ORIGINAL ARTICLE

Intranasal ketamine versus intranasal fentanyl on pain management in isolated traumatic patients

Mehdi Nasr Isfahani, Omid Shokoohi, Keihan Golshani
Department of Emergency Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Given the inadequate control of pain in patients with the trauma that refer to the emergency departments, the rapid onset of action of intranasal administration in pain management, and the avoidance of administering opioid medications, the present study aimed at evaluating the effect of intranasal ketamine versus intranasal fentanyl on pain management in isolated traumatic patients. **Materials and Methods:** The current study was performed on 125 patients that were divided into the following three groups: control group (n = 41), 1 mg/kg intranasal ketamine group (n = 40), and 1 μg/kg intranasal fentanyl group (n = 44). Then pain scores, heart rate, respiratory rate, blood pressure, and oxygen saturation were recorded at baseline, 5, 10, 15, 30, and 40 min after the intervention. **Results:** Visual analog scale (VAS) scores of patients in the intranasal ketamine group 5 and 10 min after the intervention were 61.50 ± 20.45 and 55.00 ± 21.96, respectively. The mentioned scores were significantly lower than the VAS scores of patients in the control group with the mean of 72.44 ± 22.11 and 66.59 ± 24.25 and the VAS scores of patients in the intranasal fentanyl group with the mean of 71.59 ± 22.09 and 65.00 ± 22.87 at 5 and 10 min after the intervention, respectively (P < 0.05). **Conclusion:** Given the onset of action in < 10 min, intranasal ketamine can be proposed as an appropriate analgesic medication in pain reduction of patients with isolated limb injuries. Moreover, the incidence rate and severity of adverse effects were insignificantly higher in the intranasal ketamine group as compared with the intranasal fentanyl group.

Key words: Fentanyl, intranasal, ketamine, pain, trauma

How to cite this article: Nasr Isfahani M, Shokoohi O, Golshani K. Intranasal ketamine versus intranasal fentanyl on pain management in isolated traumatic patients. J Res Med Sci 2022;27:1.

INTRODUCTION

Pain can be regarded as a frequent complaint in more than 75% of patients referring to emergency departments (EDs). The control of pain is of great significance in patients with traumatic injuries.[1]

Despite greater cognizance of the type and dosage of medications as well as the appropriate routes of administration, the level of pain control is still lower than expected.[2,3] In this regard, the choice of medications with fewer adverse effects (AEs) and faster onset of pain relief is of great interest to physicians. Specification and prescription of an appropriate and effective analgesic drug can lead to the patient's further cooperation with the physician, faster decision-making process, and patient's increased satisfaction with the quality of services provided in the ED.[4-6]

When patients receive analgesic drugs, they often confront delayed administration[7] that can be partially justified by the required time to obtain intravenous access. Currently, the route of intranasal administration has been regarded as a more efficient alternative for the administration of analgesic drugs, has increasingly more popular, and has attracted the researchers' attention due to its rapid onset of action, the minimum degree of inconvenience, and relative simplicity.[8]

In addition, currently available options to relieve the pain across the world are opioids, fentanyl, tramadol, ketorolac, and ketamine.[9]

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_505_20

Address for correspondence: Dr. Omid Shokoohi, Department of Emergency Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: omid.shokoohi@yahoo.com
Submitted: 04-Jun-2020; **Revised:** 16-Jun-2021; **Accepted:** 10-Aug-2021; **Published:** 29-Jan-2022

Opioids are the most frequently used analgesic drugs. Fentanyl is a short-acting analgesic drug with a short duration of effect. Moreover, it is used as an analgesic drug induction and maintenance of anesthesia as well as management of postoperative pain. In fact, this medication as an agonist binds to opioid receptors and affects the pain sensation, thereby exerting its analgesic effect on moderate to severe pain levels. The effect of this medication on depression of the central nervous system and respiratory tract is identical to that of morphine. However, the hypnotic and AEs of fentanyl are much less than other medications.[10]

However, as opioids in general can increase not only the risk of AEs but also the risk of hypersensitivity or allergies and the prescription of the ideal dose for adequate control of severe pain while avoiding drug-related AEs is difficult,[11] physicians are obliged to consider nonopioid options. In this regard, ketamine has been recognized as one of the potent analgesic drugs in low doses and plays a significant role in pain management in EDs. The mentioned medication is available, not expensive, and in comparison with opioids has less AEs on the hemodynamic and respiratory system at its low doses.[12]

There is no precise evidence regarding the dose and route of ketamine or fentanyl administration in different age groups of adults and children in EDs; however, previous studies generally have suggested different doses of ketamine administered through various routes to reduce pain in adults[13-15] and children[16,17] and have demonstrated low doses of ketamine to be safe and effective in pain management. In addition, some studies have mentioned the same efficacy level of intranasal ketamine and intranasal fentanyl within 30 min,[18] while another study has recognized intranasal ketamine as a safe and effective alternative analgesic in reducing moderate to severe pain in children with limb injury. In addition, in cases for whom contraindications to fentanyl or other opioids have been suggested, is a well-recognized alternative due to its fewer AEs.[17] However, considering the contradictory results in this respect, uncertainties about the best route of administration and the minimum dose with the maximum effectiveness, and the lack of studies addressing adults, the present study aimed at examining the effect of intranasal ketamine versus intranasal fentanyl on pain management in isolated traumatic patients.

MATERIALS AND METHODS

The present study was a double-blind clinical trial (with cod: NCT04414800). The study population consisted of all patients with isolated limb trauma referred to Al-Zahra and Kashani Hospitals of Isfahan, Iran from April 2017 to April 2018.

At a 95% confidence interval and 80% test power and according to the results of previous studies[17] regarding the minimum difference of 5 in the mean pain reduction in the ketamine and fentanyl drugs and the standard deviation (SD) of 9, the sample size of 50 for each group (fentanyl group, ketamine group and placebo group) was calculated using the sample size formula for between groups comparison. In another word, a total of 150 patients were selected using the nonprobability convenience sampling method.

At a 95% confidence interval and 80% test power and according to the results of previous studies[17] regarding the minimum difference of five in the mean pain reduction in the ketamine and fentanyl drugs, the sample size for each group was considered to be 50 (fentanyl group, ketamine group and placebo group) with a total of 150 patients that were selected using the nonprobability convenience sampling method.

The inclusion criteria for this study consisted of patients with isolated limb trauma, aged 15–65 years, with moderate to severe pain (45 mm; visual analog scale [VAS]), with a GCS score of 15, with the systolic blood pressure (SBP) of lower than 180 mmHg, DBP of higher than 90 mmHg, lack of pregnancy, no history of allergy to ketamine, fentanyl (or opioids), or acetaminophen, no history of liver diseases, no acute or chronic structural or functional nasal obstruction diseases, no history of drug or psychiatric addiction, no pain medication within the past 4 h, no history of heart disease, and the presentation of the written consent to participate in the study.

In addition, the patients were excluded from the study in case of a decrease in GCS score to ≤14, an elevated SBP to higher than 180 mmHg, a decreased DBP to <80 mmHg, inability to understand the VAS pain rating system, symptoms of acute heart disease and respiratory depression (respiratory rate [RR] <8/min), and the patient's dissatisfaction to continue the cooperation in study.

After receiving a code of ethics from the Ethics Committee of Isfahan University of Medical Sciences (Approved number: IR.MUI.REC.1396.3.828) and obtaining the written consent from the patient, 150 eligible patients were enrolled in the study. Then, these patients will be randomly encoded using computer software called "Random Allocation" and automatically divided into three groups. The relevant codes will be entered in the raw checklists and each of these checklists will be randomly assigned to one patient and that patient will be randomly assigned to one of the three study groups.

Initially, all patients received a standard dose of Apotel (intravenous acetaminophen) with a maximum

of 1 g (15 mg/kg). Moreover, demographic characteristics of patients such as age, gender, weight, Glasgow Coma Scale (GCS), RR, heart rate (HR), arterial oxygen saturation (SaO_2), SBP and DBP, and pain score based on VAS (pain severity score: 0 = no pain to 100 = worst pain imaginable) were recorded.

To meet the double-blindness criterion of the study, fentanyl with a dose of 1 μg/kg, ketamine with a dose of 1 mg/kg, and the placebo medication were prepared daily by a single emergency nurse (blind to the researcher). The prepared medications were colorless and odorless, poured into single-shaped vials, labeled with A, B, and C characters, and given daily to the researcher. The researcher, with no knowledge of the type of medication, used a syringe in each group to spray 0.02 mg/kg of the prepared medication with a mucosal atomizer device (MAD; Wolf Troy Medical, Salt Lake City, UT).

In addition, the appropriate position for the administration of the medication was the Lying Head Back position.[19] In case of any speculations regarding the cervical injury due to the change of supine position to other positions, the patient was excluded from the study.

In case of pain intensity level of 70 or higher within 15 min after the initial administration of the medication, an additional dose of the medication was prescribed.[14] An intention-to-treat analysis, however, was used. So that in case of no reduction in pain intensity level, the patient was excluded from the study and received intravenous morphine sulfate.

It should be mentioned that 9, 6, and 10 patients in the control, intranasal fentanyl, and intranasal ketamine groups, respectively were excluded from the study due to hypotension, low level of consciousness, depression after drug administration, lack of pain control, or lack of cooperation. Hence, the sample size in the control, intranasal fentanyl, and intranasal ketamine groups decreased to 41, 44, and 40, respectively [Figure 1].

After the initial administration of the medications at 5, 10, 15, 30, and 40 min, all three groups were reassessed, and factors such as GCS, VAS score, HR, RR, blood pressure, and SaO_2 were recorded. Moreover, the incidence of any AEs was recorded after the intervention till the end of the study, i.e., 40 min after the intervention.

Fifteen and 30 min after the intervention, the AEs were also evaluated and recorded according to the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA).[20] The mentioned scale consists of symptoms such as nausea, headache, dizziness, weakness, general discomfort, mood change, changes in hearing, feeling of unreality, and hallucinations. The severity of complications was classified into five categories. Zero means no AEs and scores ranging from 1 to 5 (1 = very low, 2 = low, 3 = moderate, and 4 = high, and 5 = very high) indicated the presence of AEs that were rated by the patient considering the severity of the AEs.

In addition, 40 min after the intervention, the patient's perception regarding the unpleasant nasal stimulation was checked. The scoring rate ranged from the score of zero indicating no unpleasant stimulation to the score of 10 indicating the highest unpleasant stimulation. Moreover, the patient's satisfaction with pain relief was self-rated by the patient on the basis of a scale ranging from zero representing no satisfaction to ten representing complete satisfaction.

Finally, the collected data were entered into SPSS software (version 22; SPSS Inc., Chicago, Ill., USA) and were presented using *n* (%) or mean ± SD An one-way ANOVA test was used to compare the mean age and weight of the patients among the three groups. Moreover, a Chi-square test was used to compare the frequency distribution of qualitative data among the three groups. In addition, considering the results of the Kolmogorov–Smirnov test that indicated the abnormal distribution of data, the Mann–Whitney *U*-test and the Friedman test were used to compare the mean of quantitative variables between pairs of groups and the mean of quantitative variables over 40 min in each group, respectively. The significance level of <0.05 was considered in all analyses.

RESULTS

In the present study, out of 41 patients in the control group with the mean age 35.25 ± 13.23 years, 34 (82.9%) and 7 (17.1%) patients were male and female, respectively. The fentanyl group consisted of 42 (95.5%) male and 2 (4.5%) female patients with the mean age of 30.51 ± 10.77 years. The ketamine group included 37 (92.5%) and 3 (7.5%) male and female patients with the mean age of 31.26 ± 12.07 years. Also, 17.1%, 6.8% and 12.5% of patients in the control, fentanyl and ketamine groups received morphine as an additional analgesic (dose: 0.05–0.1 mg/kg), respectively. The mentioned three groups were matched for age, sex, and weight ($P > 0.05$) [Table 1].

Furthermore, no significant difference was observed among the three groups before the intervention with respect to the mean of clinical parameters including RR, HR, GCS, SaO_2, SBP, and DBP ($P > 0.05$). However, 5 min after the intervention, only RR in the ketamine group with the mean of 16.10 ± 2.25 was significantly lower than that of the control and fentanyl groups with the means of 16.85 ± 2.17 and

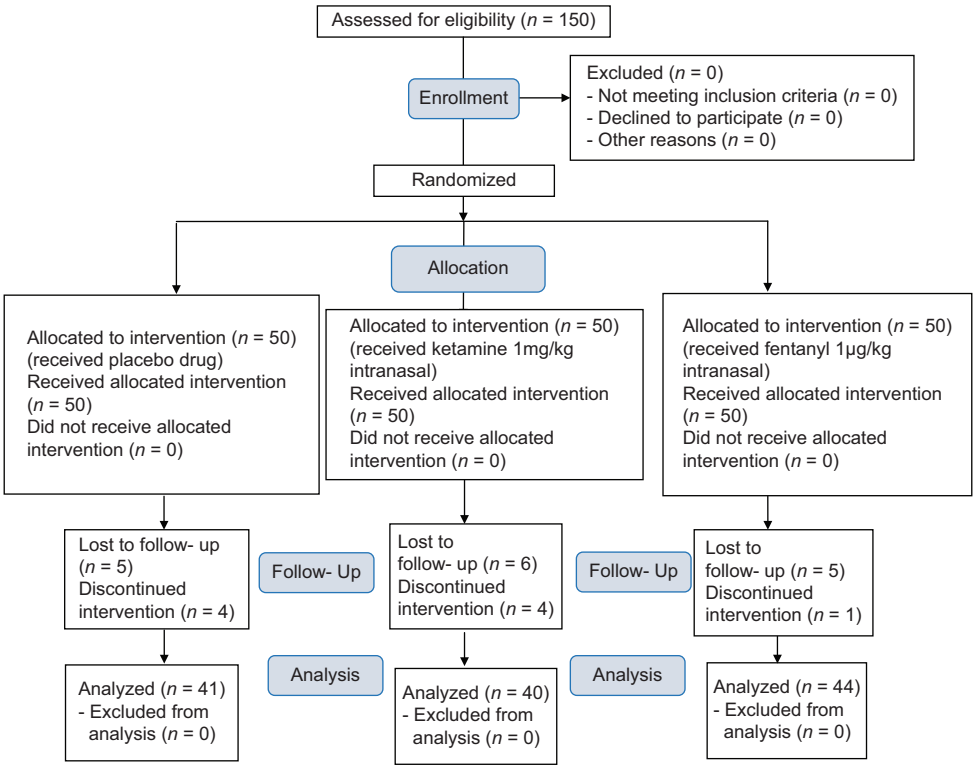

Figure 1: Consort flowchart

Table 1: Comparison of baseline characteristics of the patients in the three groups

Characteristics	Control group (*n*=41)	Fentanyl group (*n*=44)	Ketamine group (*n*=40)	*P*
Sex, *n* (%)				
Male	34 (82.9)	42 (95.5)	37 (92.5)	0.126
Female	7 (17.1)	2 (4.5)	3 (7.5)	
Age (years)	35.25±13.23	30.51±10.77	31.26±12.07	0.172
Weight (kg)	79.02±13.24	76.89±14.06	80.10±11.90	0.553
Need for additional dose of analgesic*, *n* (%)	7 (17.1)	3 (6.8)	5 (12.5)	0.336

*Patients receiving 0.05-0.1 mg/kg morphine as an additional dose of analgesic

16.77 ± 1.96, respectively ($P < 0.05$). The other parameters were not significantly different between the pairs of groups ($P > 0.05$) [Table 2].

In addition, there was no significant difference among the three groups in terms of VAS score before the intervention ($P > 0.05$). However, 5 min after the intervention, the VAS score in the ketamine group with the mean of 61.50 ± 20.45 was significantly lower than that of the control and fentanyl groups with the means of 72.44 ± 22.11 and 71.59 ± 22.09, respectively ($P < 0.05$). Moreover, 10 min after the intervention, the VAS score was still significantly lower in the ketamine group with the mean of 55.00 ± 21.96 as compared with the control and fentanyl groups with the means of 66.59 ± 24.25 and 65.00 ± 22.87, respectively ($P < 0.05$). At other times up to 40 min after the intervention, each pair of groups did not indicate any significant difference in the mean of VAS score ($P > 0.05$). In addition, all three groups indicated a significant decrease in the VAS score within 40 min after the intervention ($P < 0.001$) [Table 3 and Figure 2].

Evaluation of the AEs based on the SERSDA scale 15 and 30 min after the intervention revealed that no changes occurred in the AEs of headache, feeling of unreality, fatigue, and changes in hearing. In contrast, the AEs of general discomfort, dizziness, nausea, mood change, hallucination, and sedation indicated the highest frequency 15 min after the intervention. Furthermore, the frequency of the mentioned AEs was not significantly different among the three groups, and only the AE of mood change was significantly higher in the ketamine group as compared to the control and fentanyl groups 15 min after the intervention (15 min: Ketamine group = 7.5% vs. Fentanyl group = 0%, Control group = 0%; $P = 0.038$). In addition, it should be noted that scores for the AE severity in all three groups were less than two, which was negligible. Hence, there was no significant difference among the three groups in this regard [Table 4].

Table 2: Determination and comparison of the mean of clinical parameters in the three groups

Variables	Time	Control group (*n*=41)	Fentanyl group (*n*=44)	Ketamine group (*n*=40)	P_1	P_2	P_3
RR	Baseline	17.78±2.86	17.77±2.51	17.10±2.42	0.903	0.250	0.088
	5 min	16.85±2.17	16.77±1.96	16.10±2.25	0.893	0.044	0.033
	10 min	16.24±2.44	16.09±1.57	15.70±1.99	0.734	0.360	0.173
	15 min	15.90±2.27	16.11±1.82	15.60±1.35	0.374	0.869	0.214
	30 min	15.78±2.33	15.98±1.59	15.78±1.54	0.302	0.623	0.423
	40 min	15.93±2.40	15.80±1.68	15.40±1.58	0.904	0.351	0.247
	P_4	<0.001	<0.001	<0.001			
HR	Baseline	84.59±13.04	86.66±11.61	85.55±15.47	0.369	0.970	0.415
	5 min	84.29±11.72	87.91±11.01	87.23±14.37	0.075	0.366	0.497
	10 min	85.46±9.77	86.60±9.67	86.70±13.23	0.293	0.719	0.645
	15 min	83.83±10.04	86.51±9.44	86.60±11.85	0.068	0.219	0.691
	30 min	83.90±10.47	86.26±8.47	85.90±12.54	0.104	0.379	0.691
	40 min	83.68±10.48	85.65±9.28	85.40±11.40	0.164	0.430	0.671
	P_4	0.051	0.176	0.347			
GCS	Baseline	15.00±0.00	15.00±0.00	15.00±0.00	1.00	1.00	1.00
	5 min	15.00±0.00	15.00±0.00	14.95±0.32	1.00	0.311	0.294
	10 min	15.00±0.00	15.00±0.00	14.95±0.32	1.00	0.311	0.294
	15 min	15.00±0.00	15.00±0.00	14.98±0.16	1.00	0.311	0.294
	30 min	15.00±0.00	15.00±0.00	14.98±0.16	1.00	0.311	0.294
	40 min	15.00±0.00	15.00±0.00	14.98±0.16	1.00	0.311	0.294
	P_4	-	-	0.416			
SaO_2	Baseline	95.93±1.84	96.50±1.68	95.70±2.66	0.196	0.912	0.238
	5 min	95.95±1.90	96.59±1.47	96.03±1.28	0.078	0.335	0.393
	10 min	95.68±1.89	96.18±1.47	95.90±1.96	0.366	0.531	0.796
	15 min	95.61±2.31	96.34±1.48	95.83±2.12	0.233	0.579	0.525
	30 min	95.49±2.13	96.11±1.53	95.80±2.08	0.320	0.353	0.945
	40 min	95.53±1.88	96.27±1.45	95.54±2.37	0.128	0.589	0.306
	P_4	0.120	0.064	0.236			
SBP	Baseline	133.90±19.09	129.14±14.43	133.95±18.10	0.218	0.861	0.347
	5 min	131.29±14.67	130.98±13.90	135.15±19.76	0.768	0.910	0.578
	10 min	131.71±15.19	130.11±13.54	135.15±17.80	0.330	0.726	0.226
	15 min	130.73±15.60	128.45±13.06	133.23±17.46	0.286	0.913	0.268
	30 min	131.78±15.40	128.59±12.17	132.73±17.38	0.175	0.747	0.450
	40 min	130.63±14.87	129.39±12.73	132.46±16.97	0.516	0.954	0.630
	P_4	0.003	0.007	0.012			
DBP	Baseline	80.66±14.49	77.61±12.28	83.10±15.94	0.386	0.737	0.242
	5 min	80.66±12.60	80.95±10.65	83.60±14.82	0.812	0.674	0.664
	10 min	80.78±11.83	79.77±10.40	83.50±13.62	0.513	0.694	0.332
	15 min	80.73±10.94	79.66±10.11	83.03±12.55	0.613	0.543	0.270
	30 min	80.05±11.41	80.14±9.51	83.85±13.25	0.950	0.405	0.465
	40 min	80.24±10.01	80.43±9.94	83.59±12.71	0.940	0.468	0.498
	P_4	0.951	0.012	0.976			

P_1=Results of the Mann-Whitney U test comparing the clinical parameters of Control and Fentanyl groups, P_2=Results of the Mann–Whitney U test comparing the clinical parameters of Control and Ketamine groups, P_3=Results of the Mann–Whitney U test comparing the clinical parameters of Fentanyl and Ketamine groups, P_4=Results of the Friedman test comparing the clinical parameters of three groups over time. RR=Respiratory rate; HR=Heart rate; SaO_2=Oxygen saturation; GCS=Glasgow Coma Scale; SBP=Systolic blood pressure; DBP=Diastolic blood pressure

Finally, the number of patients with nasal discomfort in the ketamine group was higher than that of the fentanyl group (median: Ketamine group = 2.0 and Fentanyl group = 1.0; P = 0.005). Moreover, the level of patient satisfaction was also lower in the fentanyl group (median = 1.5) as compared with the control and ketamine groups (median = 4.0) ($P < 0.05$) [Table 5].

DISCUSSION

The results of the present study revealed that the pain score of all three groups including control, intranasal ketamine, and intranasal fentanyl significantly decreased 40 min after the intervention. Moreover, although the pain score at all examined times was lower in the fentanyl group as

Table 3: Determination and comparison of the mean of Visual Analog Scale score in the three groups

Variables	Time	Control group (*n*=41)	Fentanyl group (*n*=44)	Ketamine group (*n*=40)	P_1	P_2	P_3
VAS	Baseline	85.85±16.73	83.41±17.11	82.50±13.73	0.429	0.201	0.666
	5 min	72.44±22.11	71.59±22.09	61.50±20.45	0.932	0.032	0.044
	10 min	66.59±24.25	65.00±22.87	55.00±21.96	0.794	0.047	0.030
	15 min	65.37±26.84	62.95±24.74	54.50±22.64	0.673	0.072	0.152
	30 min	67.80±27.88	64.32±24.72	57.00±23.56	0.520	0.074	0.210
	40 min	67.32±27.48	62.95±25.11	57.50±24.68	0.439	0.102	0.359
	P_4	<0.001	<0.001	<0.001			

P_1=Results of the Mann–Whitney U test comparing the VAS score of Control and Fentanyl groups, P_2=Results of the Mann–Whitney U test comparing the VAS score of Control and Ketamine groups, P_3=Results of the Mann–Whitney U test comparing the VAS score of Fentanyl and Ketamine groups, P_4=Results of the Friedman test comparing the VAS score of three groups over time. VAS=Visual Analog Scale

Table 4: Determination and comparison of the frequency of adverse effects in the three groups

Variables	Time	Control group (*n*=41), *n* (%)	Fentanyl group (*n*=44), *n* (%)	Ketamine group (*n*=40), *n* (%)	P_1
General discomfort	15 min	2 (4.9)	3 (6.8)	5 (12.5)	0.422
	30 min	1 (2.4)	0	1 (2.5)	0.576
Headache	15 min	0	0	0	-
	30 min	0	0	0	-
Dizziness	15 min	3 (7.3)	1 (2.3)	4 (10)	0.337
	30 min	1 (2.4)	0	3 (7.5)	0.141
Feeling of unreality	15 min	0	0	0	-
	30 min	0	0	0	-
Nausea	15 min	1 (2.4)	0	3 (7.5)	0.141
	30 min	0	0	0	-
Fatigue	15 min	0	0	0	-
	30 min	0	0	0	-
Changes in hearing	15 min	0	0	0	-
	30 min	0	0	0	-
Mood change	15 min	0	0	3 (7.5)	0.038
	30 min	0	0	2 (5)	0.115
Hallucination	15 min	0	0	1 (2.5)	0.343
	30 min	0	0	1 (2.5)	0.343
Sedation	15 min	2 (4.9)	2 (4.5)	6 (15)	0.141
	30 min	1 (2.4)	1 (2.3)	5 (12.5)	0.071

P_1=Results of the Chi-square test

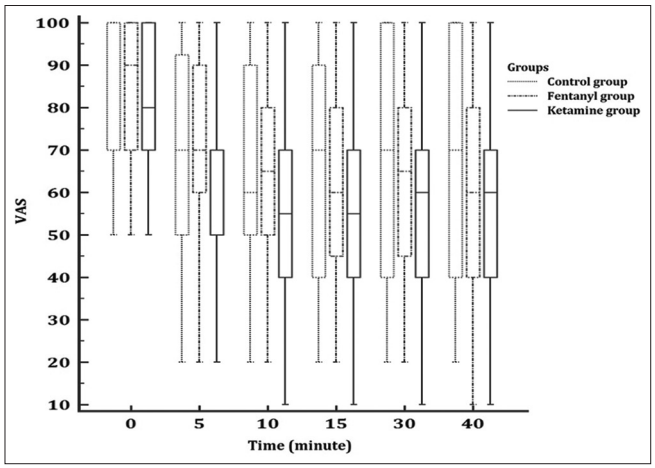

Figure 2: Box plot of VAS score from 0 to 40 min after the intervention among the three groups

compared to the control group, the observed difference was not statistically significant ($P > 0.05$). However, it must be mentioned that the pain score in the intranasal ketamine group within 5 and 10 min after the intervention was significantly lower than that of the control group and even the intranasal fentanyl group ($P < 0.05$). Moreover, there was no significant difference between each pair of groups in the follow-up of the patients' pain status during 15–40 min after the intervention ($P > 0.05$). In fact, it may be conceivable to declare that pain reduction in patients with isolated trauma that received Apotel at the beginning of the study indicated a marginally significant difference from the pain reduction of patients receiving intranasal fentanyl. In addition, the effect of medication in the ketamine group compared with that of the other groups can be realized 5 and 10 min after the administration, and then the pain level in the three groups did not differ significantly. In other words, the long-term effect of the mentioned three types of medications cannot be distinguished. However, ketamine can be recognized as an effective medication due to its rapid action in the first few minutes (up to 10 min) after the administration.

Table 5: Determination and comparison of the median of nasal discomfort and satisfaction in the three groups

Variables	Control group (*n*=41)	Fentanyl group (*n*=44)	Ketamine group (*n*=40)	P_1	P_2	P_3
Nasal discomfort*	1.0 (1.0-7.0)	1.0 (1.0-3.0)	2.0 (1.0-9.0)	0.053	0.325	0.005
Satisfaction*	4.0 (1.0-10.0)	1.5 (1.0-10.0)	4.0 (1.0-10.0)	0.506	0.047	0.045

*Data shown median (minimum–maximum), P_1=Results of the Mann–Whitney U test comparing the median of nasal discomfort and satisfaction of Control and Fentanyl groups, P_2=Results of the Mann–Whitney U test comparing the median of nasal discomfort and satisfaction of Control and Ketamine groups, P_3=Results of the Mann-Whitney U test comparing the median of nasal discomfort and satisfaction of Fentanyl and Ketamine groups

In this regard, another study showed a similar decrease in pain scores over time for both intranasal ketamine and intranasal fentanyl. Both of the mentioned medications had a relatively rapid onset of action on the pain induced by isolated limb injury. Moreover, both groups had a significant decrease in VAS score at the end of the first 30 min as approximately 80% of patients in both groups had a pain score of <20 mm.[17,21] Although in the present study, the pain score in the first 5 and 10 min was significantly lower in the intranasal ketamine group as compared with the intranasal fentanyl group, according to the results of the aforementioned studies, there was no significant difference between the two groups during the first 40 min.

The presented findings are in line with those of many previous studies addressing the efficacy of intranasal fentanyl or intranasal ketamine. Andolfatto *et al*., for instance, have indicated that intranasal ketamine significantly reduced clinical pain in adults with orthopedic injuries that referred to the Eds.[15] Similarly, Yeaman *et al*. also reported cases of adults with moderate to severe pain that was induced by a variety of reasons. The mentioned patients were treated with intranasal ketamine, after which the mean of VAS was decreased to 24 mm within 30 min.[22] The mentioned reduction was not significantly different from the pain reduction (25 mm) in the intranasal ketamine group in the current study. However, a number of other studies have indicated the efficacy of intranasal ketamine in treatment of adults with acute postoperative pain, migraine, and chronic pain exacerbations in nonemergency medical conditions.[23,24]

In addition, in line with the findings of the present study, Frey *et al*. also revealed that sub-dissociative intranasal ketamine effectively reduced the level of pain induced by severe trauma in children and had therefore a priority over intranasal fentanyl.[18]

The PICHFORK trial compared intranasal ketamine (1 mg/kg) and intranasal fentanyl (1.5 mg/kg) and reported a similar and significant decrease in patients' clinical pain within 30 min.[22] Reynolds *et al*. compared the same medications, the same doses, and the same routes and found a similar reduction in the level of pain over a period of 20 min.[16]

The findings of Crellin *et al*.'s unblinded observational study addressing the children with isolated limb injuries revealed reductions in VAS pain ratings, which were consistent with the findings of the present study[25] as well as the results of an initial intranasal ketamine dose-finding study.[26] Furthermore, 50 μg/mL of intranasal fentanyl as the most frequently accessible concentration can be used in children weighing <50 kg. Accordingly, a dose of 1 μg/kg for fentanyl was considered in the present study based on the results of previous studies. Perhaps, this dose of fentanyl may have been inadequate in the adult population and could not yield satisfactory results, but given the high analgesic potency of the mentioned medication as well as the effect of intranasal administration, the researchers preferred the most considerate dose although other doses of fentanyl are suggested to be administered in future studies. In addition, the findings indicated that the control and intranasal fentanyl groups had the least AEs 15 and 30 min after the administration, whereas the patients receiving intranasal ketamine indicated a higher rate of AEs. In general, the most common AEs were general discomfort, dizziness, nausea, mood change, hallucination, and sedation. The AEs of mood change and hallucination were reported only in the intranasal ketamine group. It should be noted that the frequency rate of each of the AEs was not significantly different among the three groups. As only the AE of mood change was reported in 7.5% and 5% of ketamine intranasal group 15 and 30 min after the administration, respectively and no cases were reported in the control and intranasal fentanyl groups, the observed difference was statistically significant ($P < 0.05$).

Furthermore, although the highest level of nasal discomfort was observed in the intranasal ketamine group, the patients' satisfaction level was significantly higher in this group as compared with the intranasal fentanyl and control groups. The high level of satisfaction in the intranasal ketamine group can be attributed to more successful pain control.

Consistent with the findings of the present study, Crellin *et al*. reported no AEs following the administration of intranasal fentanyl.[25] However, Graudins *et al*.'s study revealed that about half of the children receiving fentanyl had at least indicated one AE. The most common AEs in the mentioned study were in turn bad taste, dizziness, and drowsiness after the administration of intranasal fentanyl. They reported a higher frequency rate of these AEs for the ketamine group and asserted that 1 mg/kg ketamine or its lower doses as an adjunct to fentanyl or other opioids could

be used in adults and children for specifying differences in pain perception and management.[17]

Similar to the results of the present study, studies conducted by Reynolds *et al*.[16] and Graudins *et al*.[17] have also indicated that the AEs of both medications were identical, partial, and transient. Almost half of the AEs occurred within the first 15 min after the administration. In addition, the results of the Frey *et al*.'s study showed a greater number of AEs including dizziness and drowsiness in the ketamine-treated group, but all the AEs were mild and transient, and the patients were satisfied with their treatment.[18] In the currents study, evaluation of the AEs by means of SERSDA scale and quantification of the severity of each AE revealed that the severity of the side effects was mild and negligible in all side effects, and no significant difference was observed among the three groups in terms of the quantity and severity of the side effects.

As the SERSDA scale has rarely been used in ED research and it is proven to be too sensitive to minor side effects, making comparisons between the present study and other ED studies may be problematic. Therefore, considering the controversial evidence in this regard, it seems that more detailed studies addressing various age ranges as well as the existing genetic, ethnic, and racial differences among child and adult patients are required to shed more light on the issue. Moreover, the dosage, route of administration, or the repetition of the dose may play a role in the efficacy of the medication or reduction of the AEs of each medication. Limitations of the present study include the administration of a low dose of medications, especially fentanyl. Hence, administration of repeated dosage in patients with higher body mass index, administration of the used medications in drug abusers, and examination of the severity of trauma are suggested to be taken into account in future studies to obtain more reliable results. In addition, the strength of the present study was the use for the administration of ketamine and fentanyl, which increased the absorption level and did not induce choking and unpleasant mouth feel.

CONCLUSION

According to the results of the present study, although the efficacy of both intranasal ketamine and intranasal fentanyl was similar in reduction of patients' pain 40 min after the administration, intranasal ketamine was recognized to be a more effective analgesic medication in patients with isolated limb trauma due to the onset of action in <10 min. In addition, the frequency rate of AEs in the first 15 and 30 min in the intranasal ketamine group was higher than that of the intranasal fentanyl group although the severity of the AEs of the two medications was low.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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