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Original Article

Onset and Effect Duration of Intrabuccal Space and Intramuscular Ketamine in Pediatrics

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Abstract

Background: Painful diagnostic and therapeutic procedures performed for children are routine actions. Opioids and nonsteroidal anti-inflammatory drugs such as acetaminophens are among medications that can be used for this purpose. This study aimed to compare the onset and duration of action of intrabuccal (IB, submucosal) space and intramuscular (IM) injection of ketamine in pediatrics. **Materials and Methods:** This clinical trial study was carried out on 126 children of 1–15 years old referred to the emergency room of Al-Zahra and Kashani Hospitals in Isfahan and divided into two 63 populated groups of IM and IB. For one group randomly, 3 mg/kg IB ketamine was administered, and for another group, ketamine was injected intramuscularly at the dose of 5 mg/kg. The drug effect, surgeon satisfaction, and complications were evaluated. Data were analyzed using SPSS software. **Results:** The mean of time between injection and onset of drug effect in IM group was 5.71 min, whereas in IB group, it was 4.14 min ($P < 0.0001$). The mean of the duration of drug effect in IM group was 45.54 min, whereas in IB group, it was 24.63 min ($P < 0.0001$). Complications in IM group were significantly more reported than IB group (33.3% versus 11.1%, respectively, $P = 003$). The median of surgeon satisfaction in IM group was 3 and in IB group was 4 which was statistically significant ($P = 0.007$). **Conclusions:** IB method is preferred over IM method, and hence, it is recommended to use.

Keywords: *Injection, intrabuccal space (submucosal), intramuscular, ketamine*

Introduction

Pain relief using a good analgesic drug intra- and post-operatively is an important issue both for patients and for anesthesiologists so that it is called preventive analgesia. Opioids and nonsteroidal anti-inflammatory drugs such as acetaminophen are among medications that can be used for this purpose. Each of these drugs has serious complications such as severe respiratory depression and bleeding at the surgical that limits their use.[1] Since 50 years ago, ketamine or 2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone is another factor used as an anesthetic drug for both humans and animals. The active metabolite of ketamine which is believed to cause anesthetic effects is norketamine that is made in the liver. Ketamine acts as MDA receptor antagonist of N-Methyl-D-aspartate (NMDA) in thalamocortical pathways and limbic system and leaves its anesthetic effects. It is known that ketamine also effects on other neurotransmitter systems.[2]

In addition to the anesthetic effect, ketamine has other effects such as analgesia for reducing acute and chronic pain. This effect of ketamine is used when it is applied in low doses usually between 0.1 and 0.3 mg/kg (less than the amount used for anesthesia). Ketamine is also used for the treatment of the major depressive disorder,[3] treatment-resistant depression,[4,5] etc. It is interesting that ketamine has also the ability to stimulate the cardiovascular system which can be seen as increased heart rate, systemic vascular resistance, pulmonary arteriolar pressure, and pulmonary vascular resistance. In addition, the drug provides minimal respiratory depression.[6]

Various complications have been reported regarding the chronic and high dose of these drugs including restlessness, hallucinations, confusion, nightmares, and urinary symptoms. Nausea and vomiting induced by ketamine after surgery is usually observed in children and is less common in adults.[7] Impaired eye movements, diplopia, and nystagmus as well as a slight increase

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in intraocular pressure may also occur due to the use of ketamine.[8,9]

The onset of anesthesia administered by intravenous (IV) ketamine is between 45 and 60 s, and the duration of its effect is 10–20 min.[10] In intramuscular (IM) administration, the onset of its effect was reported between 3 and 8 min, and its duration was 15–25 min in one source[11] and another source stated as 30 min to 2 h after administration.[12]

On the one hand, according to the principle that the effectiveness and complications of ketamine depend on its administration method and type, and on the other hand, the contradicting results obtained in various studies and lack of a study on the effectiveness and complications of ketamine administration as IM and intrabuccal (IB) (injection in submucosal space), a study to examine the mentioned cases in the IM and IB administration seems necessary.

Regarding the difficulty of IV injection in children and because ketamine is lipophilic and rapidly absorbed and as it seems that due to intraoral submucosal space (IB) is congested, it can be absorbed faster and also remove hepatic metabolism cycle, so this study was done to evaluate this hypothesis that the lower dose of ketamine is needed in IB injection than IM.

Materials and Methods

In this clinical trial, the study population was selected by convenience sampling method from children 1–15 years referred to the emergency room of Al-Zahra and Kashani Hospitals in Isfahan, Iran. The patients were selected using convenience and completely randomized sampling method and were grouped into IM and IB (submucosal) with regard to the inclusion and exclusion criteria. The sample size was calculated 63 people for each group using the sample size formula for a confidence level of 0.95 and power of 0.80. The maximum acceptable error in the estimate was considered 0.05. For further study, 126 children referred to the mentioned hospitals were selected and divided into two groups (IM and IB) of 63 subjects. The involved subjects in the study were of both sexes, and the two groups were matched in terms of age. For one group randomly, IB ketamine was administered, and for another group, ketamine was injected intramuscularly. The written consent of all parents or caregivers was obtained. Inclusion criteria were based on clinical criteria to be diagnosed by a specialist. Exclusion criteria of the study included contraindications to receive ketamine. These were cases such as high blood pressure, liver disease and kidney disease, glaucoma, increased intracranial pressure, a lump in the central nervous system that causes seizure, fundamental mental disorders, porphyry, epilepsy, unwanted reaction to ketamine, and any sores in the mouth. Children were prepared for general anesthesia in the usual way. About ketamine, there is no supportive evidence of fasting before procedural sedation and anesthesia (PSA) in emergency, but it is possible to do PSA confidently in children who have been recently feed orally; however, clinical judgment is in priority.[13] Diet duration after administration of ketamine was estimated 7–8 h on average. According to the previous studies, ketamine amount was prescribed for IM as 5 mg/kg. The amount of ketamine prescribed as IB was considered based on administered average IV and IM dose. The doses prescribed for IV, IM, and IB were 1 mg/kg, 5 mg/kg, and 3 mg/kg, respectively. Given that the prescribed dose for IB was not determined, a pilot study was carried out on 10 children requiring sedation admitted to Al-Zahra and Kashani Hospitals, and ketamine was used for titration with the informed consent of the parents. The initial 1 mg/kg dose of ketamine as IB was administered until moderate sedation, and a dose of 3 mg/kg was appropriate. Therefore, this dose was considered for the project. In both IM and IB, a maximum dose of 200 mg was administered to the patient. The children under anesthesia were under the care of the emergency medicine specialist, and any complications after the administration of ketamine were recorded by nurses and the specialist.

Estimating the onset of ketamine effect in IM and IB methods was done as the time interval between the administrations of ketamine to the appearance of the first signs of anesthesia. These sings include feeling sleepy, numbness in hands and feet, loss of ability to move the body, lack of ability to obey the doctor's orders, lack of the need for airway intervention, and natural function of the cardiovascular system (moderate sedation).

Estimating the effect time of ketamine in the two IM and IB methods was done by recording the interval between the onsets of the first effects of ketamine until the patients obey the orders.

The effectiveness of ketamine in the induction of anesthesia was evaluated as a measure of sedation degree. The scale ranged from 1 to 5 as follows: 1 = fully conscious, 2 = awake but sleepy, 3 = between the state of sleep and wakefulness associated with verbal answers to the commands of the physician, 4 = between the state of sleep and wakefulness associated with response to painful stimuli, and 5 = unconscious with no response to stimulation. The severity of effectiveness and scaling it took place at regular intervals (at 5, 10, 15, 20, 30, 40, and 50 min).

Physician satisfaction of anesthesia induction by ketamine in both IM and IB groups estimated by a scale from 1 to 4 as follows: 4 = excellent (full medical consent), 3 = good (very little complaint of the doctor with the no need to other tools), 2 = middle (minor movements of the patient during surgery needing patient control and other measures), and 1 = lack of physician satisfaction.

Complications consisted of hypoventilation, apnea, any obstruction, and disorder in respiratory tract such as

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laryngospasm, cardiopulmonary disorders, vomiting, and any impairment of physiological parameters such as respiratory and heart rate and blood pressure. To measure complications such as vomiting that do not have a specific unit, numerical scale was used. For example, 0 = no nausea, 1 = vomiting once, 2 = vomiting twice, etc.

All patients were followed up with phone until 24 h after discharge from the hospital to record the likely complications.

For each of the participants, a questionnaire containing demographic information, medical condition, and history of the patient was filled, and written consent from every person was taken after the ratification of the ethics review board and hospital protocols.

The collected data were analyzed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA) and statistical tests consistent with the hypothesis and research questions. *T*-test and covariance were used to compare the efficacy of ketamine use between the groups. The level of significance 0.05 was used in the interpretation of results.

Results

Figure 1 shows flowchart of the study, 142 patients were reviewed, 11 patients did not met inclusion eligible, and five patients refused informed consent. One hundred and twenty-six eligible patients randomly assigned into two intervention groups. Patients were followed 24 h after hospital discharge. All patients in both groups complete the study follow-up period and were analyzed.

The mean of age in studied patients was 3.9 ± 2.1 years, 77 patients (61.1%) were male, and 49 patients (38.9%) were female. Table 1 shows baseline characteristics of studied patients. Patients in IM group were significantly younger than patients in IB group (P = 0.008). Sex combination and weight were not significantly different between groups. The mean of dose of ketamine in IM group was 67.94 mg/kg which was significantly higher than 44.86 mg/kg in IB group ($P < 0.0001$).

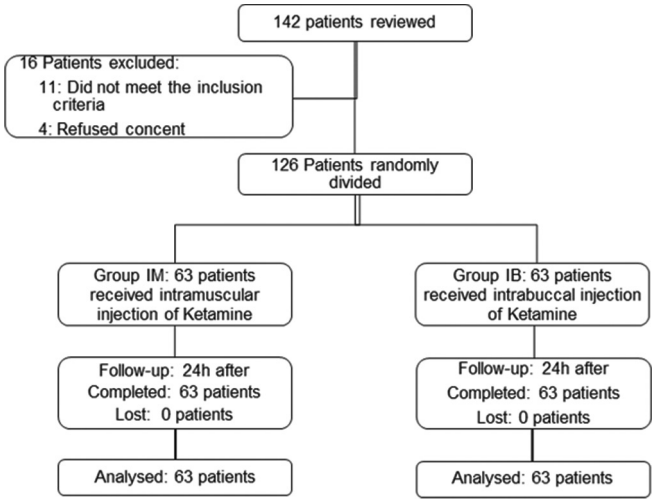

Figure 1: Study flowchart

Table 2 shows the comparison of drug effect, surgeon satisfaction, and side effects between studied groups calculated by independent sample *t*-test, Mann–Whitney U, or Chi-square test. The mean of time between injection and onset of drug effect in IM group was 5.71 min, whereas in IB group, it was 4.14 min ($P < 0.0001$). The mean of the duration of drug effect in IM group was 45.54 min, whereas in IB group, it was 24.63 min ($P < 0.0001$). The differences between studied groups after calculated by univariate analysis and stated age and weight as covariates remind statistically significant for the time between injection and onset of drug effect ($P < 0.0001$) and the duration of drug effect ($P < 0.0001$). Side effects in IM group were significantly more reported than IB group (33.3% versus 11.1%, respectively, P = 003). Furthermore, vomit in IM group significantly more reported than IB group (P = 0.007). The occurrence of low oxygen saturation level in both arms of the study was similar with no significant differences (P = 0.99). The median of surgeon satisfaction in IM group was 3 and in IB group was 4 which was statistically significant (P = 0.007).

Sedation score at time points was assessed using independent sample *t*-test and the results showed in Figure 2. As shown at min 10 and 15, the mean of

Table 1: Baseline characteristics between studied groups

Variables	IM group (*n*=63)	IB group (*n*=63)	*P*
Age	3.47±1.53	4.46±2.45	0.008*
Sex			
Male	36 (57.1)	33 (52.4)	0.59†
Female	27 (42.9)	30 (47.6)	
Weight	13.59±3.03	15.02±5.79	0.086*
Ketamine dosage	67.94±15.15	44.86±17.54	<0.0001*

Data are mean±SD, number (%). IM group received intramuscular injection of Ketamine, IB group received intrabuccal injection of Ketamine, *P* values calculated using, *Independent sample *t*-test or †Chi-square test

Table 2: Comparison of drug effect, surgeon satisfaction, and side effects between studied groups

Variables	IM group (*n*=63)	IB group (*n*=63)	*P*
Time to start drug effect (min)	5.71±2.85	4.14±1.54	<0.0001*
Drug duration effect (min)	45.54±8.43	24.63±9.33	<0.0001*
Side effects	21 (33.3)	7 (11.1)	0.003†
Vomit	19 (30.2)	6 (9.5)	0.007†
Low oxygen saturation level	1 (1.6)	0	0.99†
Surgeon satisfaction score	3 (3-4)	4 (3-4)	0.007††

Data are mean±SD, number (%) or median [IQR]. IM group received intramuscular injection of Ketamine, IB group received intrabuccal injection of Ketamine, *P* values calculated using *Independent sample *t*-test, †Chi square test or ††Mann–Whitney U

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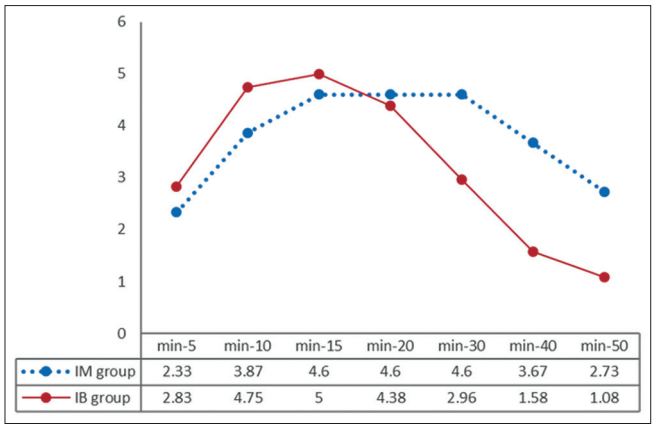

Figure 2: Comparison of sedation score between groups. IM group received intramuscular injection of Ketamine and IB group received intrabuccal injection of Ketamine. Significant level at each time point calculated by Independent sample *t*-test, as follow; min-5, *P* = 0.39; min-10, *P* < 0001; min-15, *P* = 0.005; min-20, *P* = 0.35 and min-30, 40 and 50, *P* < 0001. The trend in sedation score was calculated by repeated measurements of analysis of variance, *P* < 0001

sedation score in IB group was significantly higher than IM group ($P < 0.05$), but in min 20, sedation score was similar with no significant differences between groups ($P = 0.35$). At min 30, 40, and 50, the mean of sedation score in IB group was decreased and was significantly lower than IM group ($P < 0.0001$). The trend of sedation score in studied group was assessed by repeated measurements of the analysis of variance (ANOVA) and was significantly different between groups ($P < 0.0001$).

Discussion

The objective of this study was to evaluate the onset and duration of IB and IM ketamine. According to results of the study, IB injection method had an earlier onset of effect compared to IM injection. In addition, complications in the group IB were lower compared to IM group.

The recovery time after ketamine administration strongly depends on the way of usage. For example, Roback *et al*. found that the recovery time for IV was 49 min less than IM (80–129). In this study, a clinical trial on children revealed that administration of 4 mg/kg ketamine as IM was more effective than the administration of 1 mg/kg ketamine as IV, but IM method seems to cause more vomit than IV method[14] that may be due to not formation of higher peaks of concentrations in IM unlike IV. In another study carried out by Hollister *et al*. on 122 children, it was found that the incidence of complications of ketamine such as vomiting, hallucinations, nightmares, and frightening dreams, especially in children <11 years, in IM method of administration was lower than the IV method. That is why, this study suggests IM administration as a better way of the induction of anesthesia in children.[15]

In 2006, Stephen *et al*. suggested that ketamine administration method depends on several factors: IV administration depends on the presence of skilled nursing for administration of ketamine to reduce the injection stress in the child. On the other hand, this method of administration shall be used in cases where the need for the duration of anesthesia is low. IM administration shall be applied in cases where the need for longer duration of anesthesia is greater.[16]

Ketamine is a NMDA receptor antagonist and a phencyclidine, which is widely used for sedation and anesthesia in children require painful procedures.[13] Due to its properties, short length of the effect, and less complications, ketamine is used as favorable drug for everyday sedation.[17] The methods of using ketamine vary, including interventions injection (IV) and subcutaneous injection. Each of these methods has several advantages and disadvantages and complications, and there is still no agreement on a safe method of injection that causes full compliance and satisfaction in surgeon and a method that has fewer side effects.[18] Most studies conducted on the methods of ketamine injection have compared IV and IM injection methods,[19-21] and search in the literature and databases indicated that this study compares IB injection method with IM injection method for the first time. Studies conducted to compare IV and IM injection methods have found contradictory results, for example, in a study conducted by Momeni *et al*., two IM and IV injection methods were compared, in which 60 patients were examined. It was found that sedation duration was longer in IM compared to IV injection method, but complications in two groups did not differ significantly.[22] In a review article study that compared IM and IV injection of ketamine for pediatric sedation, they concluded that both IV and IM ketamine have been shown to provide efficacious and safe procedural sedation in children. There is limited evidence directly comparing IV and IM administration, and the larger body of evidence based on single arms of randomized trials and case series is methodologically limited. IV ketamine appears to have a better adverse events profile than IM ketamine; similarly, IV ketamine has a shorter recovery. Based on this review, they suggest that ketamine delivered IV has some advantages.[22]

In another study conducted by Roback *et al*. in 2006 on IM injection and IV injection methods, nausea complication in the group that received IM injection was higher.[23] Thus, according to studies conducted about two IM and IV methods of ketamine injection, no study proposed a reliable and safe method with fewer side effects and longer sedation duration. On the other hand, IV injection requires another vessel of the patient and an access.

Pharmacokinetics and analgesia effects of oral ketamine and IM were compared in a study, and it was found that the increase in the threshold of pain tolerance in IM administration of ketamine was between 15 and 30 min after administration when the plasma concentration of ketamine was 150 ng/ml. The threshold was increased

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30 min after oral administration when plasma ketamine concentrations was less than the IM administration, and it was about 40 ng/ml. The reason for this may be due to more accumulation of norketamine (ketamine metabolite) that is observed in oral administration of ketamine and is believed to have analgesia effects.[2] In another study by Morteza Heidari *et al*., on the analgesia effects of ketamine comparing rectal versus acetaminophen administration, it was found that ketamine can be a good alternative to acetaminophen. The study also showed that in rectal administration of ketamine, many complications such as hallucinations and nightmares are not observed. The results of the review study conducted by Boroumand Reza Zadeh *et al*., finally, recommended IV administration for children as safe and effective method.[14,15]

This study is the first study that compared the IB injection method with IM injection method. According to the results of this study, the dose used for sedation in IM injection was 67.9 mg/kg, while it was 44.88 mg/kg in IB method, indicating that the dose required for IM injection was more, which indicates the superiority of the IB. Therefore, IB injection method is better than IM injection method. Duration of drug effect onset in IM injection was 5.71 min, while it was 4.14 min in IB method, which it also indicates superiority of IB injection method compared to IM injection method. Duration of drug in IM injection was 45.54 min, and it was 24 min in IB injection. It seems that in short-term procedures, IB is more appropriate method, and complications and vomiting in the IM method were more than those in IV method. Therefore, IB method is preferred, and surgeon has more satisfaction with this method of injection. As mentioned, this study is the first study conducted on the IB and IV methods of injection, which according to the results of this study; IB method is preferred over IM method, so it is recommended to use. One limitation of this study is small sample size, and it has been conducted in various procedures. It is recommended to do similar study with larger sample size and the same procedures such as suturing. In addition, it is recommended that IB method to be compared with other injection methods such as IV or subcutaneous methods so that IB method to be used; if it is proven that it has preference over other method.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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