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Effect of ketamine as an adjunct to opioid for pain control in traumatic patients

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Abstract
Background: Pain management results in better outcomes in traumatic patients in the emergency ward. Use of non-opioids facilitates the elimination of the adverse effects of opioid. Regarding this, the present study was conducted to examine the effect of ketamine as an adjunct to opioids for pain control in traumatic patients in a tertiary healthcare center in Tehran, Iran.
Methods and materials: This double-blind randomized clinical trial was conducted on 160 traumatic patients admitted to the Emergency Department of Besat Hospital, Tehran, Iran, in 2018. The study population was randomly assigned into two groups of intervention and placebo. The intervention group one of which received 0.05 mg/kg opioid (i.e., morphine) plus 0.1 mg/kg ketamine, and placebo group the other one was provided with the same amount of morphine opioid plus placebo. The pain was recorded up to 120 min and compared between the groups.
Results: Based on the obtained results, 23 (28.8%) and 16 (20%) patients in the ketamine intervention and control placebo groups had side effects, respectively, showing no significant difference (P=0.197). In addition, the pain significantly reduced in both groups (P=0.001). However, the results of repeated measures ANOVA revealed no statistically significant difference between the two groups in terms of pain reduction trend (P=0.275).
Conclusion: Based on the results, it can be concluded that ketamine has no superior effect when administered as an adjunct to opioid for pain control in traumatic patients.
Keywords: Emergency department, Ketamine, Pain management, Trauma.

1. Introduction

Trauma is the main cause of mortality in people aged 1-44 years worldwide [1, 2]. High burden of mortality and morbidity in traumatic patients result in excess costs for the health system sector [3-5]. Prompt diagnosis of all injuries can lead to the developingment of better therapeutic plans to reduce the burden of problem [4, 6]. There are a variety of methods used as an algorithm, including correct clinical semi-interview, physical examination, and diagnostic tests (e.g., imaging) [7-9]. Applicability of these methods depends on the general conditions and vital signs of patients [10].
Pain is a common symptom among many patients with critical situations admitted to emergency wards [8, 11-13]. Pain management is essential to improve patient conditions and attain better therapeutic outcomes to reduce adverse consequences in patients and improve prognosis [14-16]. The use of morphine is common for controlling pain in patients with trauma; however, there is insufficient evidence regarding the efficacy of this medication under emergency condition [17].
Opioid analgesia may lead to excessive sedation, respiratory depression, and nausea in patients with severe trauma [18]. Therefore, the use of other analgesic agents with fewer side

effects can be effective in controlling pain in traumatic patients admitted to emergency departments. It seems that ketamine has fewer serious adverse effects in comparison to opioids and has little effect on blood pressure and pulse rate [18]. Ketamine is a dissociative anesthetic agent with analgesic effect. However, since it is not usually effective alone, it would be more beneficial when to used it in combination therapy with opioids [19].
Combination therapy by ketamine plus opioids results in better pain alleviation, longer analgesia, and use of lower analgesic dose [19]. Regarding the importance of this issue, the present study was conducted to examine the effect of ketamine as an adjunct to opioid for pain control in traumatic patients referring to a tertiary healthcare center in Tehran, Iran.

2. Materials and Methods

This double-blind randomized clinical trial was conducted on 160 consecutive traumatic patients referring to the Emergency Department of Besat Hospital, Tehran, Iran, in 2018. The inclusion criteria were: 1) age range of 18-60 years, 2) normal intelligence quotient, 3) lack of verbal problems, and 4) need for analgesic injection. On the other hand, the exclusion criteria were: 1) underlying respiratory, cardiac, and neurological disorders, 2) active psychosis, 3) clinical intoxication, 4) drug abuse, 5) inability to understand visual analog scale (VAS), 6) angina pectoris or stroke probability, 7) decision-making inability, and 8) participation in other simultaneous studies.
The study population was randomly assigned into two groups of intervention and placebo. The intervention group received 0.05 mg/kg opioid (i.e., morphine) plus 0.1 mg/kg ketamine. On the other hand, the placebo group was subjected to 0.05 mg/kg morphine plus a placebo. The pain was recorded up to 120 min according tousing VAS and compared between the groups.

Statistical Analysis

The data were analyzed in IBM-SPSS software (version 21). The normality of data was calculated by the Shapiro-Wilk test. In addition, t-test and *Chi-Square*, independent *t-test*, *Kolmogorov-Smirnov*, and repeated *measure*s *ANOVA* were employed to analyze the variables. A p-value less than 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Local Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (ethical code??). Helsinki Declaration was respected across the study, and informed consent was obtained formfrom all participants. Furthermore, the research procedure and objectives were explained to all subjects, and they were ensured about the confidentiality of data and possibility of study withdrawal at any stage.

3. Results

A total of 160 traumatic patients with a mean age of 33 years were investigated in this study, 44.4% of whom were female. The comparison of the two groups in terms of age showed no significant difference between them (P=0.545). With regard to gender, 55% (n=44) and 56.3% % (n=44) of the patients in the intervention and placebo groups were male, respectively. Accordingly, the two groups were comparable in terms of gender distribution (P=0.87). Additionally, the results indicated no significant difference between the two groups regarding weight (P=0.75; Figure 1).

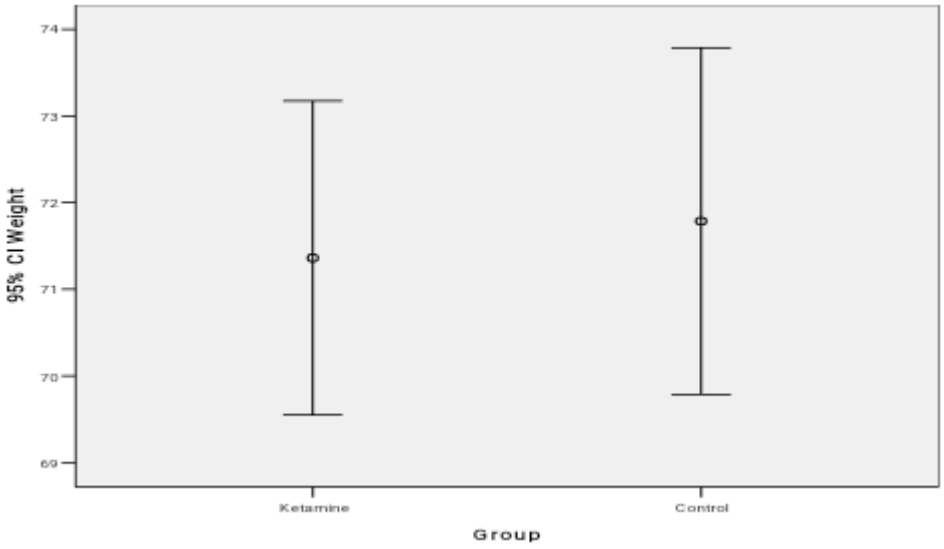

Figure 1: Weight distribution across the study groups

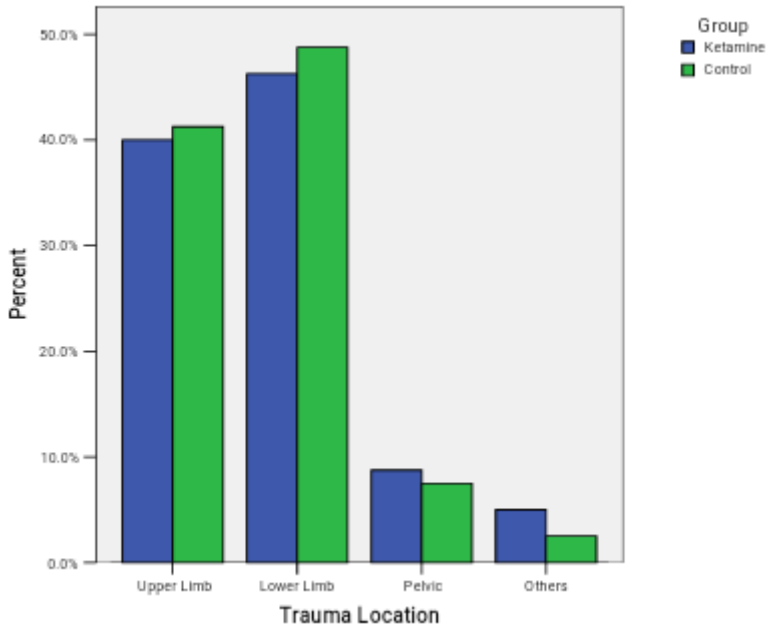

Figure 2: Frequency distribution of trauma site across the study groups

With regard to the history of opioid use, 11.3% (n=9) and 10% (n=9) of the patients in the intervention and placebo groups used opioids, respectively. The comparison of the history of opioid use between the two groups showed no significant difference (P=0.79).

As depicted in Figure 1, the anatomical location of injury was alike across the groups (P=0.847). In addition, 23 (28.8%) and 16 (20%) patients in the intervention and placebo groups showed side effects, respectively, with no significant difference (P=0.197).

As presented in Table 1, there was no significant difference between the two groups in terms of opioid doses (P>0.05). Table 2 demonstrates the pain scores at different times in research groups. The results indicated no significant difference was observed between the two groups considering the VAS score (P>0.05). However, the comparison of VAS score between study pre- and post-intervention stages showed a significant decrease in pain after the injection of ketamine and opioid (P<0.05).

Table 1: Opioid doses across the groups

Factor	Ketamine	Control	P-value
Opioid Count	1.9±0.8	2.0±0.8	0.35
Initial Opioid Dose	3.6±0.4	3.5±0.5	0.62
Total Opioid Dose	7.2±2.9	7.8±3.1	0.208
Repeat Opioid Dose	1.0±0.8	1.2±0.8	0.31

Table 2: Pain severities by visual analog scale across the groups

VAS	Ketamine	Control	P-value
Before intervention	9.1±0.7	8.7±0.9	0.209
30 minutes	7.8±0.7	7.6±1.1	0.14
60 minutes	7.2±2.9	7.8±3.1	0.31
90 minutes	4.5±0.9	4.6±1.0	0.47
120 minutes	4.2±0.8	4.3±0.8	0.31

VAS: visual analog scale

4. Discussion

The present study was targeted toward the investigating on of the efficacy of using ketamine versus placebo with opioids in traumatic patients. The pain reduced in both groups; however, the addition of ketamine to opioids for the reduction of pain resulted in no additional superior side effects. Moreover, there were no additional side effects after using ketamine.

According to the literature, single therapy is not effective for pain management in traumatic patients [20]. Accordingly, the present study involved the evaluation of combination therapy that showed no superior effectiveness versus single therapy.

A cohort study was performed to compare the patients receiving intravenous morphine alone (0.2 mg/kg) with those receiving a combination of morphine and ketamine (0.2 mg/kg). The results of the mentioned study were indicative of higher improvement in the pain score of the subjects receiving morphine plus ketamine than in the patients subjected to morphine alone. It was concluded that morphine with low-dose ketamine provides adequate pain relief in patients with trauma [21].

Similarly, in a randomized controlled trial, Jennings et al. demonstrated that the use of intravenous morphine plus ketamine resulted in better analgesic effect in patients with trauma, compared to the sole administration of intravenous morphine (5 mg). In the mentioned study, 10-20 mg intravenous morphine plus ketamine was administered every 3 min [18]. Moreover, in a systematic review addressing prehospital ketamine analgesia, the use of ketamine analgesia plus morphine was reported as an effective and safe approach for pain relief in patients presenting with acute trauma as compared to the administration of morphine [22].

The cause of discrepancy between our results and those of similar studies may be related to the difference in sample size or applied dosages of ketamine and morphine. The cause of finding no difference between our research groups can be also the use of opioids as an effective therapeutic modality in both groups. Accordingly, this complicates the accurate measurement of the effectiveness of ketamine in patients and its comparison with opioids.

Different times of measuring pain intensity may be another reason explaining the achievement of obtaining different outcomes in various studies. Our study was performed on low sample size.

Moreover, in the current study, a different dosage of ketamine and morphine was adopted, compared to those of the previous studies. In this regard, the ketamine dosage used in our

study was lower than that in other similar studies. IAdditionally, in the present research, the effectiveness of ketamine and morphine in pain intensity was assessed at 30, 60, 90, and 120 min, which was different from the procedure adopted in other similar studies.

Similar to our study, another Iranian study was performed by Jahanian et al. to compare the efficacy of morphine versus low dose of ketamine in traumatic patients. In the mentioned study, the pain intensity decreased in both study groups after 240 min of intervention. Similar to our study, they reported no difference was reported between the two study groups in terms of pain intensity at 30, 60, 90, 120, 180, and 240 min [23].

Ahern et al. reported good efficacy and safety for low-dose ketamine for reducing various pain categories in patients admitted to the emergency ward [24]. This safety pattern was also observed in our study; however, no data were indicative of the efficacy-related domain. Bowers et al. reported that ketamine had good efficacy in pain reduction during 120 min and led to lower opioid dose and count [25]. This issue was not established in our study that may be due to the use of different protocols.

In our study, the mean VAS score was nearly 9 in the subjects, which decreased to 7.7 and 4.2 about 60 and 120 min after injection, respectively. This post-injection decrease in pain intensity was observed in the two groups. It seems that the use of ketamine plus morphine leads to the reduction of the amount of morphine required in traumatic patients [22]. A decrease (by approximately 27% within 30 min) in morphine requirement was also reported by Jennings et al. for patients receiving morphine plus ketamine [18]. In another Iranian study carried out by Parvizrad et al. on 606 subjects with orthopedic trauma, low-dose ketamine was reported to have good analgesic efficacy. In addition, in the mentioned study, a lower dose of morphine, as an agent for rescue analgesia, was required in comparison to that in the placebo group. In line with our results, pain severity reduction was higher in those who received ketamine; however, the side effects had a similar rate across the groups [19].

5. Conclusion

Based on the results, it can be concluded that the use of ketamine as an adjunct to opioids for pain control exerts no superior effect in traumatic patients. However, it is required to perform more studies on the other types of combination therapy with larger sample size to obtain further evidence in this domain and determine the best analgesic option with a high safety pattern in traumatic cases.

6. References

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