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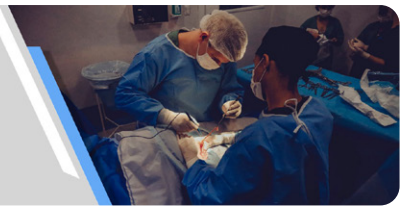

Oral Ketamine as a Premedication in Children Undergoing Day-Case Non-Invasive Procedures

Samar Adam MBBCh*, Buthaina Bucheery; CABA, Ahmed Maher; MSc

Abstract

Ketamine is a dissociative anesthetic related to phencyclidine. The mode of action is disconnection between thalamocortical and limbic systems. The outcome is a sedated patient with amnesia and analgesia. The aim of the study is to assess the minimal effective dose of oral ketamine as a premedication in pediatric patients undergoing day-case non-invasive MRI procedures and assessing any related side effects and complications.

Keywords: Ketamine; Oral; Premidcation; Children; Daycase.

Introduction

Over the past 40 years there has been a revolution in surgery. Day case surgery has become increasingly popular due to new surgical techniques, advances in anaesthesia, collection and publication of comparative data, and deliberate policies including financial incentives for hospitals. [1] Statistics show that shorter hospital stays and early mobilization reduce many comorbidities, such asthe risk of venous thromboembolism and hospital-acquired infections. [2] In general, day-case procedures are appropriate for children, since they tend to be healthy and free from systemic disease or degenerative changes. [3] Anesthesia is often the primary specialty involved in the development of selection criteria protocols, postoperative symptom control regimens, and audit coordination in pediatric day-case services. [4] Radiological studies are the most common day-case procedures under anesthesia in the pediatric age group, and given the relatively lengthy magnetic resonance imaging (MRI) study, the best possible images are obtained through sedation and general anesthesia in infants and young children Undergoing such scans, because these children may have difficulty remaining motionless and following breathing commands. [5,6] Ketamine is a dissociative anesthetic related to phencyclidine. The mode of action is disconnection between thalamocortical and limbic systems. The outcome is a sedated patient with amnesia and analgesia. [7]

Systemic Effects of Ketamine

Ketamine is primarily used to induce and maintain anesthesia. In addition, it is used as a sedative, analgesic, antidepressant, to treat bronchospasm, and to treat complex regional pain syndromes. One of the advantages of ketamine is that respiratory, cardiac function and airway reflexes are protected during drug administration. [8]

Pharmacokinetic Characteristics of Ketamine

Ketamine works as a noncompetitive NMDA receptor antagonist. Aimed to be used throughout premedication, analgesia, sedation, induction and maintenance phases of general anesthesia. [9] There is also interest in ketamine

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Adam S, et al., Anesth Crit Care 2023
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for potentially new indications, such as management of chronic pain, treatment of resistant depression, and reversing opioid-induced respiratory depression. [10]

Administration

Ketamine can be administrated via multiple routes (Table 1) [11]

Study Procedure

After the approval of the Hospital's Ethics Committee and parental/ guardian written informed consent, 100 children aged 1 - 6 years with American Society of Anesthesiologists (ASA) physical status I-II underwent day-case non-invasive MRI procedures, assigned randomly and received oral ketamine 20 minutes before the procedure, either in 6 mg.kg-1 (Group A), 7 mg.kg-1 (Group B), or 10 mg.kg-1 (Group C) mixed with clear apple juice with a total volume of 10 ml. All patients, accompanied by their parents/guardians, were taken to the holding area. [12] Vital signs were taken and recorded upon admission to the holding area. Following the administration of the sedative mixture, they were continuously monitored using a multichannel monitor (heart rate, ECG, non-invasive blood pressure, respiratory rate and pulse oximetry) and were recorded at 10 minutes intervals along with the level of sedation using Pediatric Sedation State Scale (PSSS). [13] 20-30 minutes after drinking the mixture, children were transferred to the procedure room. Children's hemodynamics were continuously monitored and they were recorded at 10, 20, 30, 40, 50 and 60 minutes after drug administration. The response of each child at the time of separation from parents, transfer to procedure room, intravenous access and acceptance of facemask were recorded in accordance with the PSSS. Sevoflurane, administered through a face mask, in a 0.4 MAC along with 50% O2 in air was delivered to all the children to prevent them from moving while the test is being done. A gas analyzer was connected to the mask to monitor inhalational anesthetic and End-Tidal CO2 (ETCO2) concentrations. [14] At the end of the procedure, the time interval between transferring the patient to the recovery area until spontaneous eye opening and response to verbal command was recorded. The occurrence of any side effects related to the procedure during the perioperative period was recorded. Discharge from the Day Case Unit (DCU) was only allowed after full regaining of consciousness, and data collection was stopped at the end of this period.

Table 1: Route of administration, bioavailability, and the starting dose of ketamine

Route of administration	Bioavailability	Starting dose
Intravenous	100%	0.25–1 mg/kg (adults)
		0.25–2 mg/kg (children)
		1–2 mg/kg
Intraosseous	100%	0.5–1 mg/kg
		1–2 mg/kg
Intramuscular	93%	4–5 mg/kg
		8–10 mg/kg
Oral	16–20%	Children: 3–15 mg/kg
		Adults: 500 mg max.
Nasal	45–50 %	0.25–4 mg/kg
		3–9 mg/kg
Rectal	25–30%	50 mg
		8–15 mg/kg

Exclusion criteria:

- Children below 1 year or older than 6 years.
- ASA > II.
- Body Mass index (BMI) > 30
- Previous negative response to ketamine.
- Emergency procedures.
- Incomplete ingestion of the sedative mixture.
- Failure to commence the procedure > 30 minutes after ingesting the sedative mixture.
- Respiratory tract infection.

Materials and Methods

A total of 112 children (aged from 1-6 years) underwent MRI scanning in Salmaniya Medical Complex hospital (SMC) fulfilling the criteria of the study between March and July 2023. Among them 1 child has reported a history of ketamine allergy , 2 children had a mass body index (MBI) more than 30 , 4 children had respiratory tract infections, and 5 had incomplete ingestion of the sedative mixture . Therefore, these children were excluded from our study. A total of 100 children were enrolled in the study.

Statistical analysis

Part 1: Participants' demographic and health characteristics

The sample consisted of 100 participants equally divided into three Ketamine dose groups. These groups are very comparable in terms of their ages, gender, weights, and ASA scores. The mean age across the groups ranged from 3 to 3.5 years with no statistically significant difference detected among them (p=0.486). Both genders were represented in very similar proportions in these dose groups without any statistically significant differences (p=0.814). Although those in 6mg.Kg-1 group weighed less than the other groups, however, this difference did not reach the statistical significance (p=0.170). The three groups did not differ in regard to scores. Each of the 2 included ASA grades were represented in very similar proportions in these in these dose groups without any statistically significant differences (p=0.521). (Table 2):

Adam S, et al., Anesth Crit Care 2023
DOI:10.26502/acc.065

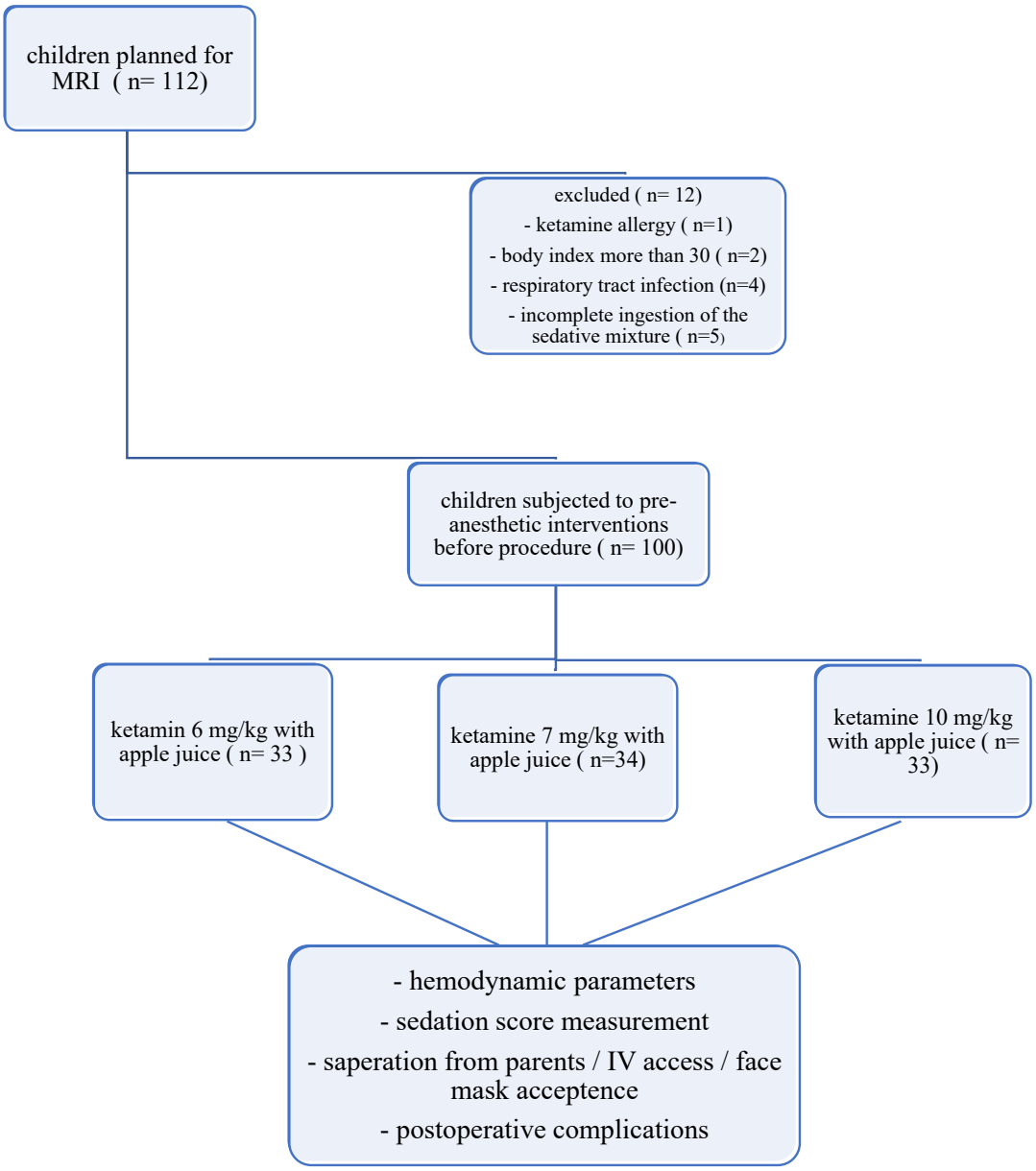


Table 2: Demographic data of the studied groups

Variable	Total	6mg.kg^{-1}		7mg.kg^{-1}		10mg.kg^{-1}		p-value
		33(33%)		34(34%)		33(33%)		
Age (Mean±SD) in years	3.3±15	3	±1.5	3.4	±1.5	3.5	±1.5	0.486*
Gender n(%)								
Male	56(56%)	17	30.40%	20	35.70%	19	33.90%	0.814**
Female	44(44%)	16	36.40%	14	31.80%	14	31.80%	
Weight (Mean±SD) in Kg	15.7±3.9	14.7	±3.9	16.1	±4.0	16.4	±3.8	0.170*
ASA								
1	82(82%)	25	30.50%	29	35.40%	28	34.10%	0.521**
2	18(18%)	8	44.40%	5	27.80%	5	27.80%	

*Statistically insignificant differences with Kruskal-Wallis test at Alpha 0.05

**Statistically insignificant differences with Chi Square at Alpha 0.05

Adam S, et al., Anesth Crit Care 2023
DOI:10.26502/acc.065

Part 2

Comparing the three dose groups based on time laps between drug administration and different phases of the study (Table 3) the three groups differed significantly in the time lapsed from dose administration till separation from parents, arriving to operation room, face mask acceptance, acceptance of intravenous (IV) line insertion, and discharge. It required around 32 minutes on average to separate the child after the dose administration in the 6 mg.Kg-1 group. This time was significantly reduced to 22 minutes in the 7 mg.Kg-1 group and even went lower in the 10 mg.Kg-1 group. A very similar results noted in the other intervals except of dose to discharge time. Interestingly, Although the 10 mg.Kg-1 group recorded the lowest time in dose to other steps, this group recorded significantly the highest time to discharge when compared the other groups (191.7±19.3 vs. 165±31.9 and 146.4±16.3, p<0.0001). The three groups showed very similar time required from arrival to the operation room till face mask acceptance without any significant differences. However, they differed significantly in duration of face mask to IV acceptance with the 6 mg.Kg-1 group recoded significantly higher duration compared to the other two groups. All the groups showed no difference in the procedure times as they recorded similar mean times.

Table 3: Intervals between drug administration and different phases of the study.

Time laps (minutes)	Total	6mg.Kg^{-1}		7mg.Kg^{-1}		10mg.Kg^{-1}		p-value
	Mean±SD	Mean	±SD	Mean	±SD	Mean	±SD	
Dose to separation	24.4±6.1	32.2	±2.7	22.4	±1.8	18.5	±2.6	**<0.0001***
Dose to face mask	27.1±6.3	35	±2.9	24.8	±1.9	21.5	±2.7	**<0.0001***
Dose to I.	34.6±6.9	43.2	±3.6	31.9	±2.3	28.7	±2.8	**<0.0001***
Dose to discharge	165±31.9	146.4	±16.3	156.8	±36.2	191.7	±19.3	**<0.0001***
Procedure time	30.5±13.7	31.2	±15.0	30.9	±13.3	29.4	±13.2	**0.851**

*Statistically significant differences with ANOVA test at Alpha 0.05

Table 4: Vital signs and PSSS at 10 minutes intervals

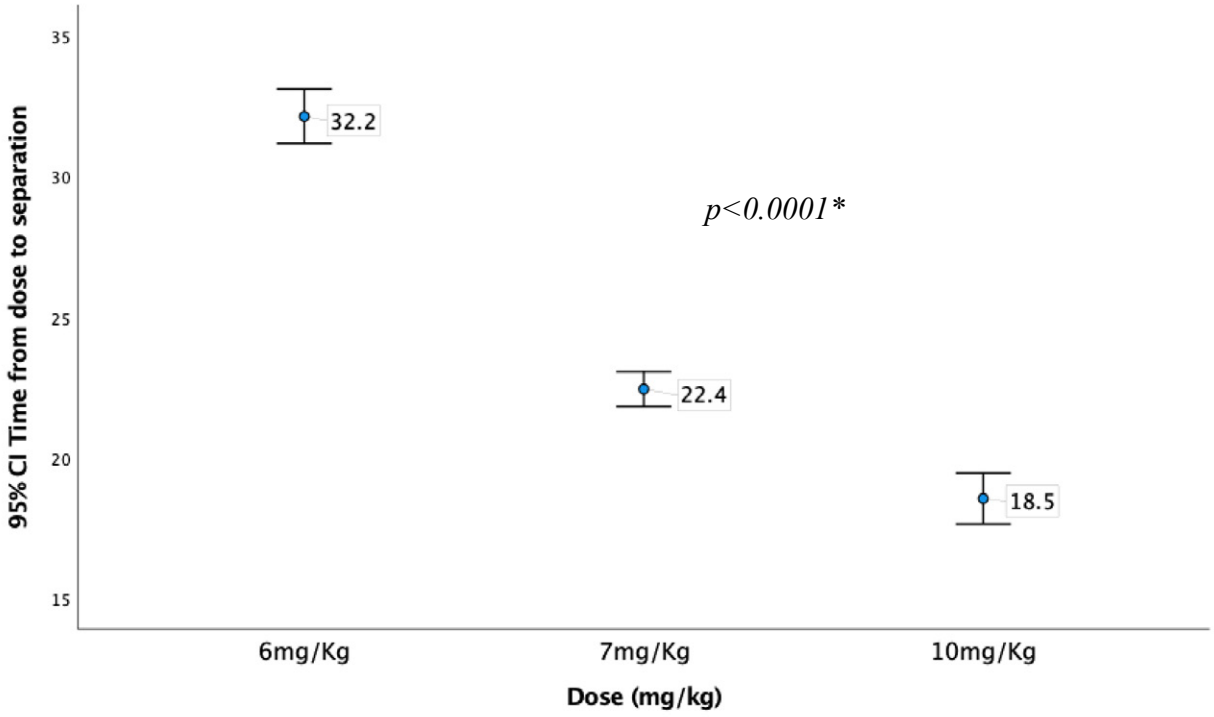
Vitals	Total		6 mg.Kg^{-1}		7mg.Kg^{-1}		10mg.Kg^{-1}		p-value*
			Mean	±SD	Mean	±SD	Mean	±SD	
Heart Rate at:									
0 minutes	98.6	±19.1	97	±18.6	95.5	±19.3	103.2	±19.1	**0.217**
10 minutes	114.5	±20.7	116.3	±22.7	114.4	±22.0	112.9	±17.4	**0.8**
20 minutes	98.3	±17.4	101.1	±17.5	95.9	±16.9	98	±17.9	**0.481**
30 minutes	96.6	±17.9	99	±18.2	94.5	±17.8	96.4	±18.1	**0.601**
40 minutes	97.3	±18.6	99.2	±20.3	95.3	±17.9	97.6	±17.9	**0.694**
50 minutes	96.8	±18.5	98.4	±19.4	94.8	±18.1	97.2	±18.3	**0.718**
60 minutes	95.7	±18.7	97.4	±19.6	93.9	±17.3	95.8	±19.7	**0.744**
Oxygen saturation (SPO_2%) at:									
0 minutes	99.7	±0.5	99.7	±0.7	99.4	±0.7	99.5	±0.7	**0.519**
10 minutes	99.5	±0.9	99.4	±1.2	99.5	±0.7	99.6	±0.7	**0.594**
20 minutes	99.6	±0.7	99.5	±0.8	99.6	±0.7	99.7	±0.6	**0.559**
30 minutes	99.6	±0.6	99.6	±0.7	99.6	±0.6	99.6	±0.7	**0.982**
40 minutes	99.6	±0.7	99.6	±0.6	99.6	±0.7	99.6	±0.7	**0.983**
50 minutes	99.6	±0.7	99.2	±0.7	99.7	±0.6	99.7	±0.6	**0.303**
60 minutes	99.6	±0.6	99.7	±0.5	99.6	±0.6	99.5	±0.8	**0.641**
PSSS at:									
0 minutes	2.3	±0.7	2.2	±0.6	2.2	±0.6	2.4	±0.8	**0.235**
10 minutes	3.2	±1.0	3.3	±1.0	3.3	±1.0	3.2	±1.0	**0.816**
20 minutes	2	±0.1	2	±0.2	2	±0.0	2	±0.0	**0.366**
30 minutes	2	±0.1	2	±0.2	2	±0.0	2	±0.0	**0.366**
40 minutes	2	±0.0	2	±0.0	2	±0.0	2	±0.0	**1**
50 minutes	2	±0.0	2	±0.0	2	±0.0	2	±0.0	**1**
60 minutes	2	±0.0	2	±0.0	2	±0.0	2	±0.0	**1**

*Statistically insignificant differences with ANOVA test at Alpha 0.05

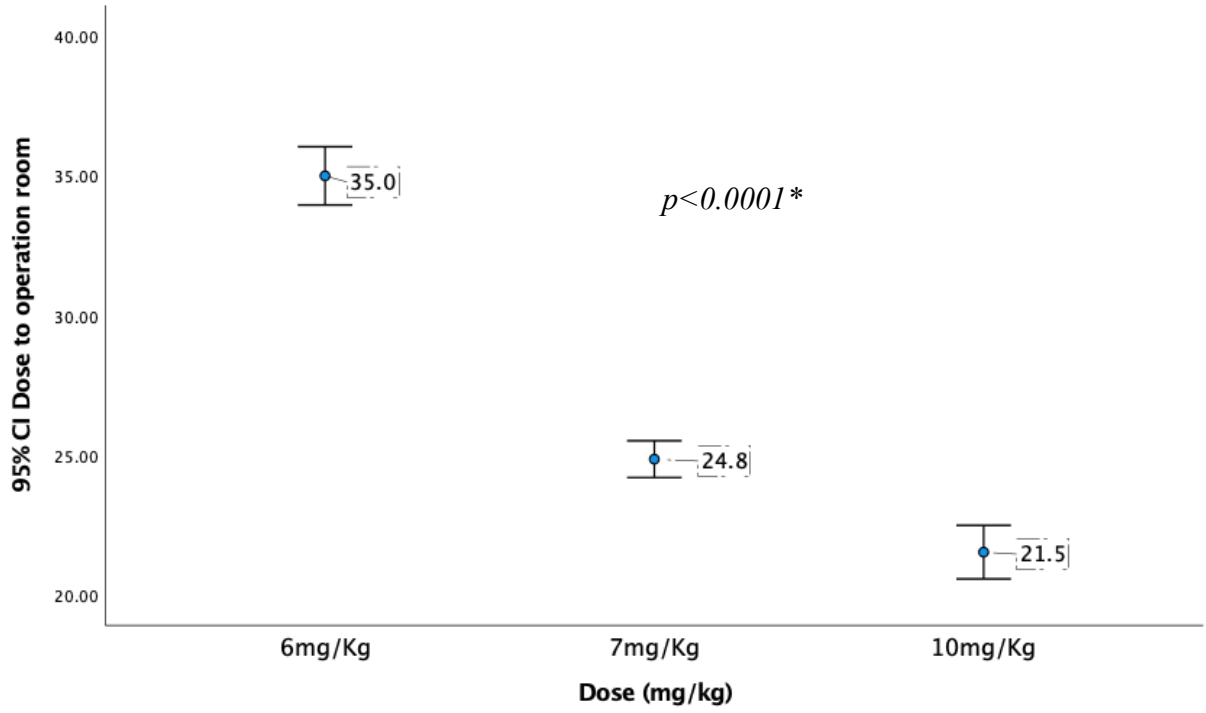
Adam S, et al., Anesth Crit Care 2023
DOI:10.26502/acc.065

Graphs

Graph 2 shows the change in dose to separation time (minutes) across the three dose groups

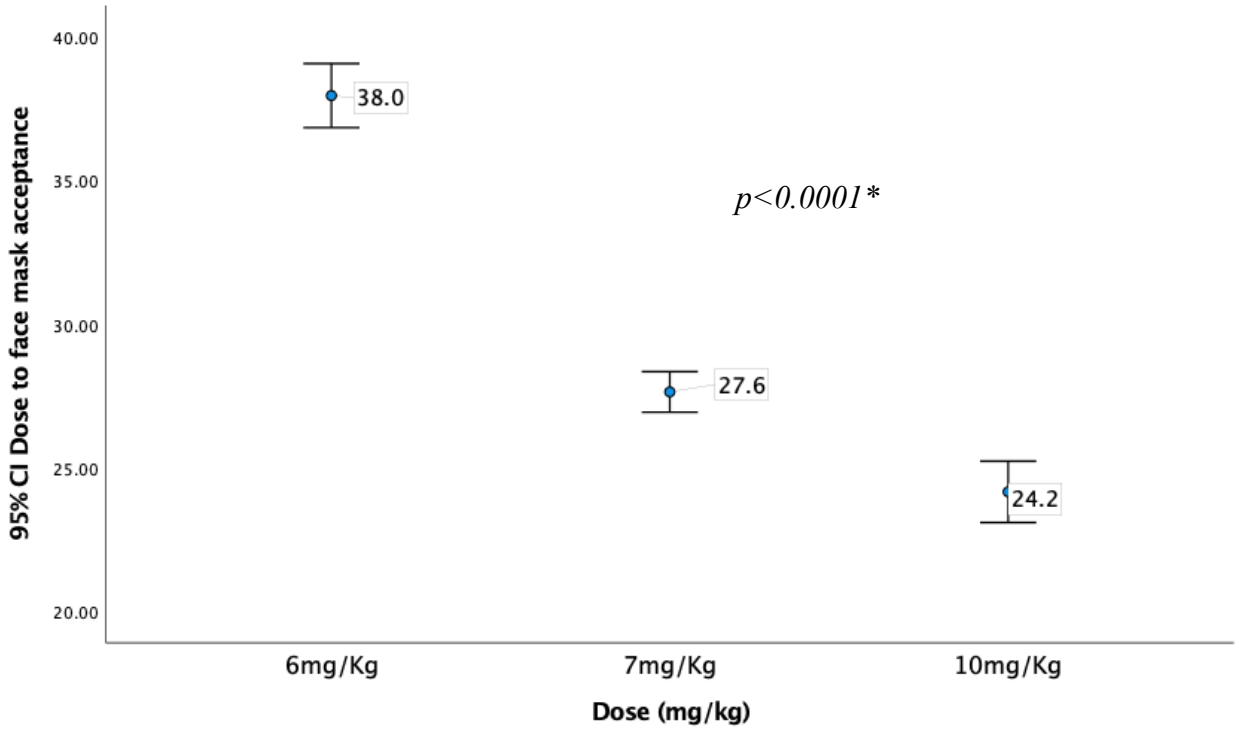


Graph 3 shows the time laps between dose administration to transfer to operation room (minutes) across the three dose groups

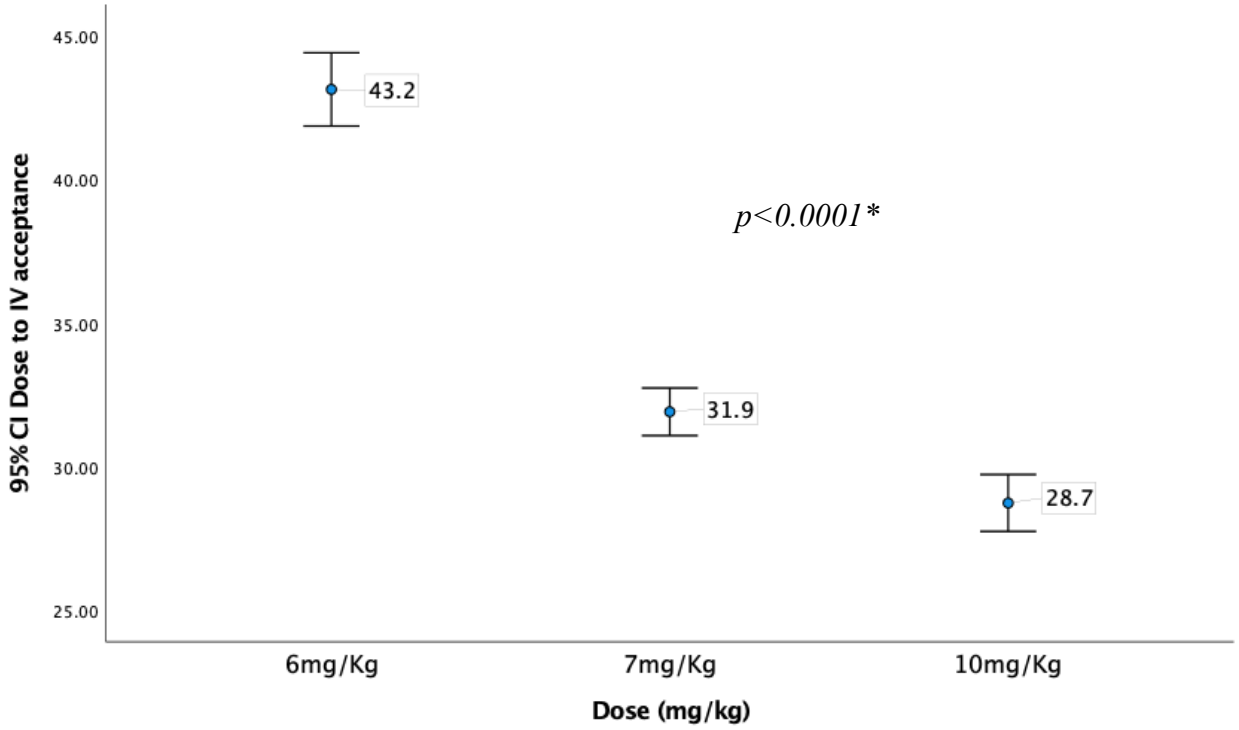


Adam S, et al., Anesth Crit Care 2023
DOI:10.26502/acc.065

Graph 4 shows the time laps between dose administration to face mask acceptance (minutes) across the three dose groups

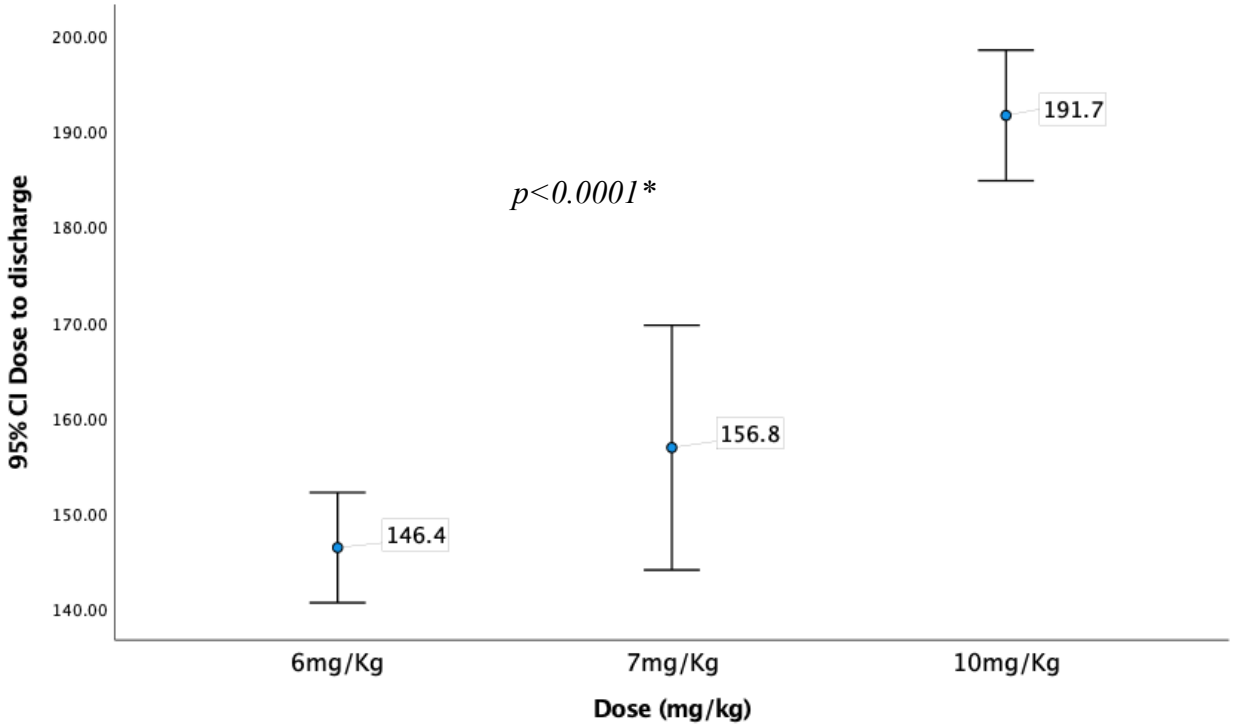


Graph 5 shows the time laps between dose administration to tolerance to intravenous line insertion (minutes) across the three dose groups.

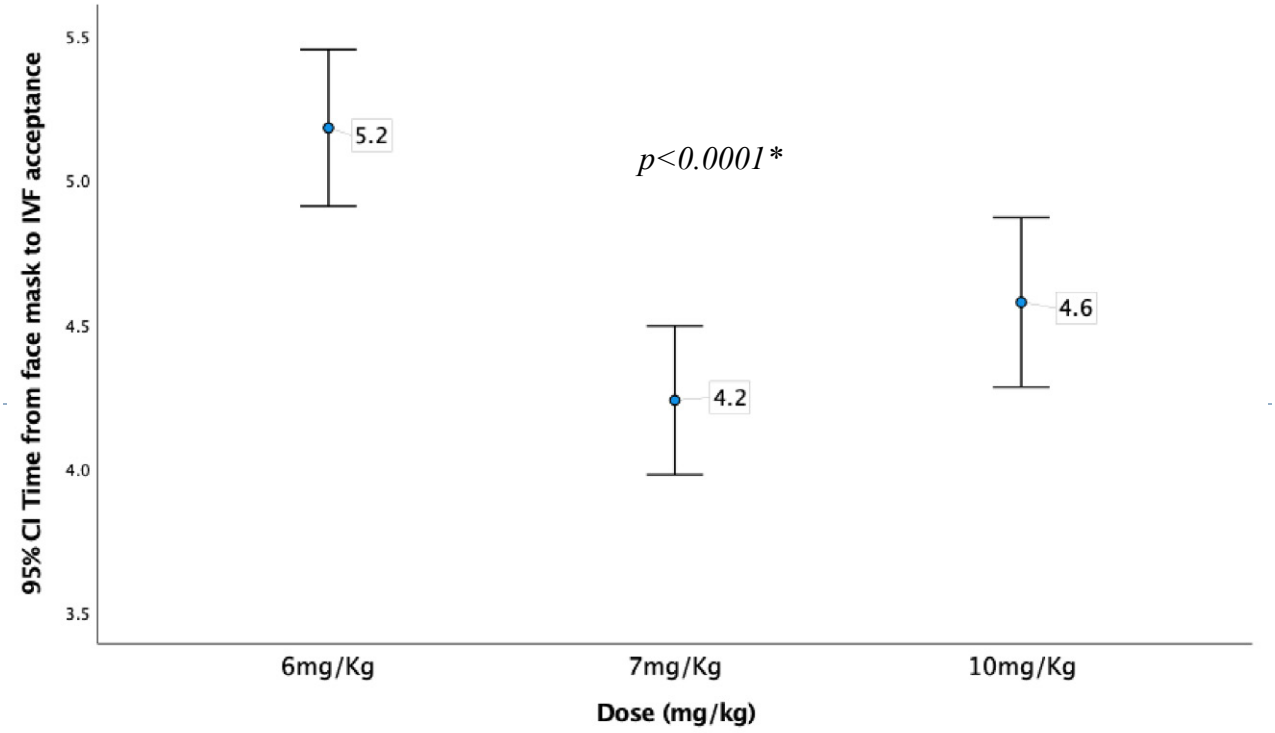


Adam S, et al., Anesth Crit Care 2023
DOI:10.26502/acc.065

Graph 6 shows the time laps between dose administration to discharge time (minutes) across the three dose groups.



Graph 7 shows the time laps between face mask acceptance and IV acceptance time across the three dose groups.



Adam S, et al., Anesth Crit Care 2023
DOI:10.26502/acc.065

C. Part 3 : Comparing vital signs and PSSS at 10 minutes intervals across the three dose groups

Despite some variations, the participants in the three groups showed very comparable heart rates, Oxygen saturations, and PSSS scores across the 10 minutes intervals of the procedure without statistically significant differences. For instant, none of the groups differed significantly in HR at 0 minutes (p=0.217) neither in the 60 minutes of the procedure (p=0.744). the same observation is true for the SPO2% and the PSS score. (Table 4)

D. Part 3 Side effects

Around 7(7%) of the sample had side effects like delirium 3(3%), excess salivation 3(3%), and obstructed breathing 1(1%).

Comparing the three groups on the incidence of these side effects, no significant differences were detected among them. (Table 5)

Discussion

Even the most cooperative child often cannot stay still for an imaging scan of prolonged length, an adequate sedation would be a helpful factor in performing high-quality imaging studies in such children, as Charron et al. stated In their book. [15] Therefore there are many studies that used different medications in order to achieve a proper sedation. There is still no completely accurate way to guarantee a smooth induction of anesthesia for children, nor to reduce the anxiety from those critical moments, mainly at the time of separation from the parents, transfer to the study room, during the intravenous access and induction of anesthesia. Choice of premedication or sedative agent is governed by several factors, which include its ease of administration, rapid action, lack of side-effects, and rapid emergence from anaesthesia. Commonly used pediatric premedication methods can be traumatic to children between 1-6 years old, and some increase the risk of respiratory depression. In our study, oral ketamine was chosen for its ease of administration as a mixture with an apple-flavored juice. The taste of the mixture was palatable for most of the children, and the volume of the mixture was limited to a maximum of 10 ml. In a previous prospective, randomized, double-blind placebo-controlled study conducted by Turhanoğlu et al., 80 children (ASA 1-11) aged 2-8 years, scheduled for surgery, were given an oral mixture of ketamine (4, 6 or 8 mg.kg-1) and cherry juice, 30 minutes before induction of anesthesia, they stated that it's safe to administer 10 ml of syrup orally without increasing risk of intraoperative aspiration. [16] In addition, a study by Kaviani et al., found that it is convenient to use 20 ml orange juice containing 0.5 $mg.kg^{-1}$of oral midazolam, as a premedication 20 minutes before starting the anesthesia, on 62 healthy non-cooperative children, candidate for dental procedures under general anesthesia. [17]

The authors used the Pediatric Sedation State scale (PSSS), that was recorded in the holding area after administration of the sedative mixture and then repeatedly to assess the efficacy of the sedation during different phases of the study. This scale was adopted in a study by Cravero et al. to help measuring the quality and safety of 25 invasive and non-invasive pediatric procedural sedation in different hospital settings. [18] In our study, 6 $mg.kg^{-1}$ showed the poorest outcomes in comparison to the other two study groups. the poorest outcomes in comparison to the other two study groups. And although 7 $mg.kg^{-1}$ dose was comparable to the 10 $mg.kg^{-1}$ dose, the latter group recorded the lowest time lapse during different phases of the study, comparable incidence of side effect and insignificant higher time to discharge statistically, when compared to the rest of groups.This is similar to the finding of Oyedepo et al. in which two different dosages of 5 $mg.kg^{-1}$ and 10 $mg.kg^{-1}$ of oral ketamine were compared. Adequate sedation was observed in 52% of children who received 5 $mg.kg^{-1}$, 68% of those who received 10 $mg.kg^{-1}$ of ketamine. Anxiolysis was better with 10 $mg.kg^{-1}$ of ketamine and no emergence phenomenon was noted despite the high dose. [19] The result of Turhanoğlu et al. study, showed that the group received oral ketamine 8 $mg.kg^{-1}$, were significantly calmer than other groups with 4 or 6 $mg.kg^{-1}$, and anesthesia induction was easier. [20] Similar to other studies, Side effects that we noticed were of short duration and minor significance, in a way that doesn't affect the stability of the patient. Both delirium and excessive salivation were reported in 3% of the patients and obstructed breathing happened in 1%. Side effects were noted more in the 10 mg.kg-1 group. In a randomized controlled trial on 78 children of ASA I or II scheduled for elective ophthalmic surgery, that was designed by Darlong et al. to evaluate whether the combination of low dose oral midazolam (0.25 mg.kg-1) and low dose oral ketamine (3 mg.kg-1) provides better premedication than oral midazolam (0.5 mg.kg-1) or oral ketamine (6 mg.kg-1), the incidence of excessive salivation was significantly higher in the ketamine alone group (P<0.05). [21] S. Şekerci et al. who evaluated Ketamine 3 - 6 mg.kg−1 given by mouth

Table 5: Side effects observed during the study

	Total		6mg.Kg^{-1}		7mg.Kg^{-1}		10mg.Kg^{-1}	
Delirium	3	3.0%	0	0%	0	0%	3	9.1%
Excess Salivation	3	3.0%	1	3.0%	1	2.9%	1	3.0%
Obstructed Breathing	1	1.0%	1	3.0%	0	0%	0	0%

to paediatric patients for anaesthetic premedication on 43 children, aged between 2–9 years, found that 3 mg.kg^{-1} has a decreased incidence of side effects such as nystagmus and vomiting. [22]

Conclusion

In conclusion, the results showed the premedication of children may be less sufficient with the lower doses of ketamine (6 mg.kg-1 – 7 mg.kg-1). We found that oral administration of ketamine with 10 mg.kg-1 provides a more rapid onset of satisfactory sedation, with less anxiety in response to separation from parents, face mask application and intravenous line insertion. We suggest that if prolonged recovery period is not an obstacle to the day care unit, oral administration of ketamine 10 mg.kg-1 may be a good choice to use as a single drug for premedication of children, since in practice the mean time to discharge from DCU was only +/- 35 minutes longer than the 7 mg.kg^{-1}1 group.

Acknowledgments

The authors are thankful to the MRI and anesthesiology staff of Salmaniya Medical Complex Hospital.

Recommendations for future studies

- Building upon findings of our research, we recommend the use of oral ketamine in a dose of 10 mg.kg^{-1} as a single sedative agent for non-invasive day-case radiological procedures.
- We also recommend that further studies should be conducted on the use of ketamine orally in other non-invasive and invasive procedures, including the effect of using ketamine orally on the consumption of analgesic and opioid drugs until the discharge of pediatric patients of Salmaniya medical complex (SMC).

Conflict of interest

The authors declare no conflict of interest.

Data Availability

The datasets supporting the finding of this study are available from the corresponding author upon reasonable request.

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