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ORIGINAL ARTICLE

Comparison between ketamine and fentanyl–droperidol for rectal premedication in children: a randomized placebo controlled trial

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Abstract
Purpose A common concern of anesthesiologists is the management of children involved in stressful scenarios, and premedication is considered, in most situations, as useful to reduce the stress responses. This randomized placebo-controlled study was designed to evaluate two premedicants, ketamine versus a combination of fentanyl–droperidol, rectally administered, in pediatric surgical outpatients.
Methods We randomly assigned 120 children to three equal groups to be rectally premedicated with ketamine 10 mg kg^{-1} (group K), fentanyl 5 μg kg^{-1} + droperidol 100 μg kg^{-1} (group F), or saline 0.2 ml kg^{-1} (group P). A blinded observer scored the children's behavior, according to a four-category behavioral scale, before premedication (time A), 45 min after premedication (time B), immediately before venipuncture (time C), and during the venipuncture (time D). Features of the premedication technique, complications, parents' opinions, and contraindications to hospital discharge were recorded.
Results Patient discharge was delayed because of anesthesia side effects in 7 cases (5.8%) and surgical problems in 9 (7.5%). Group F showed a higher rate of postoperative nausea and vomiting (PONV) than group K, whereas the latter had a higher rate of behavioral disturbances. The data showed a significant difference in the behavioral score between groups F and P, groups K and P, and groups F and K at time B, and between groups K and P at time C. The reaction score at venipuncture shows a significant difference between groups K and P only.
Conclusion In this study, premedication with rectal ketamine showed significantly better overall results in the preoperative period than premedication with either fentanyl–droperidol or placebo.

Keywords Rectal premedication · Ketamine · Fentanyl · Droperidol · Pediatric outpatients

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Introduction

A common concern of pediatric anesthesiologists is the stress response of children to hospitalization: the unfamiliar hospital environment, the loss of daily routine, the separation from parents, friends, and familiar environment, the disease state, painful events such as physical examination, instrumental investigations, injections, and medical and surgical treatments, and the fear of the day after and so on, are all important factors in this stress response [1]. Premedication with sedatives seems to be an effective tool to reduce the stress response in pediatric patients [2–4]. Other authors [1, 5–7] suggest that premedication with sedatives may be unnecessary if the anesthesiologist employs an empathic approach in daily practice, together with a good psychological preparation of both parent and child, parental presence at critical events, and application of EMLA cream before venipuncture. Moreover, midazolam, often used as a

premedication in children, has been recently questioned [5, 6], and one remaining question in this context is this: which drug or what combination of drugs should be used to best achieve our goals and to minimize potential side effects?

This prospective, randomized, double-blind, placebo-controlled study was designed, on these theoretical bases, to test the hypothesis that rectally administered ketamine would produce sedative effects comparable to that produced by rectally administered fentanyl–droperidol association, when both premedicants were evaluated at predicted peak plasma concentration and compared to placebo.

In addition, perioperative adverse effects and recovery characteristics were examined in pediatric outpatients undergoing minor surgical procedures.

Patients and methods

After approval by the hospital Ethics Committee and informed written parental consent, 120 pediatric outpatients aged from 10 months to 6 years, ASA class I–II, were studied. Children were excluded if there was a history of neurological or psychiatric disease, rectal and anal pathology, cardiopathy, medication interacting with the premedicants, or allergy to any of the study drugs. Children were randomly assigned to three equal groups of 40 using a randomized clustered list. All surgical procedures were performed at the same time of the day, from 8:00 a.m. to 2:00 p.m. (0800 to 1400). Group K was premedicated with ketamine 10 mg kg^{-1}; group F was premedicated with fentanyl 5 μg kg^{-1} + droperidol 100 μg kg^{-1}; and group P was premedicated with normal saline, 0.2 ml kg^{-1}. The solutions of test drug, or placebo, were colorless and diluted in a way that ensured the same volume (0.2 ml kg^{-1} irrespective of the test drug) was administered. A nurse blinded to the protocol administered the encoded premedicant according to the random allocation, using a 12 Fr. lubricated rectal cannula inserted 3–5 cm deep from the anal sphincter. On the same occasion, EMLA cream was applied to possible venipuncture sites and the sacral hiatus. The emotional state and awareness were assessed, by the same unaware psychologist, before premedication (time A) and 45 min [8] after premedication (time B), according to a four-category behavioral scale [4, 9, 10]: 1 = distressed, crying; 2 = awake and calm; 3 = asleep, but easily arousable by verbal commands and/or gentle stimuli; 4 = asleep, but not readily arousable. After the second evaluation the patient was transferred, together with the parent, to the operating theater, where the same blinded psychologist performed a third evaluation, immediately before the venipuncture (time C), and finally recorded the patient's reaction to venipuncture (time D) as follows: 1 = major movement requiring patient restraint; 2 = minor movement, requiring arm restraint; and 3 = no reflex movement. After intravenous sedation with propofol (1–3 mg kg^{-1}) the parent was returned to the ward, and a caudal block was performed using mepivacaine 1% at the dose of 1 ml kg^{-1}. If this regional block failed, a subarachnoid anesthesia with plain bupivacaine 0.5% was performed. The dose of bupivacaine was calculated according to the age of the child (<5 years = 0.5 mg kg^{-1}; >5 years = 0.4 mg kg^{-1}). The maximal dose for bupivacaine was 10 mg. Sedation during surgery was maintained with supplemental boluses of propofol (1 mg kg^{-1}) in the spontaneously air-breathing child. Patient monitoring consisted of electrocardiogram, pulse oximetry, noninvasive blood pressure, and clinical observation by the anesthesiologist. Postoperative analgesia was provided by rectal paracetamol at 25 mg kg^{-1} every 6 h. Problems and complications related to anesthesia, the opinion of the parents about the technique of premedication, and contraindications to hospital discharge before 6 p.m. (1800) were recorded. Before the investigation, sample size testing at an α-level of 0.05 directed a sample size of at least 32 patients per group to achieve statistical power of 0.80. Categorical data were analyzed using the Fisher test. Continuous data were analyzed using the Kruskal–Wallis test and the Wilcoxon nonparametric test with Bonferroni's adjustement for multiple comparisons. The statistical significance was indicated by P values <0.05.

Results

Demographic data, time interval, distribution of surgery, and propofol administration data are summarized in Table 1. The total propofol dose administered to patients of group P was greater in respect to the dose administered to patients of groups K and F ($P < 0.05$). Caudal block failed in 7 cases, necessitating subarachnoid anesthesia. No severe complications, defined as $SpO_2 < 94\%$, need of assisted ventilation, or hemodynamic alterations, were recorded. Of the patients, 104 (86.7%) were discharged before 6 p.m. whereas for the remaining 16 (13.3%) discharge was delayed: the delay resulted from side effects of anesthesia in 7 cases (5.8%) and surgical problems in 9 cases (7.5%). Parental opinion regarding the premedication technique was distributed as follows: just as expected 52 (43.3%), better than expected 59 (49.1%), and worse than expected 9 (7.5%). Table 2 shows the rate of postoperative problems and anesthesia-related contraindications to discharge: differences among the three groups were not significant. Group F showed a higher rate of postoperative nausea and vomiting (PONV) than group K, whereas the latter had a higher rate of behavioral disturbances. The

Table 1 Demographic, time interval, distribution of surgery and propofol administration data (mean ± SD)

Pt/Pr	Age (years)	Weight (kg)	Sex (M/F)	DS (min)	Surgery (ih/cry/hy)	Propofol total dose (mg/kg)
40/F	3.1 ± 1.4	15.8 ± 3.5	22/18	24 ± 12	20/12/8	2.2 ± 0.9
40/K	3.6 ± 1.7	17.0 ± 5.4	21/19	24 ± 18	23/11/6	1.7 ± 0.8
40/P	3.2 ± 1.4	16.3 ± 3.4	22/18	18 ± 6	25/9/6	3.5 ± 1.7*
120 total	3.3 ± 1.5	16.4 ± 4.3	65/55	24 ± 12	68/32/20	2.5 ± 1.1

Pt patients, *Pr* premedicant, *M/F* male/female ratio, *DS* duration of surgery, *F* fentanyl + droperidol, *K* ketamine, *P* placebo, *ih* inguinal hernia, *cry* cryptorchidism, *Hy* hydrocele

* $P < 0.05$ versus K and F groups

Table 2 Postoperative problems

Pre-medication	PONV	Behavioral disturbances	Itching	Urinary retention	Shivering	Total	Total delayed discharge
F	7	3 [3]	1	0	1	12 (30%)	3 (7.5%)
K	4 [1]	5 [1]	0	1 [1]	3	13 (32.5%)	3 (7.5%)
P	2	1	1	1 [1]	0	5 (12.5%)	1 (2.5%)

Number (percentage)

PONV postoperative nausea and vomiting, *F* fentanyl + droperidol, *K* ketamine, *P* placebo

Contraindications to discharge in square brackets

Table 3 Distribution of behavioral score in the three groups, before premedication (time A)

Behavioral score	$^{\square\bullet}$F *n* (%)	$^{*\square}$K *n* (%)	$^{*\bullet}$*P* n (%)
1	6 (15)	5 (12.5)	6 (15)
2	31 (77.5)	35 (87.5)	32 (80)
3	2 (5)	0	2 (5)
4	1 (2.5)	0	0

1, Distressed, crying; 2, awake and calm; 3, asleep, but easily arousable by verbal commands and/or gentle stimuli; 4, asleep, but not readily arousable

F fentanyl + droperidol, *K* ketamine, *P* placebo

Kruskal–Wallis test: P = n.s.; $^{\square}P$ = n.s.; $^{*}P$ = n.s.; $^{\bullet}P$ = n.s.

Table 4 Distribution of behavioral score in the three groups, 45 min after the premedication (time B)

Behavioral score	$^{\bullet*}$F *n* (%)	$^{\bullet\square}$K *n* (%)	$^{\square*}$P *n* (%)
1	3 (7.5)	2 (5)	8 (20)
2	28 (70)	19 (47.5)	30 (75)
3	9 (22.5)	11 (27.5)	1 (2.5)
4	0	8 (20)	1 (2.5)

1, Distressed, crying; 2, awake and calm; 3, asleep, but easily arousable by verbal commands and/or gentle stimuli; 4, asleep, but not readily arousable

F fentanyl + droperidol, *K* ketamine, *P* placebo

Kruskal–Wallis test: $P < 0.0001$; $^{*}P = 0.03$; $^{\square}P < 0.0001$; $^{\bullet}P = 0.03$

observed behavioral disturbances included sedation, dysphoria, agitation, and extrapyramidal syndrome and were the main cause of delayed discharge. In both K and F groups, the same rate of contraindications to discharge was found, but in group F delay was caused by behavioral disturbances only (sedation in two cases and transient extrapyramidal syndrome in one); one case belonging to group P required delayed discharge because of urinary retention. One case in group K showed a persistent PONV, requiring i.v. hydration, and another case suffered from urinary retention with successful bladder catheterization. The relationship between premedication and behavioral score, at the different assessment times A, B, and C, is reported in Tables 3, 4, and 5. Data reported in Table 3 show no significant differences among the three groups before the premedication (time A). Table 4 reports the distribution of behavioral score in the three groups 45 min after premedication (time B): the median value of behavioral score is 2 for all three groups, but most of the patients of group P have a behavioral score of 1 and 2, whereas patients of groups F and K show a higher score. The difference was significant between groups F and P ($P = 0.03$), between groups K and P ($P < 0.0001$), and between groups F and K ($P = 0.03$).

Table 5 reports the distribution of behavioral score in the three groups immediately before the venipuncture (time C): also in this case the median value of behavioral

Table 5 Distribution of behavioral score in the three groups, immediately before the venipuncture (time C)

Behavioral score	$^{\bullet *}$F *n* (%)	$^{\bullet \square}$K *n* (%)	$^{\square *}$P *n* (%)
1	12 (30)	6 (15)	14 (35)
2	20 (50)	22 (55)	25 (62.5)
3	8 (20)	4 (10)	0
4	0	8 (20)	1 (2.5)

1, Distressed, crying; 2, awake and calm; 3, asleep, but easily arousable by verbal commands and/or gentle stimuli; 4, asleep, but not readily arousable

F fentanyl + droperidol, *K* ketamine, *P* placebo

Kruskal–Wallis test: P = n.s.; $^{*}P$ = n.s; $^{\square}P = 0.003$; $^{\bullet}P$ = n.s.

Table 6 Distribution of behavioral score in the three groups, reaction to venipuncture (time D)

Behavioral score	$^{\bullet \square}$F *n* (%)	$^{* \bullet}$K *n* (%)	$^{* \square}$P *n* (%)
1	12 (30)	8 (20)	14 (35)
2	19 (47.5)	14 (35)	20 (50)
3	9 (22.5)	18 (45)	6 (15)

1, Major movement, necessity of patient restraint; 2, minor movement, necessity of arm restraint; 3, no reflex movement

F fentanyl + droperidol, *K* ketamine, *P* placebo

Kruskal–Wallis test: $P = 0.05$; $^{*}P = 0.03$; $^{\bullet}P$ = n.s.; $^{\square}P$ = n.s.

score is 2 for all three groups, most of the patients of group P have a behavioral score of 1 and 2, and patients of groups F and K show a higher score; the difference was significant between groups K and P ($P = 0.003$) but not between groups F and P ($P = 0.51$) or between groups F and K ($P = 0.15$). The reaction scores to venipuncture in the three groups are reported in Table 6 (time D): a significant difference was found between groups K and P only ($P = 0.03$) but not between groups F and P ($P = 0.99$) or between groups F and K ($P = 0.15$).

Discussion

The stress response of children to surgery and other invasive procedures is an important topic in pediatric anesthesia. In past years, several procedures have been introduced in the attempt to decrease this response, including psychological preparation of parent and child, behavioral empathic methods, hypnosis, and parental presence at critical events. These measures may be effective but are time-consuming techniques, whereas drugs, such as topical anesthetic cream and premedication with sedatives, seem to be effective and time-saving methods of reducing the stress response in pediatric patients. Several studies [2–4, 11–13] report a number of benefits of premedication when compared to placebo, such as (a) decreased preoperative anxiety, psychological trauma, and stress response; (b) better anesthesia induction with lower incidence of desaturation; and (c) lower frequency of postoperative behavioral disturbances. On the other hand, some authors [5, 6, 14–16] have questioned this point of view and report that premedication was found to be no better than saline, suggesting that the evidence of benefit is not strong enough to justify studies without placebo control. Furthermore, premedication may yield side effects and complications [5, 6, 17] (e.g., deep sedation, respiratory depression, paradoxical agitation, vomiting), requiring an investigation of the best compromise between advantages and disadvantages. Although premedication has been routinely used for decades, the evidence for a single "best" protocol is still lacking, because the effects may be weak and/or the results may be affected by several nonpharmacological factors, such as susceptibility of physicians and nurses and the presence and personality of parents [5, 6]. As far as specific drugs are concerned, benzodiazepines have been largely used for premedication in clinical practice in recent years [2, 4, 5, 7, 12]: among them, midazolam seems to be the most effective, due to its short half life, but it is not free from paradoxical reactions, which, curiously, can be treated with ketamine [17]; this sounds odd, because benzodiazepines were used in the past to prevent postoperative behavioral abnormalities provoked by ketamine itself. Moreover, also "beneficial" properties of midazolam, as the anterograde amnesia, may be detrimental for children because this amnesia seems to be selective for the explicit memory only. These effects of midazolam on memory, that is, suppression of explicit memory with preservation of implicit memory, are bad because the child could unconsciously memorize preoperative events with a negative and emotional content and be unable to report them consciously in the postoperative phase. In summary, it can be questioned if the current dominant position of midazolam in pediatric sedation is based on its superior properties or if it is a result of clever marketing combined with a lack of reflection among anesthesiologists [5, 6].

Ketamine has powerful analgesic effects: when used in premedication, it may decrease agitation following desflurane anesthesia without delaying recovery [18] and prevent propofol infusion pain [19]. The combined administration of ketamine and midazolam seems to be superior to that of midazolam alone [20, 21], whereas rectal ketamine alone at a dose of 10 mg kg^{-1} seems at least as effective as rectal midazolam 1 mg kg^{-1}, but may lead to prolonged postoperative sedation with possible problems in cases of a brief surgery and with outpatients [8]. Oral fentanyl at a dose of 15 μg kg^{-1} has been reported to cause preoperative vomiting [22], although lower doses seem to be a safe alternative to midazolam [23], despite a higher rate of PONV; other authors [24] have recently confirmed

that oral fentanyl can reduce early postoperative agitation but increases both PONV and recovery times, thus limiting its clinical usefulness. Rectal morphine, when compared to midazolam, shows similar postoperative and higher preoperative discomfort and is not advisable as an alternative to midazolam [25]. Bibliographic data regarding the rectal administration of fentanyl are lacking; nevertheless, it is possible to suggest some hypotheses.

1. The rate and extent of rectal drug absorption may be lower than with the oral route, an inherent factor resulting from the relatively small surface area available for drug uptake.
2. The composition of the rectal formulation appears to be an important factor in the absorption process: rapid absorption from aqueous and alcoholic solutions (e.g., diazepam in children); and slower absorption from suppositories, dependent on the nature of the suppository base, the use of surfactants, particle size of the active ingredient, etc.
3. The large variability of clinical effects may be explainable also by a variable hepatic bypass for drugs, such as fentanyl and ketamine, that undergo extensive hepatic first-pass metabolism. The extent of first-pass metabolism may be influenced, depending on the site of administration in the rectum, because of the rectal venous blood supply: the upper part is connected with the portal system, whereas the lower part is directly connected with the systemic circulation.

Droperidol is still used in anesthesia practice, although it may have some drawbacks [26], such as extrapyramidal syndromes and catalepsy. The U.S. Food and Drug Administration (FDA) issued a "black box" warning about the negative cardiac side effect of droperidol, but a review of the cases referenced by FDA has failed to show a cause–effect relationship [27–32]. The aim of our study was to compare ketamine (10 mg kg^{-1}), fentanyl (5 μg kg^{-1}) plus droperidol (100 μg kg^{-1}), and placebo, to assess which of them, if any, could be the best compromise among sedation, analgesia, and lack of perioperative side effects. The combination of fentanyl plus droperidol has been chosen in the attempt to achieve sedation and analgesia with lower PONV rather than higher doses of fentanyl alone [22–24]. Because of the lack of pharmacological data about rectal administration of fentanyl, we have assumed that the peak plasma level of both premedicants was attained about 45 min after rectal administration [8, 33, 34].

Randomization of the study has permitted the homogeneity of the groups, similar in age, body weight, male/female ratio, and duration of surgery (see Table 1). The propofol total dose administered during surgery was smaller in the two premedicated groups, F and K, compared with the placebo group; this fact may be explained by a synergistic effect between the premedicants and propofol. The observed delayed discharge may have depended on several factors: (a) surgery-related factors; (b) premedication-related factors; (c) anesthesia-related factors; and (d) time of operation. The latter is relevant for patients operated on later in the morning, in whom the premedication-related sedation depended on the shorter time elapsed between premedication and discharge time: although a fixed discharge time at 6 p.m. (1800) cannot take pharmacokinetics into account, we purposefully choose it to fit better the practical requirements of an outpatient department. The urinary retention observed in two cases was probably caused by the surgery or central block rather than premedication. In contrast to the previous report by Tanaka et al. [8], in our study ketamine was not associated with such a prolonged sedation as to increase the rate of delayed discharge. In any event, significant differences between groups and important complications related to anesthesia techniques were not reported (see Table 2). As expected, no significant differences were observed among the three groups before the premedication (time A). Forty-five minutes after premedication and later, behavioral scores were significantly different between groups at the assessment times B, C, and D, probably because the elapsed time had permitted the pharmacological actions of rectal premedicants. At times B and C most of the patients in the premedicated groups, F and K, showed greater behavioral scores, i.e., were more deeply sedated, in comparison with the patients of placebo group (see Tables 4, 5). However, as this statistical significance between groups F and K was only shown in the behavioral scores, then what is the ideal score (or state of the mind) for patient and caregiver? This is a very difficult question because differentiating the anxiolytic from the amnesic and sedative effects of the benzodiazepine is not possible for modern clinical anesthesiology. We think that "*in media res stat virtus*": scores 1 and 4 are both not preferable because of the many possible intuitive risks and drawbacks of these two extremes; in our opinion scores 2 and 3 are the quest of every patient and caregiver. Data reported in Table 6 suggest a better result of the two premedicants in comparison to placebo: the better reaction to venipuncture was obtained in the patients of F and K groups and a significant difference was observed only between patients treated with ketamine when compared to placebo, but not between fentanyl and placebo or between the two premedicants. The powerful analgesic effect of ketamine [8, 34] is probably involved in the blunted reaction to venipuncture; ketamine was shown to be effective in preventing patient discomfort at venipuncture, but the onset of its effects requires more than 30 min, probably because of slow rectal absorption [8, 34].

Conclusions

Despite ketamine being significantly better than placebo and fentanyl–droperidol, the clinical advantage of premedication remains uncertain, because the best results depend on the combination of several already-mentioned factors, all of which must be taken into account in clinical practice [1, 5, 6]. The choice of premedication is part of a larger protocol wherein the psychological evaluation and preparation of each individual child and parent, along with the parent's presence at critical events, and the use of topical anesthetics (e.g., EMLA cream), etc., are provided for. In this study, premedication of pediatric surgical patients with rectal ketamine showed significantly better overall results in the preoperative period than premedication with either fentanyl–droperidol or placebo; the latter did not improve the preoperative management while it caused an increased rate of postoperative behavioral problems, leading to delayed discharge. Our results confirm that rectal ketamine at a dose of 10 mg kg^{-1} may provide an effective and safe premedication, providing both analgesia and sedation, with no major problems at discharge. The rectal absorption of fentanyl needs further study to assess the optimal time and dose for administration, which could help improving perioperative analgesia as well as decreasing perioperative problems.

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