, qualified samples were entered into the study. The sampling method was simple random. After identifying the qualified patients, they were randomly assigned a specific three-digit code. The last digit on the right of the three-digit code determined the patient's group. If this number was 0, 1, 2, 3, or 4, patients belonged to the intravenous ketorolac group, and if it was 5, 6, 7, 8, or 9, they it belonged to the intranasal ketamine group. Thus, 70 people were assigned to the intranasal ketamine group, and 70 people were assigned to the intravenous ketorolac group. At first, the socio-demographic information form and the pain intensity of the patients were completed and recorded. After a practiced nurse placed the IV, ketorolac-treated patients received 30 mg IV ketorolac, and ketamine -treated patients received 0.75 mg/kg (maximum 75 mg) intranasal ketamine via a MAD Nasal™ intranasal mucosal atomization device affixed to a 10-cc syringe (Teleflex Medical Europe Ltd, Westmeath, Ireland) (20, 26). A specific medication was prepared, and its dose was determined by the triage nurse based on the patient's code. It was administered by the emergency physician, who was unaware of the study protocol. Subjects allocated to the intranasal ketamine arm received 1000 mL of normal saline in a bag identical to that administered to the intravenous ketorolac arm for subject blinding. Subjects in the intravenous ketorolac arm also inhaled a dose of atomized intranasal saline (0.015 mL/kg, maximum 1.5 mL) via a MAD Nasal™ intranasal mucosal atomization device affixed to a 10-cc syringe (Teleflex Medical Europe Ltd, Westmeath, Ireland). We did not blind nursing staff to the patients' medications, though we did blind patients and investigators.

Outcome

The VAS (from 0 cm: painless to 10 cm: the most severe pain) was used to measure the pain. On arrival, 30, 60, and 120 minutes after intervention, the sheet containing VAS was given to patients and asked to mark their level of pain. Also, the side effects of the drugs were recorded one hour after the intervention. The patients were asked to report if they have any side effects. These side effects included fatigue, dizziness, general discomfort, and nausea (20, 27). In addition to these side effects, increased heart rate and blood pressure were measured and recorded (28). The patients also were asked to inform the investigator if they have any other unpleasant sensation.

Data Analysis

Data analysis was performed with descriptive statistics (mean, percentage and standard deviation), and analytical statistics Kolmogorov-Smirnov test, Kruskal-Wallis test, Wilcoxon signed-rank test, Mann-

Whitney U test), and SPSS statistical software version 18.0 (SPSS Inc., Chicago, IL, USA). First, the normality of the data was investigated by Kolmogorov-Smirnov test. In order to compare the pain severity in different time ranges, repeated measures of ANOVA, and to compare the side effects between the two groups, t-test was used. The significance level was set at < 0.05 .

Ethical considerations

Approval was obtained from the Ethical Review Committee of Kermanshah University of Medical Sciences with reference number: IR.KUMS.REC.1398.068, and also registered at the Iranian Registry of Clinical Trials on 29 September 2019, with the registration number: IRCT20180108038276N3, and URL:(<https://en.irct.ir/trial/41516>). Details of the study included the aim, intervention process, and confidentiality of the explicitly described information to all subjects. Subjects that were willing to participate in this study entered the study after obtaining written consent.

Results

Three hundred people expressed willingness to participate in the study, 102 of whom were excluded from the study due to lack of inclusion criteria. Eighteen patients refused to participate in the study, and finally, out of 140 eligible patients, 70 patients were randomly assigned to the intranasal ketamine group and another 70 to the intravenous ketorolac group (Fig. 1). The mean age of the study patients was 41.6 ± 16.6 years. The age, sex, medical history, history of drug sensitivity, and history of the two groups' headache did not show significant differences (Table 1).

Table 1
Patient Baseline Characteristics.

Characteristic	Ketamine	Ketorolac	P value
Sex			0.865
male	32(45.7)	33(47.1)	
female	38(55.3)	37(52.9)	
Age			0.594
<30	23(32.9)	23(32.9)	
40 – 31	10(14.3)	18(25.7)	
41–60	11(15.7)	14(20)	
> 60	26(37.1)	15(21.4)	
Drug history			0.080
yes	11(16)	24(34)	
no	59(84)	46(64)	
Sensitivity drug history			0.080
yes	0(0)	3(4)	
no	70(100)	67(96)	
Headache history			0.716
yes	47(67)	49(70)	
no	23(33)	21(30)	
Values are presented as number (%).			

The mean pain intensity of the two groups at all time points was significantly different, according to Repeated-measures ANOVA ($P < 0.001$). According to this test, the ketamine group's pain intensity was lower than the ketorolac group at all time points except the 120th minute. The mean reduction of pain intensity in the first 30 minutes in the ketamine group (4.53 ± 1.25) was higher than the ketorolac group (4.03 ± 0.98), which was a significant difference ($p = 0.003$). The greatest decrease in pain intensity was observed in the first 60 minutes in the ketorolac group (6.58 ± 1.03), which was also significantly different ($p = 0.005$). The mean reduction of pain intensity in the ketorolac and ketamine group after 120 minutes was (8.01 ± 0.69) and (6.90 ± 1.20), respectively, significant differences were detected between the two groups ($p < 0.001$). Between 60 and 120 minutes, the mean reduction of pain severity in the ketorolac

group (0.69 ± 1.43) was greater than the ketamine group (0.42 ± 0.97), which was a significant difference (Table 2).

Table 2
Pain Score of Subjects at Different Time Intervals Based on Visual Analogue Scale

Time	Ketamine (n = 70)		Ketorolac (n = 70)		P value
	Mean \pm SD	Median (IQR)	Mean \pm SD	Median (IQR)	
On arrival	8.00 \pm 1.1	8.0 (2.0)	9.01 \pm 0.7	9.0 (3.0)	< 0.001
30	3.47 \pm 0.5	3.0 (1.0)	4.98 \pm 0.7	5.0 (0.0)	< 0.001
60	2.07 \pm 0.2	2.0 (0.0)	2.42 \pm 0.7	2.0 (1.0)	< 0.001
120	1.10 \pm 0.3	1.0 (0.0)	1.00 \pm 0.0	0.0 (0.0)	< 0.001
Pain reduction until 30th minute	4.53 \pm 1.25	4.5(4,5)	4.03 \pm 0.98	4(3,5)	0.003
Pain reduction until 60th minute	5.93 \pm 1.15	6(5,7)	6.58 \pm 1.03	7(6,7)	0.005
Pain reduction until 120th minute	6.9 \pm 1.22	7(6,7)	8.01 \pm 0.69	8(8,8)	< 0.0001
Pain reduction 60 to 120th minute	0.97 \pm 0.42	1 (1,1)	1.43 \pm 0.69	1(1,2)	< 0.0001
SD = standard deviation; IQR = interquartile					

A two-way comparison of the mean pain intensity in patients in both groups at different time points showed that the pain intensity in both groups decreased within 120 minutes, which was statistically significant ($p < 0.001$) (Fig. 2).

Side effects

No subjects were excluded from the study due to side effects. Dizziness, nausea, increased heart rate, and increased blood pressure were statistically significant differences between the ketamine and ketorolac group ($p < 0.05$). Among all the side effects, the most and the least side effects were related to increased heart rate and general discomfort, respectively. Generally side effects were greater in the ketamine group. Details of side effects have been reported in Table 3.

Table 3
Frequency of side effects in the study population

Side effect	Ketamine (n = 70)	Ketorolac (n = 70)	P value
Fatigue	5(7.14)	2 (2.86)	0.245
Dizziness	11(15.71)	2 (2.86)	0.009
Discomfort (generalized)	2 (2.86)	0	0.154
Nausea	8(11.43)	2 (2.86)	0.049
HR rising	28(40.00)	11 (15.71)	0.001
Blood pressure rising	9 (12.86)	23 (32.86)	0.005
Other	2 (2.86)	4 (5.71)	0.404
Values are presented as number (%).			

Discussion

The present study was conducted to compare the efficacy of intranasal ketamine and intravenous ketorolac on acute non-traumatic headaches in patients referred to the emergency department. The results showed that intranasal ketamine and intravenous ketorolac effectively and almost similarly reduced patients' headaches, while ketamine in the short term and ketorolac in the long term further reduced the severity of pain. Also, side effects such as fatigue, dizziness, general malaise, nausea, and increased heart rate caused by ketamine were far greater than ketorolac. Non-traumatic headaches are one of the most common complaints of patients referred to emergency departments (29). NSAIDs, neuroleptics, magnesium sulfate, and tryptan are used to manage and treat headaches (30). Ketamine is used as a sedative drug to manage and treat headaches (15, 17, 31). Sadove et al. were among the first to study the effect of low-dose ketamine (32). However, the effectiveness of ketamine as an analgesic is still being discussed. Various studies have shown the antifungal effectiveness of ketamine is stronger than the analgesic effect (33, 34). Few studies have examined the effect of intranasal ketamine on the severity of headaches. The present study results showed that in the first 30 minutes, ketamine intranasal reduced the severity of pain more than intravenous ketorolac. Andolfatto et al., in their study on the effectiveness of intranasal ketamine for analgesia in the emergency department patients, found that intranasal ketamine reduced the VAS pain score in 88% of patients in the emergency department and relieved the pain quickly and effectively(35). Shrestha et al. (2016), the effect of ketamine intranasal on treating patients with severe pain in the emergency department was investigated; the results indicated a significant reduction in the severity of pain in patients (36). Additionally, Benish in a study compared analgesia with metoclopramide and diphenhydramine versus intranasal ketamine on patients with primary headache. The results showed that VAS changes were greater after 30 min in the ketamine group (29.0 mm) compared to the metoclopramide-diphenhydramine group (22.2 mm) (20). One of the most

important advantages of ketamine is its various prescription methods (20, 37). The Ketamine acts through various mechanisms, including the supraspinal mechanisms, cholinergic and monoamine effects, local anesthetic action, sigma receptor interaction, and NMDA receptor antagonism (34). These mechanisms can be accompanied by favorable or unfavorable clinical effects (38). Among the favorable effects can be noted to the lack of inducing platelet function disorders and the suitable replacement for morphine in patients with asthma (due to histamine release in response to morphine) (34, 39). Adverse effects of ketamine may manifest in various forms, including increased systolic blood pressure, tachycardia, nausea, vomiting, fatigue, dizziness, discomfort, mood change, and feeling of unreality (19, 28, 40, 41). In the present study, the incidence of side effects, including fatigue, dizziness, general discomfort, nausea, and increased heart rate, was higher in the ketamine group. Also, due to the irritability and low threshold of consciousness impairment following ketamine administration, physicians are not willing to prescribe this drug (38, 42). Ketorolac is an NSAID with analgesic and anti-inflammatory properties (43). According to a systematic review by Taggart et al., intravenous ketorolac has been recommended as a second-line drug in the management of migraine (26). In this regard, the results of other studies have shown that ketorolac may take effect after 30 to 60 minutes (44, 45). Baratloo et al. in their study, they examined the efficacy measurement of ketorolac in reducing the severity of the headache. The results showed that ketorolac reduced the severity of pain in the first 60 minutes more than in the second 60 minutes (10). The results of a study by John et al., Which was conducted to compare the effectiveness of nasal sumatriptan versus intravenous ketorolac on migraine headaches, showed that intravenous ketorolac reduced pain more than sumatriptan after one hour (18). Our results are in line with this study. Additionally, Kasmaei et al. (2017) concluded that magnesium sulfate and ketorolac effectively reduced pain in patients with acute migraine headaches, but the reduction in pain by magnesium sulfate in the first and second hours after administration was greater than ketorolac (30). It is possible that the difference in results between our study and this study was due to different methods and sample size.

The strengths of our study are double-blind and large sample size. The doubling of the sample size compared to the required sample size for the present study indicates the study's strength and the generalizability of the data to the general population.

Study limitations

The present study's first limitation was the diversity of patients' mental responses to the mental perception of pain and their encouragement to participate in the study. Patients' perception of pain is affected by drug pharmacokinetics and is sometimes different. Another limitation was that all patients responded to treatment, and no response was observed in any of the subjects. Another important limitation of this study was that patients entered the study when the investigators were available. The times of the investigator's presence in the hospital included morning, evening shifts on all days of the week; however, headache patients presenting to ED were not recorded during times when investigators were not available. Also, the date and time of referral of these patients, as well as the date and time of the investigator's absence, were not regularly recorded. According to the results of the present study, although

intranasal ketamine further reduced pain in a short time and also due to more side effects of ketamine than ketorolac, it is recommended that future studies should be investigated the effectiveness of these two drugs on different categories of headaches, the long-term effects of ketamine and ketorolac as well as other side effects of these two drugs.

Conclusion

The present study showed that intranasal ketamine has a more analgesic effect than ketorolac in a shorter period of time and can be used as a selective drug for the management and treatment of headaches.

Abbreviations

Emergency department: ED

KUMS: Kermanshah University of Medical Sciences

Declarations

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Authors' contributions

The authors and the institution are consented to publish the paper in your journal. HR and HB designed the concept and primary proposal of the project. Data was collected by MN and HB and analyzed by RS. The paper was written by MN, HR, HB, and AM and the final draft was approved by all researchers.

Competing interests

The authors declare there are no competing interests.

Consent for Publication

All authors and samples are consent to the publication of this article.

Ethics approval and consent to participate

This study was approved by research ethics committee of Kermanshah University of medical.

Availability of data and materials

Data will be available by contacting the corresponding author.

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Figures

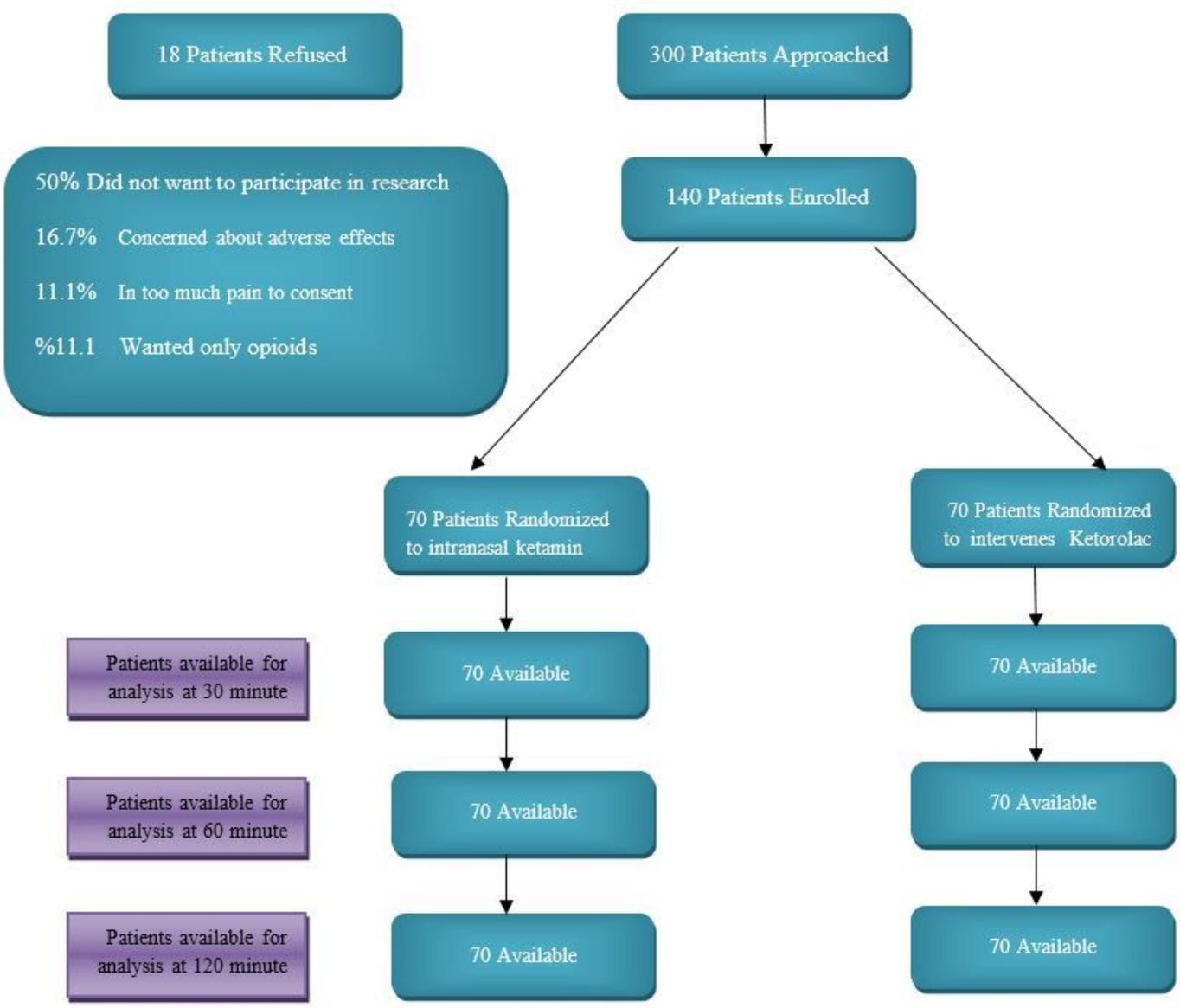


Figure 1

CONSORT flow diagram of the study.

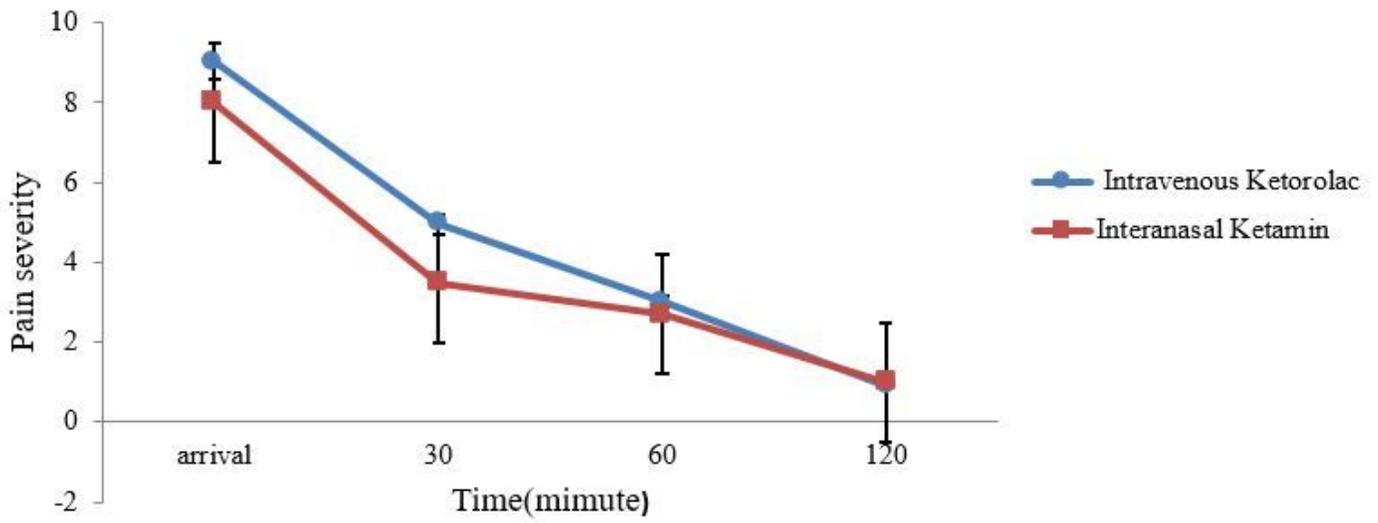


Figure 2

Changes of pain severity based on VAS in patients receiving intravenous ketorolac and intranasal ketamine versus during the study period. VAS: Visual Analogue Scale