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Archives of Emergency Medicine and Critical Care

Research Article

Comparison of Intranasal Ketamine Spray and Intravenous Morphine in Reducing Headache among Patients with Headache

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Submitted: 22 September 2023

Accepted: 27 October 2023

Published: 30 October 2023

ISSN: 2476-2016

Keywords

- Intranasal Ketamine
- Intravenous
- Morphine
- Headache
- Patients

Abstract

Background & Aim: Primary headaches are a common presentation in emergency departments, and the current standard treatments involve the use of NSAIDs and opioids. However, there is growing interest in exploring alternative therapies, such as ketamine, for pain management in headache patients. This study aimed to compare the efficacy of intranasal ketamine with intravenous morphine in patients with acute headache, considering the rapid and painless administration route of intranasal ketamine.

Materials and Methods: This double-blind clinical trial was conducted on patients with acute headache who were referred to the emergency departments of Shahid Sadougi and Rahnamon Hospitals in Yazd between 2019 and 2021. Using Simple Random Sampling, patients were divided into two groups: the case group, which received intranasal ketamine, and the control group, which received intravenous morphine. Pain intensity, assessed using the Visual Analogue Scale (VAS), along with side effects, treatment response, need for additional doses, pain relief, treatment failure, SERSDA (Side effects rating scale for dissociative anesthetics), and onset of drug effect were measured and recorded at various time intervals (0, 5, 10, 15, 30, and 60 minutes). Data analysis was performed using the SPSS software.

Results: A total of 100 patients with acute headache participated in the study, with half receiving intranasal ketamine and the other half receiving intravenous morphine. After 60 minutes of treatment, the average pain score in the morphine group was 1.95 ± 0.35, while in the ketamine group, it was 1.47 ± 0.34. The ketamine group showed a treatment response (4.73 ± 0.61) within 5 minutes of starting the treatment, whereas the morphine group exhibited a response (4.25 ± 0.52) after 15 minutes. The most common side effects in the morphine group were nausea, dizziness, and hypotension, while burning and irritation of the nasal mucosa, nausea, lightheadedness, and hallucinations were the most common side effects in the ketamine group.

Conclusion: Based on the findings of this study, intranasal ketamine demonstrated similar analgesic efficacy to intravenous morphine in the management of acute headaches (after ruling out secondary causes). Moreover, intranasal ketamine exhibited a faster onset of action compared to intravenous morphine. Therefore, intranasal ketamine may be considered a suitable alternative to intravenous morphine for pain management in patients with acute headaches.

ABBREVIATIONS

SERSDA: Side Effects Rating Scale for Dissociative Anesthetics; VAS: Visual Analogue Scale

INTRODUCTION

Headache is one of the most common complaints among patients visiting the emergency department [1], and is even more prevalent than the common cold [2]. Approximately half of all adults experience a headache at least once a year [3]. Headaches are categorized as either primary or secondary. Primary headaches cause significant daily pain and disability but are not physiologically dangerous. On the other hand, secondary headaches may indicate underlying pathology. The presence of Red Flags assists doctors in diagnosing secondary headaches [4]. Examples of secondary headaches include meningitis, intracranial hemorrhages, subarachnoid hemorrhage, aneurysm rupture, arteriovenous malformation, intraparenchymal hemorrhage, temporal arthritis, acute angle-closure glaucoma, seizures, digestive disorders, brain tumors, hypertension, dental infections, allergies, and overuse of painkillers [5].

Migraine, recognized by the World Health Organization as one of the top 20 debilitating diseases worldwide [2], is a type of primary headache. The direct cost associated with this

disease is estimated at one billion dollars per year. Cluster headaches and tension headaches are also common types of primary headaches that frequently lead patients to seek care in emergency departments and other medical centers [6]. However, there are over 200 types of headaches, ranging from harmless to life-threatening [7]. Most cases of headaches are benign and only require symptomatic treatment. Therefore, headaches are considered symptoms rather than diseases. In severe and intolerable cases, they may indicate an underlying condition, and individuals with chronic headaches are at an increased risk of developing depression, according to psychiatrists [3].

Currently, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, such as morphine, are commonly used for headache treatment in the emergency department after ruling out life-threatening causes. Morphine, an opioid widely used for acute headache attacks, takes one to six minutes to take effect when administered intravenously, with peak effect occurring after 20 minutes. Its half-life is approximately two to three hours. Due to side effects such as nausea, vomiting (especially during initial use), constipation, drowsiness, hypotension, orthostatic hypotension, apnea, respiratory suppression, dry mouth, sweating, facial flushing, dizziness, decreased heart rate, decreased body temperature, hallucinations, mood changes, dependence, addiction, and cognitive impairment, physicians aim to minimize its usage [8].

Ketamine is a central nervous system depressant with various applications in anesthesia [9]. Compared to other anesthetic drugs, ketamine is considered less hazardous because it does not depress the respiratory center or impair blood circulation, nor does it suppress the gag reflex [10]. When administered intravenously, ketamine takes effect within 5-10 minutes, with a half-life of approximately two to three hours [11,12].

Nasal administration of medication is a painless method that provides rapid pain relief with minimal delay. From a pharmacokinetic perspective, the nasal mucosa, rich in blood vessels, facilitates rapid drug absorption with minimal side effects [13,14]. In recent years, numerous studies have investigated the effects of ketamine in the form of nasal spray, intravenous injection, rectal administration, and even topical application for reducing various types of pain, including renal colic, with positive effects reported [15].

Given the significance of pain management in patients presenting to the emergency department and the limited studies comparing the analgesic effects of intranasal ketamine spray and intravenous morphine in acute headache patients, this clinical trial aimed to assess and compare the efficacy of intranasal ketamine spray and intravenous morphine in reducing headache severity among patients attending the emergency departments of Shahid Sadougi and Rahnamon Hospitals in Yazd between 2019 and 2021.

MATERIALS AND METHODS

Design & setting

This study is a double-blind randomized controlled clinical trial that was conducted on 100 Patients with acute headache, older than 14 years and younger than 65 years old, who referred to the emergency departments of Shahid Sadougi and Rahnamon Hospitals in Yazd during 2019-2021.

This study was reviewed and approved by the ethics committee of Shahid Sadouqi University of Yazd (ethics code: IR.SSU.MEDICINE.REC.1400.188) and before the research, the objectives of the study were explained to the patients and if they want to participate in the study, a written consent was obtained from them.

If the patient was unable to give written consent due to reasons such as language difference or inability to write, consent was obtained from the patient's legal guardian, and the authors fully adhered to the Declaration of Helsinki Principles during the study.

Sample Size

With an alpha error rate of 5% and a power of 80%, and taking into account the standard deviation of 5.3 to reach a significant difference of 2 units in the average VAS score, the number of 50 people was determined. 55 people in each group and a total of 110 people were considered with a 10% drop (if there is no drop, 100 people). After explaining the goals of the project to the patients and obtaining written consent from them, the patients were entered into one of the intervention and control groups by Simple Random Sampling.

Procedure and Intervention

The inclusion criteria for this study were older than 14 years and younger than 65 years, all headaches referred to the emergency department including migraine, cluster and tension with a pain score greater than or equal to four.

Patients with consciousness level less than 15, symptoms of increased ICP, symptoms of nerve lateralization, O2 saturation less than 90%, suspected of subarachnoid hemorrhage (SAH), fever and Neck stiffness, history of psychosis, known liver and kidney disease, taking painkillers in the last 4 hours, eye complications (symptoms of increased IOP, eye pain, blurred vision and eye redness), pregnancy and breastfeeding, nasal congestion, drug addiction, systolic blood pressure less than 90 and more than 180, respiratory rate less than 10, pulse rate less than 60 and more than 140, history of allergy to any of the drugs used in the study, brain tumor and not consenting to participate in the project were excluded from this study.

100 patients who met the conditions for entering the study, after obtaining informed consent from the patient or legal guardian and explaining the process of this study and performing Primary Care, as well as after rolling out secondary headaches, they were evaluated for the absence of nasal septum deviation and other structural disorders of the nose and then they were divided into group A (case group) and B (control group) by Simple Random Sampling.

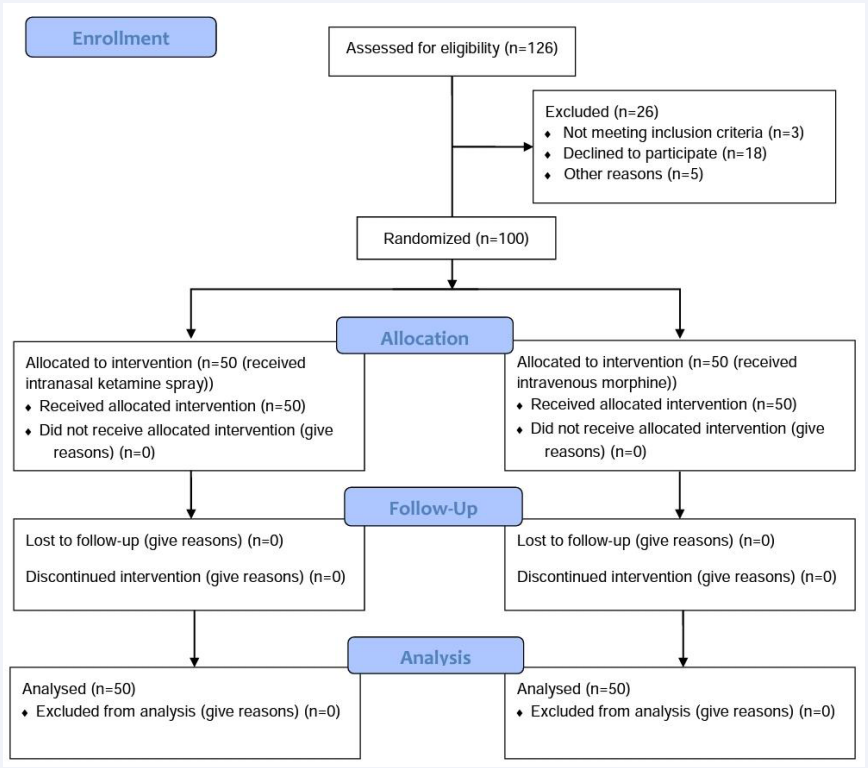

Figure 1 CONSORT flowchart of study patients

In group A, 50 patients who were treated with intranasal ketamine at a dose of 0.7 mg/kg (the maximum dose was considered 40 mg) in the form of three puffs inside each nostril (each puff containing 7 mg of ketamine) and 10 cc of normal intravenous saline were injected slowly.

In group B, 50 patients were treated with placebo nasal spray and 0.1 mg/kg intravenous morphine (the maximum dose was considered 5 mg) were injected slowly which was diluted with 10 cc of normal intravenous saline.

How to make ketamine nasal spray: In this study, ketamine vials manufactured by Sterop company were used. Each 10 cc vial contained 500 mg of ketamine and 50 mg of benzalkonium chloride (as a preservative). Desmopressin nasal sprays of Raha Company with a volume of 10 cc were emptied and sterilized, then prepared solution was poured into it. Each spray puff contained 7 mg of ketamine and the sprays could be used up to one month after opening the vial.

How to make the placebo spray: 10 cc vials of distilled water made by SunLife Company were used to make the placebo spray. 50 mg of benzalkonium chloride (as a preservative) made by Behsa company was dissolved in 10 cc vials of distilled water. Desmopressin nasal sprays of Raha Company with a volume of 10 cc were emptied and sterilized, then prepared solution was poured into it and the sprays could be used up to one month after opening the vial.

All the drugs were unlabeled. Neither the research doctor nor the patient knew the type of drug prescribed (double blind). When the patients entered the study, the necessary demographic information was collected based on the prepared checklists. The clinical symptoms of the patients were evaluated by the research doctor, and then the drugs were injected and used by the nurse. The clinical symptoms of the patients, pain intensity and possible side effects of the drugs (Nausea and vomiting, hot flushing, irritation and burning of nasal mucosa, systolic blood pressure less than 90 or more than 180, hallucination and agitation) were investigated by the research doctor at 0, 5, 10, 15, 30, and 60 minutes after drug administration. Also, side effect rating scale for dissociative anesthetics (SERSDA) was used to measure the effects of ketamine identity disorder (dissociative).

In this study, response to treatment was considered a reduction of at least two pain scores based on the patient's VAS criteria after receiving the first or second dose, and painlessness was considered as a pain score based on VAS criteria of less than four.

If there is no reduction of 2 scores of pain intensity according to the VAS criterion, after 15 minutes, the second dose was prescribed in the amount of half of the initial dose. If after 30 minutes of receiving the first dose (after 15 minutes of receiving the Second dose), the patient's pain was not improving and also if drug side effects occur, was considered the failure of the

treatment and was used the rescue drug. The rescue drug was 30 mg of intravenous ketorolac.

Demographic information was collected from the patients through interviews and recorded in the prepared checklists. Patients' pain was evaluated based on VAS. The Visual Analogue Scale (VAS) index is a 10 cm horizontal bar that shows the patient's pain status on the axis from zero to ten [16] (Figure 2).

The Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) was employed to evaluate the side effects of ketamine. This nine-component scale assesses the severity of each component from "0" (no side effects) to "4" (very bothersome). The components include fatigue, headaches, dizziness, feelings of unreality, generalized discomfort, changes in hearing, changes in mood, hallucinations, and changes in vision. Although not validated, SERSDA was chosen as it is regularly used in studies of ketamine's side effects and provides a comprehensive overview of the drug's potential adverse effects [17] (Figure 3).

Statistical Analysis

The data was analyzed using SPSS version 26 statistical software and with the help of The Paired-Samples T Test, Independent-Sample, Mann-Whitney U Test, Chi-Square Sample and ANOVA statistical tests and all P-value values less than 0.05 were considered statistically significant.

Primary and Secondary Outcomes

Primary outcome, the time to start responding to treatment and secondary outcome, the time to reach painlessness and the rate of complications in both groups was considered.

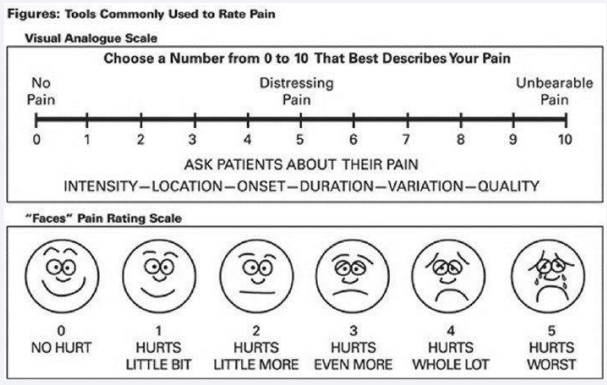

Figure 2 Assessment of pain intensity based on VAS

Side effect:	Scoring:
Fatigue	4=very bothersome
Dizziness	3=bothersome
Nausea	2=modest
Feelings of unreality	1=weak
Changes in hearing	0=no change
Changes in vision	
Mood change	
Generalized discomfort	
Hallucinations	

Figure 3 Side effects rating scale for dissociative anesthetics (SERSDA) (18)

RESULTS

This study included a total of 100 patients with acute headache who were divided into two groups: intranasal ketamine (n=50) and intravenous morphine (n=50). Of the patients, 52% (52 individuals) were male and 48% (48 individuals) were female. The mean age of the patients was 36.53 ± 12.73 years. The two groups were comparable in terms of age (p-value = 0.76) and gender (p-value = 0.54), showing no significant differences (Table 1).

Table 2 presents the results of the study. The average pain score of patients treated with morphine prior to treatment initiation was 6.78 ± 0.68, which significantly reduced to 1.95 ± 0.35 sixty minutes after intravenous morphine administration. In the group treated with intranasal ketamine, the initial pain score was 6.89 ± 0.72, which decreased to 1.47 ± 0.34 sixty minutes after treatment initiation.

The group treated with intranasal ketamine exhibited a response to treatment (4.73 ± 0.61) within five minutes of treatment initiation, reaching a pain-free state (3.15 ± 0.57) after ten minutes. On the other hand, the group treated with morphine responded to treatment (4.25 ± 0.52) after fifteen minutes, achieving a pain-free state (3.39 ± 0.43) after thirty minutes (Table 2). Based on the study results, 92% (46 patients) in the morphine group and 96% (48 patients) in the ketamine group achieved pain relief.

According to Table 1, 8% (4 individuals) of the patients treated with intravenous morphine and 4% (2 individuals) of the

Table 1: Baseline Characteristics

Variable	Ketamine (n = 50)	Morphine (n = 50)
Age, mean (SD), y	35.83(12.87)	37.23(13.32)
Male No. (%)	24(48)	28(56)
Female No. (%)	26(52)	22(44)
Response to treatment No. (%)	48(96)	46(92)
Treatment failure No. (%)	2(4)	4(8)
Baseline VAS score, mean (SD), mm	6.89(0.72)	6.78(0.68)

Table 2: Pain score (VAS) at 5, 10, 15, 30 and 60 Minutes

Time After Study Medication	mean (SD), mm
5 min	
Ketamine	4.73(0.61)*
Morphine	5.61(0.71)
10 min	
Ketamine	3.15(0.57)**
Morphine	4.98(0.67)
15 min	
Ketamine	2.26(0.45)
Morphine	4.25(0.52)*
30 min	
Ketamine	1.78(0.45)
Morphine	3.39(0.43) **
60 min	
Ketamine	1.47(0.34)
Morphine	1.95(0.35)
*Response to treatment; **painlessness	

patients treated with intranasal ketamine did not respond to the treatment. The Chi-square test indicated no significant difference in treatment success between the two study groups (p-value = 0.14). Additionally, 20% (10 patients) in the morphine group and 32% (16 patients) in the ketamine group required a second dose.

Table 3 displays the occurrence of complications. Among the patients treated with morphine, 42% (21 patients) experienced complications, with nausea being the most common (10%). In the ketamine group, 50% (25 patients) experienced complications, with burning and irritation of the nasal mucosa being the most frequent (18%). Furthermore, 30% (15 patients) in the ketamine group exhibited side effects that met the criteria of the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) (Table 3). Except for SERSDA, there were no significant differences in the incidence of drug side effects between the two medications (p-value = 0.033).

DISCUSSION

The findings of our study demonstrate that intranasal ketamine treatment elicits a faster response compared to intravenous morphine, resulting in a shorter time to achieve pain relief. However, the changes in pain scores within 60 minutes after treatment initiation indicate that intranasal ketamine and intravenous morphine exhibit similar efficacy in alleviating headaches. Furthermore, the incidence of drug side effects, excluding SERSDA, is comparable between the two treatment groups. Common side effects observed in patients treated with morphine include nausea, dizziness, and hypotension, while patients treated with intranasal ketamine experienced burning and irritation of the nasal mucosa, nausea, lightheadedness, and hallucinations. Additionally, the assessment of identity disorder indicators (SERSDA) in patients treated with intranasal ketamine indicates the safety of ketamine in this regard. This lack of occurrence of identity disorder can be attributed to the dosage of ketamine used and the intranasal route of drug administration.

A study conducted by Abbasi et al., in 2018 examined the comparison between the combined effect of intravenous morphine and ketamine and intravenous morphine alone in patients presenting with renal colic in the emergency department.

Table 3: Complications

Variable	No. (%)	
	Ketamine (n = 50)	Morphine (n = 50)
Nausea	4(8)	5(10)
Vomiting	1(2)	2(4)
Dizziness	0(0)	3(6)
Hypotension	0(0)	3(6)
Hypertension	1(2)	0(0)
hot flashes	0(0)	1(2)
Lightheadedness	4(8)	4(8)
Delusion	5(10)	0(0)
Decrease in blood oxygen saturation	1(2)	1(2)
Decreased respiratory rate	0(0)	2(4)
Agitation	0(0)	0(0)
Irritation of the nasal mucosa	9(18)	0(0)
SERSDA	15(30)	0(0)

Consistent with our study, this research demonstrated that the combination of intravenous morphine and ketamine resulted in significantly higher speed and effectiveness compared to intravenous morphine alone. The side effects of ketamine in this study, similar to ours, included O2 saturation below 90%, nausea, vomiting, and nystagmus. Notably, nausea and vomiting were the most common side effects observed in both the intravenous morphine and ketamine combination treatment group [19]. Although nystagmus is a common side effect of ketamine, its reversibility and benign nature were not investigated in our study.

In another study by Shrestha et al., in 2016, which aligns with our findings, the effects of intranasal ketamine in managing acute pain in patients visiting the emergency department were investigated. Dizziness and mood changes were reported as the most common side effects of ketamine in this study [20]. Finally, the results of this research indicated that intranasal ketamine can be utilized as an effective analgesic in the emergency department.

Stacy Reynolds et al., conducted a study in South Carolina in 2017 comparing the effects of intranasal ketamine with intranasal fentanyl on 80 children with limb fractures. The most common side effect observed with ketamine was a bad taste (90%), followed by dizziness (73%), drowsiness (46%), and nasal irritation (24%). The study concluded that intranasal ketamine can serve as an effective pain reliever for reducing pain in patients after orthopedic procedures (21), which is consistent with our study. However, the investigation of intranasal ketamine side effects in these two studies yielded different results, which could be attributed to variations in sample size and age range among the studied patients.

According to our study results, the average pain score in patients treated with intranasal ketamine was 6.89 out of 10, which decreased to 1.47 after 60 minutes. Only 2 patients (4%) from the ketamine group did not respond to the treatment. In a 2010 study by Krusz et al., the effects of intravenous ketamine on headache and pain disorders in 247 patients were investigated. The results showed an average reduction of 5 points on the pain scale after treatment with intravenous ketamine. Of the patients, 151 received two doses, 90 received three doses, and 6 patients did not respond to the treatment despite receiving three doses of the drug [22]. This reduction in response rate compared to our study can be attributed to the difference in sample size. Overall, both studies yielded similar results, highlighting the speed and efficacy of ketamine in reducing and alleviating headaches.

LIMITATIONS

One of the main limitations of our study was the short follow-up period for patients. Evaluating the effectiveness of the drug over longer follow-up periods is recommended for future studies. Another limitation was the absence of a placebo group, as ethical considerations prevented following patients without medical intervention. It is advisable to explore alternative routes of drug administration (such as intramuscular and local) and different administration regimens (continuous and infusion) in future studies.

CONCLUSION

Based on the results of our study, intranasal ketamine significantly alleviates headaches in patients with acute primary headache (after ruling out secondary causes). Compared to intravenous morphine, intranasal ketamine exhibits similar effectiveness in reducing patients' pain scores according to the Visual Analog Scale (VAS) criteria, without inducing a higher incidence of side effects. Nausea, dizziness, and hypotension were the most common side effects of intravenous morphine, while burning and irritation of nasal mucosa, hallucinations, nausea, and lightheadedness were the most common side effects of intranasal ketamine.

ACKNOWLEDGEMENTS

The authors appreciate the insightful cooperation of Medical Sciences and the staff of the Emergency Departments of Shahid Sadougi and Rahnamon Hospital, Yazd, Iran.

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