The effect of 2 different concentrations of rectal ketamine on its premedicant features in children

Murat M. Sayin, MD, Arzu Mercan, MD, Hatice Ture, MD, Ozge Koner, MD, Selami Sozubir, MD, Bora Aykac, MD.

ABSTRACT

الأهداف: التحقق من ما إذا كان تغيير التركيز وحجم الكيتامين لما قبل المعالجة عبر المستقيم سوف يغير من الصفات قبل المعالجة والشفاء.

الطريقة: أجريت دراسة وصفية عشوائية سريرية بمستشفى يديتيب الجامعي – تركيا، في الفترة ما بين 2006م إلى 2007م. تراوحت أوزان الأطفال ما بين 10–20 كيلوجرام، جدولت الجمعية الأمريكية لطب التخدير – الدرجة الأولى، من أجل إصلاح الفتق الأربي أو الختان تحت التخدير العام مع تركيب أنبوب فموي رغامي وتخدير موضعي ذيلي. أعطي الأطفال عقار كيتامين قبل المعالجة عبر المستقيم بمقدار $10mg/kg^{-1}$ ل5% في المجموعة (K)، و 2.5% في المجموعة (K½) قبل 45 دقيقة من التخدير. تم تحريض التخدير وإجراءه بواسطة المنشقة. سُجلت نقاط التسكين بواسطة 15 دقيقة في المنطقة ما قبل المعالجة، ونقاط الانفصال الوالدي، وصفات التأثير والشفاء، ووقت الخروج والاستبيان عند الساعة الرابعة والعشرين بعد العملية.

النتائج: تم تقسيم مئة طفل إلى مجموعتين بشكل عشوائي بعدد 50 طفل في كل مجموعة. ثلاثين دقيقة (1.2 مقابل 0.48، p=0.018) و45 دقيقة (2.24 مقابل 1.8، p=0.027) عقب ما قبل المعالجة حصلت المجموعة (K½) على متوسط نقاط تسكين أكثر انخفاضاً من المجموعة (K) وذلك بشكل ملحوظ. كانت نقاط الانفصال، وجودة التأثير، وفترة التأثير، ونقاط الإفرازات إما قبل التحريض أو في الفترة ما بعد العملية، وصفات الشفاء، جميعها متماثلة في كلتا المجموعتين.

خاتمة: على الرغم من إعطاء التسكين المطابق لمعظم الأطفال في كلتا المجموعتين، تبين أن المعالجة الأولية للمستقيم بنسبة 5% من الكيتامين يؤدي إلى ظهور إرتفاع في مستوي التسكين أبكر من المعالجة بنسبة 2.5% من الكيتامين، بينما لم يكن لتغير الحجم والتركيز أي تأثير على صفات الشفاء.

Objective: To investigate whether changing concentration and volume of ketamine for rectal premedication would change the premedication and recovery characteristics.

Methods: A prospective, randomized, clinical study was designed in Yeditepe University Hospital, Istanbul, Turkey in 2006-2007. The study group included children weighing 10-20 kg, American Society of Anesthesiologists grade I, scheduled for inguinal hernia repair or circumcision under general anesthesia with orotracheal intubation and caudal blockade. Children were rectally premedicated with 10 $mg.kg^{-1}$ ketamine 5% in group K, and 2.5% in the Group K1/2, 45 minutes before anesthesia. Anesthesia was induced and maintained by inhalation. Sedation scores at 15 minutes intervals in the preinduction area, parental separation scores, induction and recovery characteristics, time to discharge and a questionnaire at 24th postoperative hour were recorded.

Results: One hundred children were randomized into 2 groups of 50. Thirty minutes (1.2 versus 0.48, p=0.018) and 45 minutes (2.24 versus 1.8, p=0.027) following premedication group K½ had significantly lower mean sedation scores than group K. Separation, induction quality scores, induction duration, secretion scores either during induction or postoperative period, and recovery characteristics were all comparable in both groups.

Conclusion: Although adequate sedation was obtained for most of the children in both groups, rectal premedication with 5% ketamine resulted in higher levels of sedation appearing earlier than that of 2.5% ketamine, while change of volume and concentration had no effect on recovery characteristics.

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From the Department of Anesthesiology (Sayin, Mercan, Ture, Koner, Aykac) and the Department of Pediatric Surgery (Sozubir), Yeditepe University School of Medicine, Istanbul, Turkey.

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Address correspondence and reprint request to: Dr. Arzu Mercan, Department of Anesthesiology, Saad Specialist Hospital, PO Box 30353, Al-Khobar 31952, Kingdom of Saudi Arabia. Tel. +966 (3) 8012218. E-mail: arzumercan66@hotmail.com (Formerly affiliated to the Department of Anesthesiology, Yeditepe University School of Medicine, Istanbul, Turkey).

Premedication reduces preoperative stress in pediatric patients and makes anesthesia induction well tolerated by children. Ketamine is a sedative anesthetic agent, which also has analgesic properties. The advantages of ketamine are cardiovascular stability and minimal respiratory depression.[1,2] Despite all the above mentioned advantages, ketamine may lead to prolonged recovery due to late peak of its active metabolite nor ketamine, when applied rectally.[3] Although low drug concentrations in large volumes are known to increase the bio-availability by enlarging the mucosal surface in contact with the drug, hepatic circulation might be bypassed by direct venous drainage from the rectum to the systemic circulation via the vena cava.[4] Changing the concentration of ketamine applied rectally was proposed to affect the relative distribution of the drug between the portal and systemic circulation.[5] This study was designed to investigate whether 2 different ketamine concentrations and volume used for rectal premedication would change the premedication characteristics and postoperative residual sedative effects.

Methods. This prospective, randomized, clinical study was performed in the Department of Anesthesiology and Reanimation, School of Medicine, Yeditepe University, Istanbul, Turkey between January 2006 and July 2007. During the planning, practice, assessment, and the publication of this research no contact has been made for any commercial, political, or individual reason with any financing foundation. After hospital Ethics Committee approval and parents' informed consents, 100 children weighing 10-20 kg in a physical status of I according to American Society of Anesthesiologists (ASA) guidelines, scheduled for inguinal hernia or circumcision under general anesthesia were included in the study. Patients with gastrointestinal tract disorders and deformities, previous history of general anesthesia, known reactions to the drugs used, failed caudal anesthesia, and patients receiving cleansing enemas were excluded from the study. After a 4-6 hour fasting period, patients were randomly allocated into one of the 2 groups. Patients in group K (n=50) were premedicated with a dose of 10 $mg.kg^{-1}$ by 5% ketamine (Ketalar®, Pfizer, 50 mg/ml in 20 ml vial), and group K1/2 (n=50) with the same dose of ketamine by 2.5% concentration (Ketalar®, Pfizer, 50 mg/ml in 20 ml vial, diluted by saline to 2.5%), 45 minutes before the procedure. Heart rate, non-invasive blood pressure, and saturation of peripheral oxygen (SpO_2) levels were monitored throughout the study in all patients. The liquid premedicant drug, in a concentration planned to be given and prepared by the nurse in the preinduction area, was administered via a rectal applicator and to prevent leakage following application, buttocks were tightly apposed for 5 minutes with the help of parents in the preinduction area for all patients. A 5-point sedation scale[6] (1: awake, restless/crying 2: awake and calm, 3: sleepy, 4: asleep and easily arousable, 5: asleep, not arousable) was used to evaluate the sedation scores of the patients and the results were recorded at 15 minutes intervals after drug application at the preinduction area. Forty-five minutes after premedication, sedation was assessed for the last time in the preinduction area. Following sedation assessment, parents were left in the preinduction area while an investigator blinded to the study design graded the parental separation anxiety of the children according to a 4-point scale;[5] 1: asleep, 2: calm but awake, 3: restless, 4: agitated, crying, or upset. These observations were repeated by the same investigator during induction and were again graded according to another 4-point scale[5] as 1: asleep, 2: calm but awake and apprehensive, 3: awake and struggling, 4: agitated or crying with restraint. Amount of secretion during induction was also graded as 1: dry, 2: wet, 3: wet, requiring aspiration. Anesthesia was induced via a facemask with sevoflurane 7% in 50% oxygen (O_2)-nitrous oxide (N_2O) mixture, and maintained with sevoflurane 1-3% in 50% O_2-N_2O mixture. Heart rate, non-invasive blood pressure, end-tidal carbon dioxide ($ETCO_2$) and SpO_2 were monitored throughout the anesthesia period. Induction quality, amount of secretion, and duration of induction were recorded. Following volatile anesthesia induction, a venous cannula was introduced and endotracheal intubation was performed with appropriate sized endotracheal tube under deep inhalational anesthesia. Children were placed in the left lateral decubitus position, and caudal blockade was performed with a total volume of 1 $ml.kg^{-1}$ of 0.25% bupivacaine (Marcaine 0.5%, AstraZENECA) solution by an appropriate sized caudal needle (Epican Paed® Braun). After emergence, the children were transported to the recovery room. Emergence reactions such as agitation, increased secretions graded as previously explained, gagging, and vomiting were noted. Duration of induction and operation, the rate of recovery by modified Aldrete scale,[7] time to oral intake, and discharge were recorded. If the pain-discomfort scale score[5] was greater than 3 at any time in the recovery room, 0.75 $mg.kg^{-1}$ intravenous meperidine was planned to be given slowly in divided doses as a rescue analgesic. All surgical procedures were performed on an outpatient basis and during discharge patients were prescribed to receive 15 $mg.kg^{-1}$ oral paracetamol suspensions in case of pain. The day after surgery, parents were questioned by phone call for the presence of pain, vomiting, agitation, sleep disorders, nightmares, and hallucinations in the following 24 hours.Power analysis was carried out by statistical software Package

GPower 3.0® and while α=0.05, 1-ß = 0.95, d = 0.67, allocation ratio N_1/N_2 = 1, the effective sample size was 100 for comparison of independent means. The results were evaluated using statistical software package SPSS 9.01® with independent samples t-test, Chi-square, and Fisher's exact tests where appropriate, and significance was set at the level of 0.05.

Results. The groups were comparable with respect to demographic characteristics, duration of surgery and anesthesia in a study population of 100 children (**Table 1**). Five children in group K and 7 children in group K1/2 were operated for inguinal hernia, and 45 children in the group K, 43 children in the group K1/2 were operated for circumcision. The groups were also comparable regarding the operation type. There were no significant differences among the groups in terms of heart rate, and systolic blood pressure before premedication (**Table 2**). None of the patients developed SpO_2 lower than 97% on room air in the preinduction area and in the recovery room. Mean heart rate and mean systolic blood pressure of the patients in group K and K1/2 at all times were statistically similar (**Table 2**). Mean sedation scores of the patients in both groups were comparable 15 minutes after the premedication. Mean sedation score of the group K1/2 was significantly lower than the group K values (p=0.018) 30 minutes following premedication. Peak sedation scores, reached 45 minutes after the premedication in both groups, were significantly lower in group K1/2 than group K (p=0.027) (**Table 3**). Forty-five patients (90%) in group K and 36 patients (72%) in the group K1/2 had a sedation score of ≥2, 45 minutes after premedication. Although the difference was not statistically significant, duration of induction was longer in the patients of the group K1/2 than the group K (**Table 3**). Forty-five patients (90%) in group K and 40 (80%) in group K1/2 had adequate separation quality scores, the difference among the

Table 1 - Surgical and demographic data of the 2 groups.

Demographic data	Group K (n=50)	Group $K_{1/2}$ (n=50)
Age (years)	3.5 ± 1.06	3.86 ± 1.27
Gender (M/F)	46/4	44/6
Weight (kg) (mean±SD)	14.5 ± 2.96	14.9 ± 3.05
Hemoglobin level (g dL^{-1}) (Mean±SD)	11.9 ± 0.96	11.7 ± 0.9
Operation Type (inguinal hernia repair/ circumcision)	5 / 45	7 / 43
Operation duration (min) (Mean±SD)	23.3 ± 14.3	24.0 ± 15.9

M - male, F - female, kg - kilogram, g - gram, dL - deciliters, min - minute

Table 2 - Mean heart rate and systolic blood pressure values of the 2 groups at specific times.

Hemodynamic parameters	Group K (n=50)	Group $K_{1/2}$ (n=50)
Before premedication		
HR (bpm) (mean±SD)	119 ± 9	116 ± 7
SBP (mm Hg) (mean±SD)	94 ± 7	92 ± 7
Before induction		
HR(bpm) (mean±SD)	124 ± 8	123 ± 8
SBP (mm Hg) (mean±SD)	93 ± 8	95 ± 7
After intubation		
HR (bpm) (mean±SD)	118 ± 8	114 ± 7
SBP (mm Hg) (mean±SD)	96 ± 8	94 ± 6
After extubation		
HR (bpm) (mean±SD)	145 ± 9	144 ± 8
SBP (mm Hg) (mean±SD)	105 ± 7	105 ± 8

(bpm: beats per minute, SD: standard deviation, mmHg: millimeters mercury).

Table 3 - Sedation scoring at preinduction area and induction characteristics of the 2 groups.

Characteristics	Group K (n=50)	Group $K_{1/2}$ (n=50)
Sedation score 15 minute (mean±SD)	0.12 ± 0.33	0.14 ± 0.35
Sedation score 30 minute (mean±SD)	1.12 ± 0.82	0.48 ± 0.5*
Sedation score 45 min (mean±SD)	2.24 ± 0.72	1.8 ± 067§
Separation quality (1/2/3/4)	40/5/5/0	36/4/9/1
Induction quality (1/2/3/4)	25/25/0/0	22/25/3/0
Induction duration (seconds) (mean±SD)	136 ± 33	150 ± 47
Secretion score (1/2/3)	42/5/3	41/6/3
Laryngospasm (Yes/No)	2/48	1/49
O_2 desaturation (Yes/No)	0	0
Vomiting (Yes/No)	0	0

*p=0.018, §p=0.027, Sedation scoring: 1. awake, restless/crying, 2. awake and calm, 3. sleepy, 4. asleep, easily arousable, 5. asleep, not arousable, Parental separation quality scoring: 1. asleep, 2. calm but awake, 3. restless, 4. agitated, crying, or upset, Secretion scoring: 1. dry, 2. wet, aspiration not required, 3. wet, aspiration required. Induction quality scoring: 1. asleep, 2. calm but awake and apprehensive, 3. awake and struggling, 4. agitated or crying with restraint required.

Table 4 - Postoperative recovery characteristics of the 2 groups.

Characteristics	Group K (n=50)	Group $K_{1/2}$ (n=50)
Postoperative secretion score (1/2/3)	40/6/4	37/7/6
Spontaneous eye opening (minute) (mean±SD)	14.18 ± 9.51	12.02 ± 6.25
Recovery time (minute) (mean±SD)	27.14 ± 10.6	30.2 ± 5.9
Time to first postoperative oral intake (minute) (mean±SD)	97.2 ± 21.6	99.8 ± 22.3
Discharge time (minute) (mean±SD)	177.3 ± 45.92	176.4 ± 47.54

Table 5 - Analgesic requirement of the patients according to groups.

Analgesic requirements	Group K (n=50)	Group $K_{1/2}$ (n=50)
Analgesic treatment (number)	8	11
Time to 1st analgesic (hours) (Mean±SD)	8.47±2.27	7.89±3.4
Number of analgesics within 24 hours (0/1/2)	19/29/2	22/24/4

groups was insignificant. All patients (100%) in group K and 47 patients (94%) in group K1/2 had adequate induction quality scores (**Table 3**). Anesthesia induction quality scores were identical among the groups and all evaluated as "asleep" or "calm but awake" by having the scores of either 1 or 2 except for 3 children (6%) in the group K1/2 evaluated as "awake and struggling" (**Table 3**). No complications were observed in any of the groups. Only 3 patients (6%) in each group required aspiration due to the increased airway secretion during anesthesia induction (**Table 3**). Despite not being statistically significant, the number of patients with increased secretions in the recovery room was higher in the group K1/2 than the group K (**Table 4**). Mean recovery rate (time to reach full points on the modified Aldrete score) and mean spontaneous eye opening time of patients in both groups were identical (**Table 4**). There was no statistically significant difference in time to first oral intake and time to discharge between the groups (**Table 4**). None of the patients have experienced agitation, gagging, and vomiting at the emergence. None of the patients required rescue analgesia medication during their hospital stay. Number of children requiring analgesics, first analgesic requirement time, and analgesic requirement within 24 hours of the 2 groups were comparable (**Table 5**). Five patients (10%) had vomiting,

15 (37.5%) had restlessness, 3 (6%) had sleeplessness (sleep disturbances), 3 (6%) had nightmares, and none of them had hallucinations through the postoperative 24 hours in group K. Six patients (12%) had vomiting, 15 (37.5%) had restlessness, 5 (10%) had sleeplessness, 4 (8%) had nightmares and none of them had hallucinations in group K1/2. Complications were comparable among the groups.

Discussion. Serum concentrations have been reported to reach peak level within 25-45 minutes following rectal ketamine application,[8,9] which was similar with our results. After 45 minutes, 90% of the children in group K, and 72% in the group K1/2 had adequate sedation levels and mean sedation score of the patients in group K was significantly higher than group K1/2. Different volumes of ketamine have been proposed to affect relative distribution of the drug between the portal and systemic circulation.[5] If the same amount of drug is given in high concentration with a smaller volume, a larger proportion of drug absorbed would be directed to the systemic circulation resulting in faster initial effect and shorter emergence time or vice versa. That is why this study was designed with 2 different concentrations of rectal ketamine. Since a concentrated form of ketamine was not available, this study was performed by diluted ketamine, expecting diluted ketamine would have lower initial effect and delayed recovery and reduced side effects due to the larger proportion of the drug directed into the portal circulation. When the volume is decreased, a larger proportion of the drug could be directed into systemic circulation. The bioavailability of 5% ketamine in the absence of a first-pass metabolism was published to be twice when it was given via nasal route compared with rectal route.[10] In this study, mean sedation scores of patients in the group K1/2 were lower and less compared with Group K patients had adequate sedation levels. This might be due to the portal circulation when the concentration was lower and volume was higher. However, rectal diclofenac suppository was published to be rapidly absorbed and have blood levels similar with intravenous administration of the same drug.[11] This difference may be due to some other factors related either with diclofenac itself or its preparation properties such as the small volume of regular suppositories compared with liquid ketamine volume, pH and vehicle of the drug.[4] The ketamine preparation used in this study has a pH value of 5-5.5. Jantzen and Diehl[4] did not mention the pH value of the diclofenac preparation they used.[4] The number of postoperative patients with increased secretions in group K1/2 was higher than group K, the reason may be the delayed effect of diluted ketamine, which was metabolized to nor-ketamine by the liver. It is obviously impossible to come to a conclusion in the light of the findings of the present study that alleging higher concentrations of rectal ketamine causes faster salvation of side effects than the lower concentrations. However, another study evaluating the drug plasma levels using an optimized ketamine preparation would have yielded different results. This is important as an aspect that could pave the way for more concentrated ketamine preparations for rectal application, which in turn may cause shorter occupation of either preinduction or recovery areas, and may let us take advantage of the benefits of ketamine in premedication. Recovery characteristics and late postoperative findings of patients in both ketamine groups were similar. This finding indicates that changing the concentration of rectal ketamine solutions does not seem to affect the induction and recovery characteristics.

As a conclusion, decreasing the rectal ketamine concentration from 5 to 2.5% seems to affect the initiation of sedation in children, without any affect on the recovery characteristics. However, studies with more sophisticated methods may open new aspects for ketamine premedication.

References

1. Diaz JH. Intranasal ketamine preinduction of paediatric outpatients. ***Paediatr Anaesth*** 1997; 7: 273-278.
2. White PF, Way WL, Trevor AJ. Ketamine: Its pharmacology and therapeutic uses. ***Anesthesiology*** 1982; 56: 119-136.
3. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. ***Can J Anaesth*** 1989; 36: 186-197.
4. Jantzen JP, Diehl P. Rectal administration of drugs. Fundamental and application in anaesthesia. ***Anaesthesist*** 1991; 40: 251-261.
5. Tanaka M, Sato M, Saito A, Nishikawa T. Reevaluation of rectal ketamine premedication in children. Comparison with rectal midazolam. ***Anesthesiology*** 2000; 93: 1217-1224.
6. Marhofer P, Freitag H, Höchtl A, Greher M, Erlacher W, Semsroth M. S(+) Ketamine for rectal premedication in children. ***Anesth Analg*** 2001; 92: 62-65.
7. Aldrete JA, Kroulik D. Postanesthetic recovery score. ***Anesth Analg*** 1970; 49: 924-934.
8. Mlaquin JM. Ketamine par voie rectale pour l'induction de l'anesthèsie pèdiatrique. ***Can Anaesth Soc J*** 1984; 32: 373-374.
9. Idvall J, Holosek J, Stenberg P. Rectal ketamine for induction of anaesthesia in children. ***Anaesthesia*** 1983; 38: 60-64.
10. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. ***Br J Anaesth*** 1996; 77: 203-207.
11. Murphy DB, Kavanagh P, O'Connor P, Sherrin P, Mc Namara S, O'Hare B. Pharmacokinetic profile of rectally administered diclofenac sodium in children undergoing tonsillectomy. ***Pediatr Anesth*** 2000; 10: 694-695.