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The Effects of Different Doses of Submucosal vs. Intravenous Ketamine for Conscious-sedation in Children Candidates for Diagnostic-Therapeutic Procedures in Emergency Department

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Abstract

Introduction: Ketamine is a commonly used medicine for reducing pain and stress in patients, including children in emergency department (ED). The intravenous (IV) injection of ketamine is gold standard though difficult in children, but other routes are also possible.

Objective: This study was conducted to compare the effects of the submucosal at different doses versus IV injections of ketamine on sedation with proper consciousness in children candidates for diagnostic-therapeutic procedures in ED.

Methods: This randomized clinical trial was conducted with 4 groups; groups 1, 2 and 3 respectively received 4, 3 and 2 mg/kg of submucosal ketamine and group four 1.5 mg/kg of IV ketamine. Eligible subjects selected from 46 patients of children's age as the candidates for subcutaneous wound healing were randomly assigned to the four groups and followed up 5, 10, 15 and 30 minutes after the injection. The Ramsay score was obtained by measuring the heart rate, the breathing rate, the time to start affecting and duration of the effect. The data were ultimately analyzed in SPSS and Excel.

Results: The baseline data were matched and confounding variables eliminated included age, gender, weight and hemodynamics. Compared to other doses of submucosal ketamine, 4 mg/kg was found to exert its effect the fastest (4.08±1.01 minutes) ($p<0.05$) and for the longest duration (23.09±1.12 minutes) ($p<0.05$). The Ramsay score in groups 1 and 4, i.e. 5.9, was significantly higher than that in groups 2 and 3 ($p<0.05$).

Conclusions: The results showed that 4 mg/kg and 3 mg/kg of submucosal ketamine are appropriate alternatives to IV ketamine. Although the time to start affecting was shorter in the intravenous group compared to in the other groups, the duration of the effect was the longest with 4 mg/kg of submucosal ketamine. Surgeon satisfaction scores were found to be very good and not significantly different between groups 1, 2 and 4. Vomiting was also prevalent with no significant differences between the four groups.

Key words: Administration, Buccal; Children; Conscious Sedation; Drug Administration Routes

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INTRODUCTION

Taking care of patients who need emergency services is an important duty in emergency department (ED), especially when they need diagnostic-therapeutic procedures (1, 2). Analgesics and sedatives are required in EDs to prevent the potential pain and stress caused by diagnostic and therapeutic procedures (3-5). Ketamine is a popular non-barbiturate dissociative agent that induces rapid and profound sedation, analgesia and amnesia (6-8). In addition to anesthetic effects, analgesia is induced by ketamine at doses as low as 0.1-0.3 mg/kg and below the anesthetic doses to relieve acute and chronic pains (9-11). Ketamine is now commonly administrated intramuscularly or intravenously for sedation in pediatric EDs. The advantages of the intramuscular administration include no needs for venipuncture and those of the intravenous (IV) administration include faster effects and recovery (12). Recently, some recommend that the submucosal administration to offer both these advantages, and preferred the submucosal to intramuscular injection (13). For as much as the comparison of IV and submucosal injection effects have not been

studied in the case of emergency procedures and surgeon satisfaction until now and injection in the buccal region due to extensive vascular system and high absorption and localized anesthetic by local gel is a good way to calm the children, whom should tolerate a very painful and stressful moments for their proper venipuncture. The present study was therefore conducted to investigate the effects of the submucosal at different doses versus IV injections of ketamine on sedation with proper consciousness in children as candidates for diagnostic-therapeutic procedures in the ED.

Methods

Study design and setting

This randomized clinical trial was conducted in the EDs of Al-Zahra and Kashani hospitals, Isfahan, Iran. The study was performed after receiving the approval of the Research Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.REC.1396.3.110). The investigators were adhered to Declaration of Helsinki Principles throughout the study. Signed informed consent were received from the patients' parents before starting the intervention.

Study population

The inclusion criteria comprised an age of 2-8 years candidates for diagnostic-therapeutic procedures in the ED. The exclusion criteria consisted of allergies to ketamine, psychophysical disabilities, immune system disorders, other urgent needs for IV injections in group 4, contraindications for ketamine administration such as hypertension and recent seizures, history of thyroid diseases, glaucoma, active upper respiratory tract or lung infections, hydrocephalus, central nervous system masses, porphyria and heart diseases such as angina pectoris, history of airway disorders and tracheal stenosis, major procedures causing posterior nasopharyngeal inflammation and sever damage to the head, any breathing and hemodynamic disorders requiring support and emergency interventions.

The sample size was calculated as 42 in each group using the mean difference formula for the Ramsay score (mean difference=0.8 and standard deviation=1.3) at a confidence interval of 0.95 and a power of 0.8. Sampling was performed via convenience method.

Intervention and data gathering

The eligible patients were randomly assigned to the 4 groups using a random-allocation software package. Groups 1, 2 and 3 respectively received 4, 3 and 2 mg/kg of submucosal ketamine and group four 1.5 mg/kg of IV ketamine. Blinding was impossible in the four groups, although double blinding was performed in terms of ketamine dose in groups 1-3. Ketamine hydrochloride made by Rotexmedica company in Germany was injected in the present study with a Gaj insulin syringe 28.

Baseline variables included age, gender and weight. Surgeon satisfaction scores comprised 0: very bad, 1: bad, 2: moderate, 3: good and 4: very good. The Ramsay sedation scale scores included 1 meaning the patient is anxious, agitated and restless, 2 meaning the patient is cooperative, oriented and tranquil, 3 meaning the patient is responsive to commands only, 4 meaning the patient quickly responds to light glabellar taps or loud auditory stimuli, 5 meaning the patient slowly responds to light glabellar taps or loud auditory stimuli and 6 meaning the patient does not respond to light glabellar taps or loud auditory stimuli (1, 14).

The time during which ketamine begins to exert its effects was the interval between injecting ketamine and beginning to disobey the commands by the patient. The effect duration was also the interval between beginning to disobey and to obey again. Homodynamic parameters, including the heart rate, the breathing rate and oxygen saturation, were measured before and 5, 10, 15 and 30 minutes after the injection.

Statistical analysis

The data were expressed as frequency, relative frequency and mean values. The Chi-squared test and Fisher's exact test were used to assess differences in the distribution of the categorical variables such as gender and vomiting among the study groups. ANOVA was performed to assess mean differences in the numerical variables among the study groups. Moreover, repeated measures ANOVA was used to assess mean differences in the numerical variables between the five time points. The Bonferroni method was used for the pairwise comparison of the independent groups and the Shapiro-Wilk test to investigate the normality distribution of the data. Level of statistical significance was set at $P<0.05$. The statistical analyses were performed in SPSS-25 (IBM Corp., Armonk, N.Y., USA).

Results

According to figure 1, this study analyzed the data of 173 patients in four groups. Submucosal ketamine was administered at 4 mg/kg in 35 patients, at 3 mg/kg in 43 and at 2 mg/kg in 47 and intravenous ketamine was administered at 1.5 mg/kg in 48 patients. The mean age of the patients obtained as 3.3 years was not significantly different between the four groups (p=0.988). Approximately

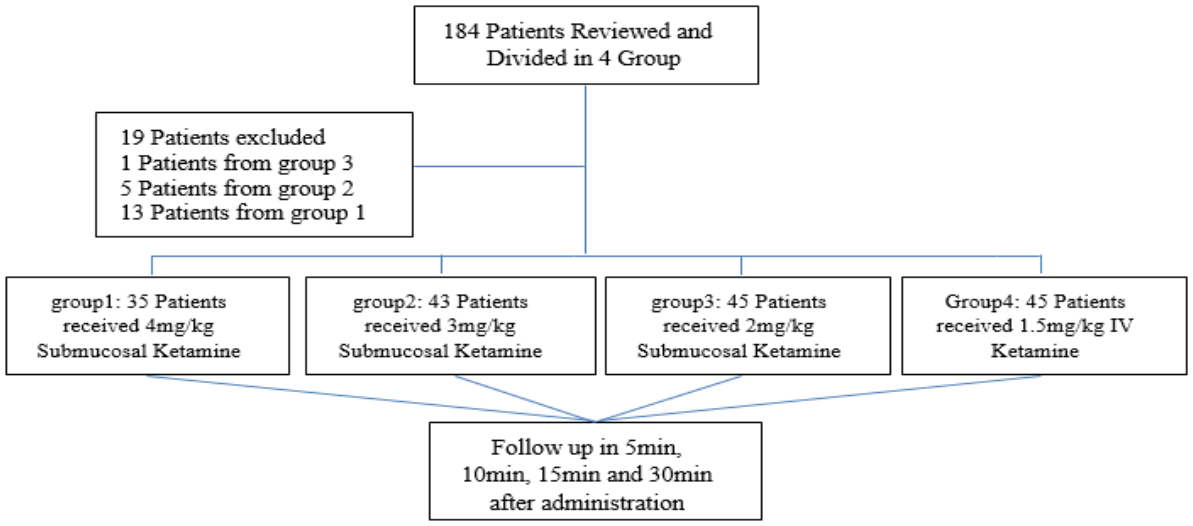

Figure 1: The study flowchart

50% of the patients in each group were male and no significant differences were observed in gender distribution (p=0.916) and weight (p=0.408) between the study groups (table 1).

Statistically-significant differences were observed between the groups in terms of the time to start affecting in minutes (p<0.001). The intravenous administration with the dose of 1.5 mg/kg resulted in the minimum time to affect after the injection (1.13±0.35 minutes), which was significantly different from that in the three submucosal groups. The times to start affecting obtained as 4.09 minutes with 4 mg/kg of submucosal ketamine and 4.05 minutes with 3 mg/kg were shorter than that with 2 mg/kg (4.77 minutes), suggesting statistically-significant differences (p<0.001); the difference between the submucosal injection at 4 and 3 mg/kg was, however, insignificant (p=1.0) and between 4 and 2 mg/kg was marginally significant (p=0.051) (table 1).

The longest (23.09±1.12 minutes) and shortest (14.15±1.23 minutes) durations of the effect were respectively associated with 4 and 2 mg/kg of submucosal ketamine. The duration of the effect obtained as 17.94±1.26 minutes in the intravenous group was shorter than that of 2 mg/kg of submucosal ketamine and lower than that of 3 mg/kg of submucosal ketamine. Table 1 shows significant differences in the mean duration of the effect for all the pairwise comparisons among the four study groups (p<0.001).

The mean surgeon satisfaction score obtained as 2.02 at 2 mg/kg of submucosal ketamine was lower than that in the other three groups, which was over 3.0. The difference in the mean satisfaction score was statistically significant between the 2 mg/kg

Table 1: Comparing demographic information and the intervention effect among the four groups

	Submucosal ketamine			Intravenous ketamine	P	Significant difference*
	4 mg/kg (n=35)	3 mg/kg (n=43)	2 mg/kg (n=47)	1.5 mg/kg (n=48)		
Age; mean±SD	3.37±0.71	3.39±0.94	3.34±1.04	3.33±0.9	0.988	-
Gender; n(%)						
Male	20(57.1)	24(55.8)	25(53.2)	24(50.0)	0.916	-
Female	15(42.9)	19(44.2)	22(46.8)	24(50.0)		
Weight; mean±SD (Kg)	13.42±2.06	13.69±1.8	13.95±1.83	13.33±2.0	0.408	-
Mean time to start the effect; mean±SD (min)	4.09±1.01	4.05±1.17	4.77±1.54	1.29±0.65	<0.001	1,4; 2,3; 2,4; 3,4
Mean duration of the effect; mean±SD (min)	23.09±1.12	20.35±1.25	14.15±1.23	17.94±1.26	<0.001	All the pairwise comparisons
Surgeon satisfaction score; mean±SD	3.80±0.53	3.84±0.48	2.02±1.01	3.83±0.48	<0.001	1,3; 2,3; 3,4
Ramsay score; mean±SD	5.8±0.2	4.93±0.23	4.01±0.18	5.91±0.21	<0.001	1.2; 1.3; 2.3; 2,4; 3,4
Vomiting; n(%)	5 (14.28)	6 (13.95)	6 (13.04)	5 (9.5)	0.869	-

*Pairwise comparison based on the Bonferroni method

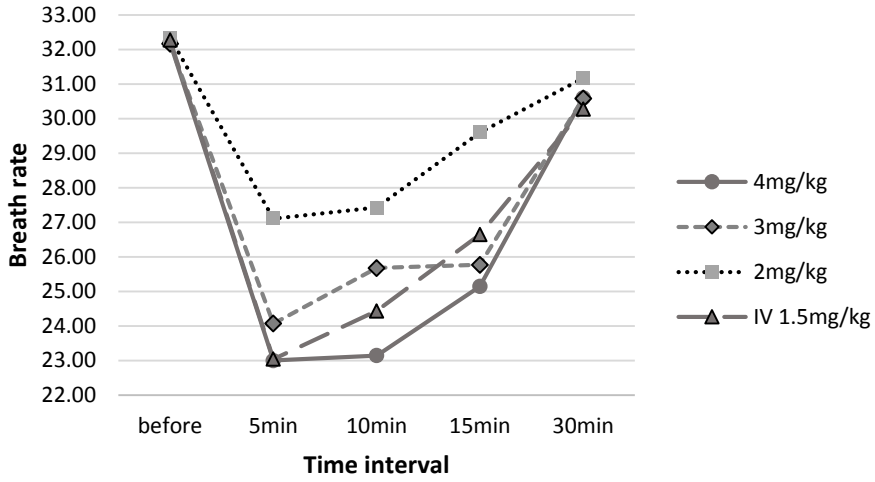

Figure 2: Breathing rate in the four groups at different time points

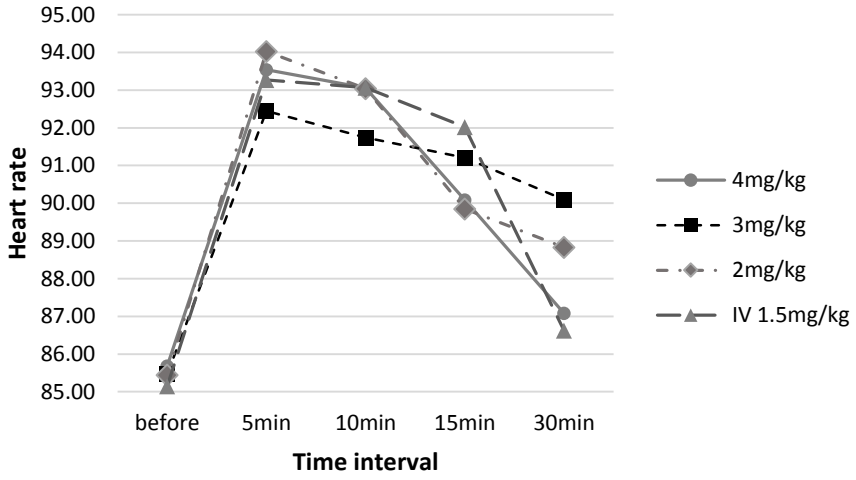

Figure 3: The heart rate in the four groups at different time points

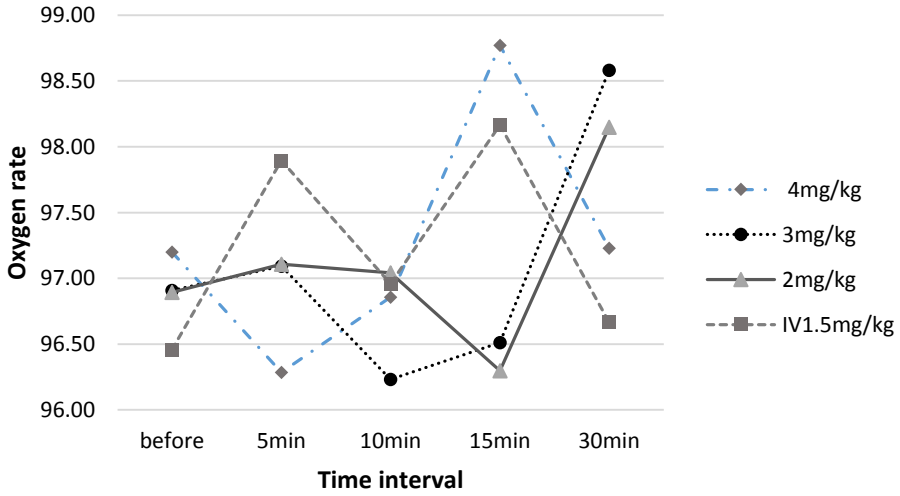

Figure 4: The heart rate in the four groups at different time points

submucosal group and the other three groups (p<0.001) (table 1).

The Ramsay scores obtained as 5.91±0.21 in group 4 and 5.80±0.2 in group 1 were higher than the score in the other two submucosal groups. Pairwise comparison showed a significant difference between every two groups, except for between groups 1 and 4 (table 1).

The mean satisfaction score obtained as 2.02 at the lowest submucosal dose (2 mg/kg) was lower than the mean satisfaction score of over 3.0 in the other three groups, suggesting a statistically-significant difference (p<0.001) (table 1).

Vomiting in the intravenous group obtained as 9.5% was lower than 13.0%-14.3% in the other three groups, suggesting a statistically-insignificant difference among the four groups (p=869) (table 1).

The breathing rate was significantly different among the five time points in all the study groups (p<0.001). No statistically-significant differences were observed in the breathing rate of approximately 32.0 observed in the four groups before the administration (p=0.878). The breathing rate was minimized at 23.0±1.08 in group 1 and 27.11±1.40 in group 3 five minutes after the injection (p<0.001). Also, the breathing rate in other time interval was lowest and highest in SI 4mg/kg and SI 2mg/kg group, respectively. Pairwise comparison showed statistically-significant differences in the breathing rate only between groups 3 (31.17±1.11) and 4 (30.27±1.09) thirty minutes after the intervention (p=0.005). Table 2 presents the results of the pairwise comparison between the four groups at all the time points. According to figure 2, the increase observed at this rate at minute 30 was insignificantly lower than the rate before the administration.

Figure 3 shows variations in the heart rate, suggesting no significant differences between the study groups before the intervention (p=0.572). The heart rate was maximized five minutes after the intervention in all the four groups and the maximum was the lowest (92.44±2.34) and highest (94.02±1.34) in groups 2 and 3, respectively (p<0.001). The heart rate was gradually decreased after minute 5 and minimized at minute 30 in groups 1 (87.09±1.50) and 4 (86.63±1.02) (p<0.001) and difference between other pairwise was significant (table 2).

According to figure 4, the critical reduction in oxygen saturation within the first 5 minutes in group 1 (96.29±0.79) required support for the patients. Oxygen levels increased after minute 5 with the reduction in the effect of the medicine and reached normal levels at minute 30. The difference in the breathing rate was significant between every two groups at the five time points (p<0.001). Table

Table 2: Breathing rate, heart rate and oxygen rate at different time points and pairwise comparison among the study groups

Group	Time Point					P
	Before intervention	5 min after intervention	10 min after intervention	15 min after intervention	30 min after intervention	
	Respiratory rate; mean±SD (/min)					
1	32.20±1.11	23.0±1.08	23.14±1.03	25.14±0.88	30.60±1.38	<0.001
2	32.16±1.0	24.07±0.83	25.67±1.19	25.77±1.0	30.58±1.31	<0.001
3	32.34±1.15	27.11±1.40	27.43±1.36	29.60±1.47	31.17±1.11	<0.001
4	32.27±1.12	23.04±1.07	24.44±0.97	26.65±0.96	30.27±1.09	<0.001
P	0.878	<0.001	<0.001	<0.001	0.005	
Significant difference*	-	1,2; 1,3; 2,3; 2,4; 3,4	All pairwise comparisons	1,3; 1,4; 2,3; 2,4; 3,4	3,4	
	Heart rate; mean±SD (/min)					
1	85.69±1.37	93.54±2.09	93.06±1.95	90.09±1.69	87.09±1.50	<0.001
2	85.47±2.02	92.44±2.34	91.74±2.79	91.21±2.51	90.09±2.42	<0.001
3	85.45±1.90	94.02±1.34	93.04±1.38	89.85±1.30	88.83±1.22	<0.001
4	85.15±1.61	93.27±1.20	93.06±1.06	92.02±1.08	86.63±1.02	<0.001
P	0.572	0.001	0.002	<0.001	<0.001	
Significant difference*	-	1,2; 2,3	1,2; 2,3; 2,4	1,2; 1,4; 2,3; 3,4	1,2; 1,3; 2,3; 2,4; 3,4	
	Oxygen saturation; mean±SD (%)					
1	97.0±0.80	96.29±0.79	96.86±0.77	98.77±0.43	97.23±0.94	<0.001
2	96.91±0.89	97.09±1.06	96.23±0.68	96.51±0.67	98.58±0.73	<0.001
3	96.89±0.84	97.11±0.87	97.04±0.93	96.30±0.66	98.15±1.08	<0.001
4	96.46±0.90	97.90±0.52	96.96±0.87	98.17±1.10	96.67±1.06	<0.001
P	0.016	<0.001	<0.001	<0.001	<0.001	
Significant difference*	1,4	1,2; 1,3; 1,4; 2,4; 3,4	1,2; 2,3; 2,4	1,2; 1,3; 1,4; 2,4; 3,4	1,2; 1,3; 2,4; 3,4	

*Pairwise comparison based on the Bonferroni method

2 presents the results of pairwise comparison between the four groups at all the time points

Discussion

This study was conducted to compare the effects of 2, 3 and 4 mg/kg of submucosal ketamine and 1.5 mg/kg of intravenous ketamine. Ketamine can be administered in intravenous, intramuscular, intrabuccal and subcutaneous manners. Although the advantages and disadvantages of these administration methods have been addressed in literature, there is no consensus among clinicians about the superiority of any of these methods (15). No significant differences observed between the study groups in the baseline characteristics, including gender, age and weight, suggested the absence of confounding variables. The results of this study showed the shortest time to start affecting in group 4 with a mean difference of approximately 2.5 minutes respectively followed by group 2 (4.05 minutes) and group 1 (4.09 minutes), suggesting a significant difference from that in group 3.

The present study also found the effect duration in group 1 to be the longest and at least five minutes longer than in group 4. The longest duration of the effect was also reported for intramuscular ketamine compared to intravenous ketamine. Comparing the effects of intravenous ketamine with those of intramuscular ketamine in children admitted to emergency departments showed a significantly longer mean duration of sedation in the intramuscular group than in the intravenous group (14).

Similarly, the mean length of time between receiving the sedative and awakening was significantly shorter in the intravenous ketamine group (36.2±0.5 minutes) compared to in the intramuscular ketamine group (56.5±0.6 minutes) (14). A randomized clinical trial recruiting 120 patients found a time to start affecting of 1.7±1.1 minutes with 1.5 mg/kg of intravenous ketamine and 8.6±3.1 minutes with 4 mg/kg of intramuscular ketamine and a mean duration of optimal sedation of 20.6±12.0 minutes in the intravenous group and 37.2±11.8 minutes in the intramuscular group (16). Investigating pediatric patients receiving ketamine for orthopedic procedures also found duration of sedation to be significantly longer with 4 mg/kg of intramuscular ketamine (median: 129 minutes) compared to with 1 mg/kg of intravenous ketamine (median: 80 minutes) (14).

Momeni et al. (14) found intravenous ketamine more desirable while reporting a longer duration of sedation in the intramuscular ketamine group compared to in the intravenous ketamine group. The present study found 4 mg/kg of submucosal ketamine to cause a mean duration of the effect of 23.09±1.12 minutes, as opposed to the significantly-longer duration of 45 minutes reported for intramuscular ketamine. Submucosal administration of ketamine therefore appears more appropriate than the intramuscular and intravenous administration.

Majidi et al. (13) found the time to start affecting to be shorter for intrabuccal injection compared to for intramuscular injection. They reported fewer complications in the intrabuccal group than in the intramuscular group, which is consistent with the present findings, which recommended the submucosal administration rather than the intravenous administration. According to Majidi Nejad et al., although intravenous ondansetron can reduce the side effects (17), the problems of the intravenous administration of ondansetron still persist, which suggests the use of ondansetron intramuscularly or in other ways.

The present study found the surgeon satisfaction score (very good) to be equal in groups 1 and 4. Insignificant differences in this score were also reported between different methods of administering ketamine in literature; for instance, no significant differences were reported in the satisfaction score between the intramuscular and intravenous methods of administering ketamine (16). In contrast, Majidi et al. reported a significantly-lower median surgeon satisfaction score in the intramuscular group compared to in the intrabuccal group (13).

The present study found the prevalence of vomiting to range from 9.5% in group 4 to 14.28% in group 1, suggesting insignificant differences between the four groups. Research suggests a very high incidence of nausea in children receiving ketamine and that nausea and vomiting are the only side effects (16, 17). Similarly, the incidence of vomiting was obtained as 17.8% in the intramuscular ketamine-placebo group and 26.7% in the intravenous ketamine-placebo group (17). Roback et al. also reported a higher prevalence of vomiting with intramuscular ketamine (26.3%) compared to with intravenous ketamine (11.9%) (16).

The analgesic effect of submucosal ketamine (4 mg/kg) was found to resemble that of intravenous ketamine and higher than that in groups 2 and 3 in terms of the Ramsay score. In contrast to intravenous ketamine, submucosal ketamine resulted in a higher reduction in the breathing rate

in groups 1-3. Submucosal ketamine should be therefore administered more cautiously and carefully while monitoring patients, especially in the first 5 minutes. Variations in the heart rate were the same in all the four groups. The highest increase in this vital sign was observed in the first five minutes, especially in group 3 by 94 bpm. The heart rate was, however, almost the same in groups 1 and 4.

The fall in the breathing rate was followed by a decrease in oxygen saturation in the first 5 minutes in group 1. In other words, the patients receiving 4 mg/kg of submucosal ketamine required respiratory support. Many studies have compared intravenous ketamine with intramuscular ketamine. Submucosal ketamine, however, offers more advantages and causes fewer side effects than those of intravenous and intramuscular ketamine. The present research conducted to compare these methods with different doses to select the best one, especially for children in emergency departments

Limitations

As in the case of any studies, the present research suffered limitations; for instance, vomiting was the only investigated side effect with a low prevalence that resulted in a low statistical power in assessing differences between the groups. It is therefore recommended that future studies be conducted with larger samples and address other side effects. Given the failure of this study to investigate the contribution of confounding variables to the effect of the medicine in different groups, future studies are required to address these factors.

Another limitation of this study was to evaluate satisfaction in the physicians using a single question. Future studies are therefore required to explore different effective dimensions in the satisfaction with a higher number of questions and in more detail.

Conclusions

The present findings suggested a significantly-shorter time to start affecting in emergency unit procedures in the intravenous group compared to in the other submucosal groups. The duration of the effect was also found to be significantly longer using 4 mg/kg of submucosal ketamine compared to using intravenous ketamine. The surgeon satisfaction score was significantly lower in group 3 compared to in the insignificantly-different groups of 1, 2 and 4. Complications such as vomiting was prevalent with no significant differences between the submucosal groups and the intravenous group. The present study pioneered the investigation of intravenous and submucosal ketamine at different doses to select the best method and dose. Moreover, 4 mg/kg and 3 mg/kg of submucosal ketamine were found to constitute appropriate alternatives to intravenous ketamine. Submucosal administration is therefore recommended and preferred over the intravenous administration.

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Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

None declared.

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