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Original Article

Effects of different doses of oral ketamine for premedication of children

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Summary

Background and objective: A need exists for a safe and effective oral preanaesthetic medication for use in children undergoing elective surgery. The study sought to define the dose of oral ketamine that would facilitate induction of anaesthesia without causing significant side-effects.

Methods: We studied 80 children undergoing elective surgery under general anaesthesia who received oral ketamine 4, 6 or 8 mg kg^{-1} in a prospective, randomized, double-blind placebo controlled study. We compared the reaction to separation from parents, transport to the operating room, the response to intravenous cannula insertion and application of an anaesthetic facemask, the induction of anaesthesia and recovery from anaesthesia.

Results: In the group receiving ketamine 8 mg kg^{-1}, the children were significantly calmer than those of the other groups, and anaesthesia induction was more comfortable. Recovery from anaesthesia was longer in the group receiving ketamine 8 mg kg^{-1} compared with the other groups, but no differences between the groups were observed after 2 h in the recovery room.

Conclusions: It is concluded that oral ketamine 8 mg kg^{-1} is an effective oral premedication in inpatient children undergoing elective surgery.

Keywords: ANAESTHETICS, INTRAVENOUS, anaesthetics, dissociative, ketamine; PAEDIATRICS; PREMEDICATION.

Anaesthesia and surgery can be stressful and traumatic experiences for children. Children are especially vulnerable to long-term psychological impairment resulting from stress. The aims of giving premedication of children are to relieve anxiety, reduce the trauma associated with separation from their parents and facilitate induction of anaesthesia without prolonging the recovery period [1]. There are various combinations of drugs and routes of administration for premedication. However, there is still no entirely satisfactory way to ensure smooth induction of anaesthesia for children [2]. Oral premedication is the most common mode of delivery, probably due to better patient acceptance and ease of administration [3].

Ketamine is an easily administered parenteral anaesthetic that produces profound analgesia in subanaesthetic doses and lacks the cardiorespiratory depression seen with most other general anaesthetics [4]. There are an increasing number of reports of the use of oral ketamine [2,5]. In this prospective, randomized double-blind placebo-controlled study, we evaluated the effects of oral ketamine and attempted to define an optimal dose of ketamine that would provide adequate premedication in paediatric patients.

Methods

We obtained approval from our hospital Ethics Committee and informed parental consent. Eighty children (ASA I–II) aged 2–8 yr and scheduled to

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undergo anaesthesia for surgery (herniorrhaphy, tonsillectomy) entered the study. The children were allocated randomly to one of four groups. Thirty minutes before induction of anaesthesia, Group 1 ($n = 20$) received 4 mg kg^{-1}, Group 2 ($n = 20$) 6 mg kg^{-1} and Group 3 ($n = 20$) 8 mg kg^{-1} ketamine by mouth in a 0.4 mL kg^{-1} sour cherry juice. Group 4 ($n = 20$) received only sour cherry juice and served as a control group. The mixture of ketamine and sour cherry juice was fixed as the total volume would be a maximum of 10 mL. All patients were taken, with their parents, to a special children's reception area adjacent to the operating room by an impartial investigator. In the reception area, the children's vital signs were monitored using a Propaq 106 EL monitor® (Welch Allyn Protocol, Inc, Beaverton, OR, USA). Heart rate (HR), electrocardiography (ECG), non-invasive systolic and diastolic arterial pressures (SAP, DAP), respiration rate (RR) and pulse oximetry (S_pO_2) were continuously displayed and recorded every 5 min. The sedation and emotional states of all patients were evaluated according to (a) a sedation scale (SS) (1: rarely arousable, asleep, needs shaking or shouting to arouse; 2: asleep, eyes closed, arouses with soft voice or light touch; 3: sleepy, eyes open, but less active and responsive; 4: awake; 5: agitated), and (b) an emotional state scale (ESS) (1: calm; 2: apprehensive, not smiling, tentative behaviour, withdrawn; 3: crying; 4: thrashing, crying with movement of arms and legs, resistive). Recordings were made every 5 min from just before the mixture of ketamine and sour cherry juice was administered and continued throughout the induction of anaesthesia and during the postoperative period [2]. The onset of sedation was determined when SS ≤ 3. All mixtures were given to the children by their parents. At the time of administration, the ease of drinking the ketamine solution was evaluated by either asking the co-operative children what the mixture tasted of or else by watching the reactions of the others (we saw, at the time of drinking, children crying or resisting because they did not like the taste of the ketamine mixture) and the results were noted. The values on the SS at the start of sedation together with that for the ESS at the time of separation from the parents were also determined.

Thirty minutes after drinking the mixture, the children were transported to the operating room and the variables of haemodynamic, respiratory, ESS and SS were recorded by the same investigator. The child's responses to intravenous catheter insertion and application of an anaesthetic facemask were evaluated with ESS. In all children, anaesthesia was induced with propofol until loss of the eyelash reflex and the total dose was recorded. Vecuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation. Secretions at the time of intubation were graded by the same anaesthesiologist according to a secretion scale (1: decreased; 2: normal; 3: increased) [2]. Anaesthesia was maintained with halothane in nitrous oxide 60% and oxygen 40%. The halothane concentration was maintained at the minimum level necessary for haemodynamic stability. At the end of surgery, the time interval from the discontinuation of the anaesthetic until tracheal extubation, spontaneous eye opening and verbal command were recorded. The occurrence of nystagmus and other complications during the perioperative period were recorded. All children were observed in the recovery room for 2 h and data collection was stopped at the end of this period.

Continuous variables were examined using one-way analysis (ANOVA) and Scheffé's test for *post hoc* between-group comparisons. Nominal variables were analysed by χ^2-test analysis. Differences from baseline within each group were assessed using a paired *t*-test. Data were reported as mean ± SD. $P < 0.05$ was considered as significant.

Results

There were no significant differences between the groups with respect to age, weight or male/female ratio (Table 1). Three children in Group 1, three children in Group 2, two children in Group 3 and one child in Group 4 complained about the taste of the premedication, but no child spat it out and the difference between the groups were not significant ($P > 0.05$).

The mean onset time of sedation was 12.9 ± 1.9 min in Group 1, 10.4 ± 2.9 min in Group 2 and 9.5 ± 1.9 min in Group 3. The time required to achieve sedation for patients in Group 1 was longer than for those in Groups 2 and 3 ($P < 0.05$). Adequate sedation was observed for 80% of patients receiving 8 mg kg^{-1} ketamine, for 45% of patients receiving 6 mg kg^{-1} ketamine and in none of the patients from Group 1 after 10 min from drinking the mixture. Thirty minutes after the premedication sedation was significantly more profound in all treatment groups than in Group 4 and the baseline values of the groups (Fig. 1). In the recovery room, the sedative behaviour was continued to be assessed for 1 h in Groups 2 and 3; however, at the end of 2 h in the

Table 1. Means ± SD of age, gender and weight of the children.

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)	Group 4 ($n = 20$)
Age (yr)	4.05 ± 2.4	5.49 ± 2.99	4.77 ± 1.85	4.1 ± 2.96
Gender (f/m)	12/8	9/11	13/7	14/6
Weight (kg)	17.9 ± 5.91	18.2 ± 8.9	19.1 ± 4.48	18 ± 7.6

recovery room there were no significant difference in sedation between the groups (Fig. 2).

The reactions to separation from parents were significantly stronger in patients from Groups 1 and 4. Nineteen patients from Group 3 (95%) and 11 patients from Group 2 (55%) were calm at the moment of separation from their parents. The children in Group 3 showed less reaction than those in the other groups when the intravenous catheter was inserted just before induction of anaesthesia. The application of the anaesthetic facemask was easy in Groups 1–3; this difference was significant compared with Group 4 (Fig. 3).

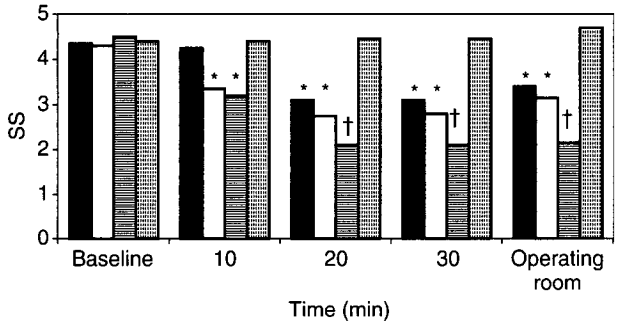

Figure 1.
Preoperative sedation scale (SS) of the children. $^{*}P < 0.05$ *compared with control group (Group 4);* $^{\dagger}P < 0.05$ *compared with the other groups.* ■: *Group 1;* □: *Group 2;* ▤: *Group 3;* ▦: *Group 4.*

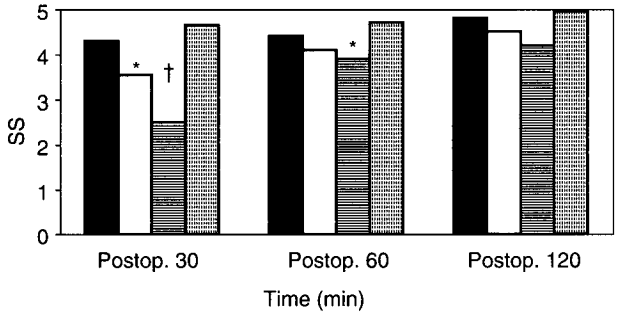

Figure 2.
Postoperative sedation scale (SS) of the children. $^{*}P < 0.05$ *compared with control group (Group 4);* $^{\dagger}P < 0.05$ *compared with other groups.* ■: *Group 1;* □: *Group 2;* ▤: *Group 3;* ▦: *Group 4.*

There were no significant differences in HR, SAP and DAP, respiratory rate and pulse oximetry between groups ($P > 0.05$). The mean dose of propofol used during induction was significantly lower in Group 3 ($P < 0.05$). The operation times between the groups were similar with no significant difference ($P > 0.05$). The times to tracheal extubation, spontaneous eye opening and verbal command were significantly longer in Group 3 ($P < 0.05$) (Table 2).

The amount of oral secretions present at tracheal intubation did not differ significantly between groups ($P > 0.05$). In the recovery room, the incidence of nausea and vomiting did not differ between groups ($P > 0.05$). The number of patients exhibiting nystagmus was significantly higher in Group 3 ($P < 0.05$) (Table 3). No emergence delirium occurred in any child and no other complication occurred during the perioperative period.

Discussion

The principal aims of sedative premedication used in children are to reduce anxiety, facilitate separation from parents and accomplish smooth induction of anaesthesia. The ideal premedication should be

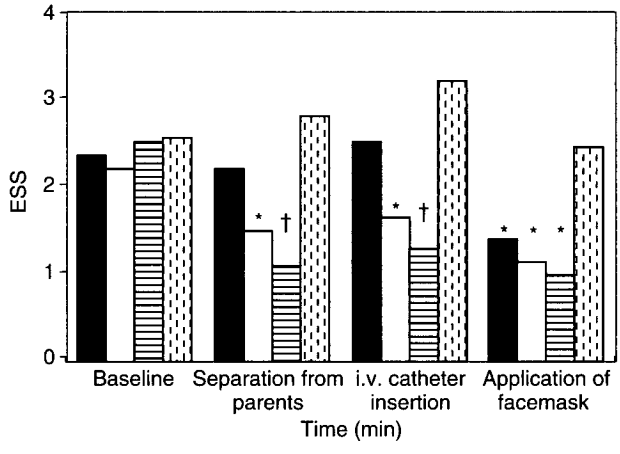

Figure 3.
Emotional State Scale (ESS) of the children. $^{*}P < 0.05$ *compared with control group (Group 4);* $^{\dagger}P < 0.05$ *compared with other groups.* ■: *Group 1;* □: *Group 2;* ▤: *Group 3;* ▦: *Group 4.*

Table 2. Means ± SD of propofol dose, operation time and the time to tracheal extubation, spontaneous eye opening (SEO) and verbal command.

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	Group 4 (n = 20)
Propofol dose (mg)	48.1 ± 15.3	44.75 ± 12.4	36.75 ± 11.2*	50 ± 17.5
Operation time (min)	34.3 ± 12.7	36.21 ± 14.3	33.27 ± 13.5	31.29 ± 14.254
Extubation (min)	9.3 ± 2.36	9.55 ± 2.8	11.6 ± 3.2*	9.05 ± 2.5
Verbal command (min)	19.0 ± 3.2	19.3 ± 4.5	29.0 ± 5.5*	18.15 ± 3.252
SEO (min)	23.5 ± 3.1	22.0 ± 6.9	30.85 ± 8.7*	20.65 ± 4.1

*$P < 0.05$ compared with the other groups.

Table 3. Number of patients with nausea and vomiting, and nystagmus.

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	Group 4 (n = 20)
Nausea	2	2	3	2
Vomiting	1	2	2	1
Nystagmus	2‡	4†	9*	–

*$P < 0.05$ compared with other groups; †$P < 0.05$, compared with Groups 1 and 4; ‡$P < 0.05$ compared with Group 4.

easily administered and acceptable, act rapidly, not prolong emergence from anaesthesia and have few side-effects [2]. In our study, oral ketamine was administered easily and most of the children accepted its taste. Nystagmus was the only side-effect significantly seen in the ketamine groups. The onset time of sedation was shorter in Groups 2 and 3. However, the children receiving ketamine 6 or 8 mg kg^{-1} needed significantly more time to awaken completely. After 30 min of premedication, most of the children in Group 1 were sedated, but they showed significantly more reaction to separation from parents, insertion of the intravenous catheter and application of the facemask than those in Groups 2 and 3.

Most studies concerning the use of oral ketamine, alone or in combination with another drug, for premedication in children were performed fairly recently [2,5–9]. The dose of ketamine given by the oral route is important for its effect in children as only 17% of oral ketamine is absorbed because of extensive first-pass metabolism [10]. However, oral administration is associated with much greater concentrations of the metabolite norketamine, which may contribute to the analgesic effect after repeated doses [6]. There are different dose regimens mentioned in these studies, and although high dose oral ketamine was commonly found effective, the results of low-dose ketamine were controversial. Sekerci and colleagues compared oral ketamine 3–6 mg kg^{-1} given by mouth to premedicate children and suggested that ketamine 3 mg kg^{-1} was as effective as 6 mg kg^{-1} with a lower incidence of side-effects such as nystagmus and vomiting [7]. However, in another study, the same dose of ketamine, 3 mg kg^{-1}, did not always cause sedation or a tranquil separation from the parents [2]. Tobias and colleagues used oral ketamine 10 mg kg^{-1} to alleviate the stress of invasive procedures and found that oral ketamine was effective for procedure-related distress in paediatric oncology patients without cardiorespiratory side-effects [8]. Our study did not find that ketamine 4 mg kg^{-1} was effective for the premedication of children. In another study, Warner and colleagues suggested that a mixture of ketamine 4 mg kg^{-1} and midazolam 0.4 mg kg^{-1} was more effective than ketamine 6 mg kg^{-1} [9].

The taste of the drug is important when used for oral premedication in children. A cola-flavoured soft drink as a vehicle for ketamine administration was used in one study for minimizing the taste of ketamine instead of a soft drink such as apple juice [2]. A recent study suggested that administration of small amounts of fluid (e.g. 5–10 mL) to children before induction of general anaesthesia did not increase the risk of aspiration of gastric contents [11]. We used sour cherry juice 0.4 mL kg^{-1} to mix with ketamine, and the volume of the mixture was limited to a maximum of 10 mL. The taste of the mixture was accepted by most of the children. Apart from nystagmus, the side-effects (nausea, vomiting) observed were similar in all groups and there were no significant differences. Nystagmus was reported in many children in the ketamine group given 8 mg kg^{-1}, but we believe that nystagmus has no effect on the outcome of the operation except for ophthalmic surgery.

The time to recovery was significantly prolonged in the group given ketamine 8 mg kg^{-1}. However, at the end of 2 h spent in the recovery room, there was no significant difference between the groups according to the SS. In a study with 10 mg kg^{-1} ketamine administered orally, the majority of patients showed recovery from sedation within 2 h following the procedure and our results are in agreement with those [8].

In conclusion, we compared three different doses of ketamine. The results show that the premedication of children may be insufficient with the lowest dose of oral ketamine (4 mg kg^{-1}). We found that oral administration of ketamine 8 mg kg^{-1} provided a more rapid onset of satisfactory sedation, less separation anxiety, and less reaction to intravenous catheter insertion and the application of a facemask than administration at 6 mg kg^{-1}. We suggest that if a prolonged recovery period does not affect the discharge time from the postoperative recovery room as in outpatients, oral administration of ketamine 8 mg kg^{-1} may be a good choice when used as a sole drug for premedication in children.

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