Comparison of the effectiveness of two different combinations of oral ketamine and midazolam premedication in autistic children

Otistik çocuklarda iki farklı oral ketamin+midazolam premedikasyonunun etkilerinin karşılaştırılması

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Abstract

Objective: Effective premedication is one of the key factors for anesthetic management of autistic children. We designed a study protocol to compare two different dose regimens of midazolam plus ketamine for premedication of autistic children.

Methods: We performed a prospective randomized double-blind study in 142 autistic children, aged 1-17 years, undergoing brain SPECT imaging procedure. Group I received oral 0.5 mg/kg midazolam with 3 mg/kg ketamine and Group II received oral midazolam 0.25 mg/kg with ketamine 6 mg/kg. Onset of sedation and sedation score just before the induction of anesthesia were recorded. Anxiety of children was assessed by a four point scale at admittance, during separation from parents and at venipuncture. Post-anesthetic recovery was assessed using the modified Aldrete score. Postoperative vomiting and any other side effects were recorded when seen. Ten days after the procedure, parents were interviewed for changes in behaviors, sleep disturbances and feeding difficulties.

Results: Acceptable sedation scores were obtained in both groups. Success rates for parental separation and intravenous cannulation were higher than 85% in both groups. There were no differences between two groups in terms of sedation onset time, intravenous cannulation anxiety score, parental separation anxiety score, side effects and changes in behaviors, sleep disturbances and feeding difficulties. The only significant difference between two groups is sedation scores before induction of anesthesia. Children in high ketamine group had deeper sedation state than those in the other group.

Conclusion: Our results showed that both dose regimens provided successful premedication in autistic children.

Key words: Oral, premedication, midazolam, ketamine, autism.

Özet

Amaç: Otistik çocukların anestezi yönetiminde etkin bir premedikasyon hayati önem taşır. Çalışmamızda otistik çocuklarda premedikasyon amacıyla kullanılan iki farklı midazolam+ketamin kombinasyonunun etkileri karşılaştırılmıştır.

Yöntem: Prospektif, randomize ve çift-kör olan bu çalışmaya beyin SPECT görüntüleme yöntemi uygulanabilecek yaşları 1-17 arasında 142 otistik çocuk dâhil edilmiştir. 1. gruba 0.5 mg/kg midazolam + 3 mg/kg ketamin, 2. gruba ise 0.25 mg/kg midazolam + 6 mg/kg ketamin oral yoldan verilmiştir. Sedasyon başlama süresi ve anestezi indüksiyonu öncesi sedasyon skoru kayıt edilmiştir. Çocuklarda başlangıçta, aileden ayrılırken ve damar yolu açılırken anksiyete dörtlü bir skala ile, anestezi sonrası derlenme ise modifiye Aldrete skoru ile değerlendirilmiştir. Postoperatif dönemde bulantı ve benzeri yan etkiler kayıt edilmiştir. İşlemden 10 gün sonra hasta yakınları aranmış ve davranış değişiklikleri, uyku bozuklukları ve beslenme sorunları açısından sorgulanmıştır.

Bulgular: Her iki grupta da kabul edilebilir sedasyon skorları elde edilmiş, aileden ayrılma ve intravenöz kanülasyonda %85'in üstünde başarı elde edilmiştir. Sedasyon başlangıç süresi, aileden ayrılma, intravenöz kanülasyonda anksiyete skorları, yan etkiler, postoperatif davranış değişiklikleri ve beslenme sorunları açısından iki grup arasında bir fark bulunmamıştır. Gruplar arasında tek anlamlı fark, indüksiyon öncesi sedasyon skorunda tespit edilmiş, yüksek doz ketamin içeren grupta daha derin bir sedasyon düzeyi sağlanmıştır.

Sonuç: Her iki rejimin de otistik çocuklarda başarılı premedikasyon sağladığı görülmüştür.

Anahtar sözcükler: Oral, premedikasyon, midazolam, ketamin, otizm.

Autism is a complex neurodevelopmental disorder defined by the presence of social deficits, abnormality in communication, the presence of repetitive and stereotyped patterns of behavior and hyperactivity. Characteristically, autistic patients have fixed routines in their everyday life. Any change in their routine can be very distressing and placing such children in a new environment with strangers can therefore be stressful and problematic for the patient, the parents and the medical staff.

The key points of perioperative care can be summarized as a well-planned procedure that exposes the child to this unpleasant environment as little as possible, a close cooperation with parents and a premedication regimen to effectively reduce the emotional trauma. A smooth anesthetic induction and emergence avoid early and late postoperative maladaptive behaviors.[1,2]

There is few published literature regarding the premedication of combative autistic children. Although various case reports and series have addressed autism as a challenge for the anesthetist,[3-7] we have so far not come across any publications, which compare different premedication methods in children with autism. In children, several reports indicate that both oral midazolam[2,3] and oral ketamine[3,5,8,9] may fulfill many of the characteristics of an ideal premedication. However there are known side effects to both. In studies that use midazolam, doses have to be increased in order to obtain effective sedation and this prolongs recovery time.[10,11] On the other hand, salivation, psychotic side effects, vertigo and emesis restrain the use of ketamine as in premedication therapy.[9,12] To overcome the drawbacks of midazolam and ketamine alone, combinations of both drugs in different doses have been used since 1992.[7,13]

Our study took into consideration the varying results of a number of different studies performed on children. We then designed the following study to compare the effectiveness of oral ketamine 3 mg/kg and midazolam 0.5 mg/kg (Group I) with oral ketamine 6 mg/kg and midazolam 0.25 mg/kg (Group II) in autistic patients.

Materials and Methods

After obtaining institutional approval, 142 autistic children (ASA I-II), and aged 1-17 years undergoing brain SPECT imaging procedure were enrolled in the study. Written informed consent was obtained from children's parents at least 24 hours before the procedure. Exclusion criteria were ASA physical status III or higher and severe cardiovascular or central nervous system dysfunction. The study was conducted in a randomized, double-blind manner.

Children started fasting 4-6 hours prior to anesthesia. Each child was randomly assigned to one of the two premedication groups according to a computer generated list. Group I received 0.5 mg/kg midazolam with 3 mg/kg ketamine and Group II received midazolam 0.25 mg/kg with ketamine 6 mg/kg 30 minutes before anesthesia. An anesthetist prepared the drug mixtures using 0.5 ml/kg apple juice. The same anesthetist also observed its application by the parents. Children who refused to take the premedication or spit it out were excluded from the study protocol.

Evaluation of sedation, anxiolysis and recovery was performed by another anesthetist who was unaware of the contents of the oral premedication. Sedation was assessed by a 5 point scale (Table 1) every 5 minutes following administration of premedication. Onset of sedation (sedation score 3 or less) and sedation score just before the induction of anesthesia were recorded. Anxiety of children (Table 2) was assessed by a four point scale at admittance, during separation from parents and venipuncture. Sedation and anxiolysis scores were adopted from published studies[13] investigating pediatric premedication.

Thirty minutes after oral premedication in the ward, children were taken to the procedure room. In the procedure room, ECG and peripheral oxygen saturation were monitored. Following intravenous cannulation, all children

Table 1. Level of sedation on five-point scale.

Score	Sedation level
1	Barely arousable (full sleep)
2	Eyes closed (light sleep)
3	Eyes opened but looks drowsy
4	Awake
5	Agitated

Table 2. Level of anxiety on four-point scale.

Score	Anxiety level
1	Calm and sleepy
2	Apprehensive but withdrawn from surroundings
3	Crying
4	Agitated and difficult to control

received atropine 0.01 mg/kg. Anesthesia was induced by a facemask with incremental administration of sevoflurane up to 8% inspired concentration with 40% O_2 in air. Anesthesia was maintained with 1-1.5% sevoflurane via a laryngeal mask in all children.

Duration of SPECT was 27 minutes for cases and sevoflurane was stopped in 24th minute. Laryngeal mask was removed at the end of the procedure when the children were deeply anaesthetized. Post-anesthesia recovery was assessed using the modified Aldrete score[14] every 5 minutes. The time between the cessation of the anesthetic and reaching an Aldrete score of 9 points was recorded as recovery time. Postoperative vomiting was recorded as a single event irrespective of the frequency and size of the vomiting. Side effects such as laryngospasm, respiratory depression and post-anesthetic excitement were recorded when observed.

Ten days after the procedure, parents were interviewed by telephone for changes in behaviors (anxiety, apathy, restlessness, aggression against authority), sleep disturbances and feeding difficulties following the anesthetic.

Data are expressed as mean ± SD or percentages. Chi-square or Fisher's exact test, Mann-Whitney U test and unpaired Students t-test are used to test the significance of the difference between the groups. Statistical significance was assumed as $p<0.05$.

Results

Three children who refused to drink oral premedication and two children that spit it out were excluded from study. A total of 137 children were studied.

Two groups were comparable in age, sex and weight (Table 3). Onset time of sedation was 11.67±2.38 min. in Group I and 12.71±4.14 min. in Group II. The difference in onset time is not statistically significant between two groups (p= 0.176). Sedation scores just before induction of anesthesia were 1.52±0.69 in Group I and 1.13±0.45 in Group II (p< 0.01).

Anxiolysis scores at admittance, during separation from parents and venipuncture are shown at Table 4. The difference between the groups was not statistically significant at any assessment period. At separation from parents 86.5% of children in Group I and 86% of children in Group II were calm and sleepy (score 1) whereas the rest of patients had an anxiety level of 2 in both groups (p= 0.82). Success rate at intravenous cannulation was 88% in Group I and 94% in Group II, respectively.

The vomiting rate was slightly higher in Group II (16.2%) than in Group I (12.1%), but the difference between two groups was not statistically significant (p= 0.5).

One child in Group I demonstrated episodes of ventricular arrhythmia in perioperative period but arrhythmia was not continued after the procedure. No side effect was detected in Group II.

Recovery time was 32.4+14.8 minutes in Group I and 31.2+10.5 minutes in Group II (p=0.753). During recovery from anesthesia no difference was observed as assessed by an Aldrete score of 9 or 10 points. All the children were discharged two hours after the end of the procedure.

Data collected by telephone interview did not demonstrate statistically significant differences between the groups. Five children (7.5%) in Group I and six children (8.3%) in Group II had behavioral changes like anxiety and restlessness, whereas five parents (7.5%) in Group I and four parents (5.5%) in Group II reported decrease in appetite. Only two parents (3%) reported restless sleep in Group I whereas restless sleep was not observed in Group II. All the changes returned to normal within one week.

Discussion

In order to deal with problems in autistic children, we previously used oral midazolam in mild cases and oral ketamine in severe cases as premedication based on the previous study by van der Walt and Moran.[3] When we used only midazolam, we had unsatisfactory sedation in a signif-

Table 3. Patient data.

	Group I (n=66)	Group II (n=71)	p value
Age (years)	7.54±4.11	7.31±4.34	0.845
Weight (kg)	30.92±17.26	28.46±20.41	0.327
Gender (M/F)	25/41	21/50	0.305

Table 4. Anxiolysis score at admitance, at intravenous cannulation and at parenteral seperation.

	Group I (n=66)	Group II (n=71)	p value
At admittance	1.82±0.78	1.98±0.65	0.154
At IV cannulation	1.73±0.71	1.71±0.57	0.826
At separation from parents	1.14±0.35	1.14±0.31	0.913

icant proportion of patients. All the children given oral ketamine were successfully sedated but hallucination and nystagmus were observed in some. We therefore decided to mix ketamine and midazolam. To the best of our knowledge, there is no published literature that compares different combination of ketamine and midazolam in autistic children. Therefore, we based our study on previous studies made on non-autistic children.[15-19] This study provides evidence that both groups experienced effective premedication in autistic children without any serious side effects. The only statistically significant difference in the two groups is sedation scores before induction of anesthesia. The mean sedation score of the high ketamine group is significantly lower from that of the low ketamine group.

In this study, onset of sedation time was found to be approximately 12 minutes in both groups. The most extensive study on anesthesia management strategies for autistic children has been done by van der Walt and Moran.[3] They used midazolam, ketamine and a mixture of midazolam and ketamine. However onset time of sedation has not been recorded in that particular study. In a prospective study that compares oral ketamine with oral midazolam for premedication in normal children, onset time of sedation was found to be 13.6 minutes in the ketamine group and 10 minutes in the midazolam group.[13]

Previous studies reported that when ketamine is used as a single drug for premedication in children, increase in ketamine dose results in better premedication.[8,20] We found that, children in Group II have a deeper sedation state than those in the other group before the induction of anesthesia. This better sedation in Group II was most likely due to higher dose of ketamine as the authors suggest.

We had no problems in parental separation in both groups. In a study conducted on normal children, Warner et al.[17] used a combination of midazolam 0.4 mg/kg and ketamine 4 mg/kg for oral premedication and obtained a successful separation rate of 100 %. Funk et al.[16] compared a combination of midazolam 0.5 mg/kg and ketamine 3 mg/kg with both drugs alone. Their success rate at separation was greater than 90% in the combination group. These success rates are consistent with the 86.5% and 86% separation rates obtained in the present study. The authors also reported painless venipuncture in greater than 90% of the cases with combination. Our success rates for intravenous cannulation which was 88% in Group I and 94% in Group II are also parallel to this study.

In our study, recovery time was 32 minutes in Group I and 31 minutes in Group II. In a study by van der Walt

and Moran.[3] the mean recovery time of 9 autistic children premedicated with midazolam plus ketamine was 47 (30-100) minutes. However, the dose of each drug, the duration of surgery and the medication used for maintenance of anesthesia and postoperative analgesia have not been reported for this group. Darlong et al.[15] compared a combination of oral midazolam 0.25 mg/kg and oral ketamine 3 mg/kg with ketamine or midazolam alone in 78 normal children. The recovery time was 22 minutes in the combination group. Their shorter recovery time may be related to lower doses of midazolam and ketamine. On the other hand, our recovery times are shorter than those of some other studies that use similar doses in normal children. Trabold et al.[18] compared 0.5 mg/kg midazolam plus 1.8 mg/kg ketamine with 0.5 mg/kg midazolam plus 3 mg/kg ketamine. Their recovery time was 51 minutes in the low dose ketamine group and 54 minutes in the high dose ketamine group. Operation durations were more than one hour in that study and sevoflurane and alfentanyl were given for the maintenance of anesthesia. In another study, recovery time was found to be 72 minutes for 0.5 mg/kg midazolam plus 3 mg/kg ketamine group.[16] Anesthesia was also maintained with sevoflurane and alfentanyl in that study. We used only sevoflurane 1-1.5% for the maintenance of anesthesia. This may explain why our recovery times in both groups are shorter than the values reported in the two previous studies. On the other hand, our shorter recovery times may be due to a factor inherent in autistic children.

No serious side effects were noted in our study except nausea and vomiting. It was shown that preoperative administration of ketamine may increase the incidence of postoperative emesis.[9,16] This side effect is dose related and can be diminished with the use of a lower doses of oral ketamine[9,16,19] Ghai et al.[19] used a combination of oral ketamine 2.5 mg/kg and oral midazolam 0.25 mg/kg for premedication in children. They have seen postoperative emesis in 2 of 49 children. Funk et al.[16] reported no nausea and vomiting in 39 children that were premedicated with a combination of oral ketamine 3 mg/kg and midazolam 0.5 mg/kg. Our vomiting incidence (12% in Group I, 16% in Group II) is higher than these two studies. This high incidence may be intrinsic to autistic children. van der Walt and Moran[3] reported that postoperative nausea and vomiting (PONV) were seen in 4 of 9 autistic children in the ketamine/midazolam group. The overall incidence of PONV in this study on autistic children was 27%. Although they used prophylactic antiemesis with tro-

pisetron, their incidence of PONV in both ketamine and ketamine-midazolam groups is higher than that reported in the literature. Further works are needed to investigate the effects of antiemetics and different doses of ketamine on the incidence of vomiting in autistic population. On the other hand, we did not see emergence delirium and hallucinations in either group. This may be due to different factors. First, our study groups are children. It was known that ketamine causes awakening hallucinations,[21] but these emergence reactions are rare in children under 10.[22] If the drug is being used as a pure sedative for a painful procedure, emergence reactions may be of some concern. This study was performed for procedural anesthesia, so pain was of no importance. It is unknown whether the concomitant use of midazolam in autistic children is a factor for the absence of hallucination and emergence delirium or not. In two previous studies that used ketamine alone in premedication for children, the authors did not observe emergence delirium and agitation.[4,23] Rainey van der Walt[4] reported that there was no emergence delirium in three autistics that were given oral ketamine without midazolam and they concluded that midazolam was not necessary for a successful premedication. Kulkarni et al.[23] used 7 mg/kg oral ketamine in 50 non-autistic children and he reported no emergence agitation. van der Walt and Moran[3] also did not observe any problems with postoperative agitation or dysphoric reactions in the recovery area.

When we look at the late post-anesthetic period, we find that sleep disturbances, behavioral changes and appetite changes are similar in both groups. All these changes returned to normal within maximum five days. Using a standardized questionnaire, Funk et al.[16] investigated changes in behavior (eating, sleeping and toilet training) after premedication with oral ketamine plus midazolam on days 1 and 7 after the operations. They reported restless sleep in 9 of 39 children and nightmares in 2 of 39 children. We have only two cases of restless sleep in Group I. Because children with autism already suffer sleep disturbances, gastrointestinal dysfunction, mood disorders and aggressive behavior, so understanding minor behavioral changes in these children after general anesthesia needs careful parental observation.[24,25] Because of these questionnaire difficulties it would be unreliable to compare our results with those of other studies that were done in non-autistic children.

In conclusion, our study showed that both regimens provided effective premedication without serious side effects in autistic children undergoing procedural seda-

tion. This data encourage clinicians because if optimum premedication is achieved, the reaction to hospital environment and operation processes observed in autistic children is not far different than that of the normal population.

Conflict of Interest: No conflicts declared.

References

1. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg 2004;99:1648-54.
2. Mc Caan ME, Kain ZN. The management of preoperative anxiety in children: an update. Anesth Analg 2001;93:98-105.
3. van der Walt JH, Moran C. An audit of perioperative management of autistic children. Paediatr Anaesth 2001;11:401-8.
4. Rainey L, van der Walt JH. The anesthetic management of autistic children. Anaesth Intensive Care 1998;26:682-6.
5. Bachenberg KL. Oral ketamine for the management of combative autistic children. Anesthesiology 1988;89:549-50.
6. Chistiansen E, Chambers N. Induction of anesthesia in a combative child; management and issues. Paediatr Anesth 2005;15:421-5.
7. Shah S, Shah S, Apuya J, Gopalakrishnan S, Martin T. Combination of oral ketamine and midazolam as a premedication for a severely autistic and combative patient. J.Anesth 2009;23:126-8.
8. Gutstein H, Johnson K, Heard M, Gregory G. Oral ketamine preanesthetic medication in children. Anesthesiology 1992;76:28-3.
9. Sekerci CM, Donmez A, Ates Y, Okten F. Oral ketamine premedication in children (placebo controlled double blind study). Eur J Anaesthesiol 1996;13:606-11.
10. Viitanen H, Annila P, Viitanen M, Tarkkila. Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. Anesth Analg 1999;89:75-9.
11. Viitanen H, Annila P, Viitanen M, Yli-Hankala A. Midazolam premedication delays recovery from propofol-induced sevoflurane anesthesia in children 1-3 yr. Can J Anaesth 1999;46:766-71.
12. Filatov SM, Baer GA, Rorarius G, Oikkonen. Efficacy and safety of premedication with oral ketamine for day-case adenoidectomy compared with rectal diazepam/diclofenac and EMLA. Acta Anaesthesiol Scand 2000;44:118-24.
13. Debnath S, Pande Y. A comparative study of oral premedication in children with ketamine and midazolam. Indian Journal of Anaesthesia 2003;47:45-7.
14. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995; 7: 89 -91.
15. Darlong V, Shende D, Subramanyam MS, Sunder R, Naik A. Oral ketamine or midazolam or low dose combination for premedication in children. Anaesth Intensive Care 2004;32:246-9.
16. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic premedication for children: double-blind randomized study of com-

bination of midazolam and ketamine alone. Br J Anaesth 2000;84:335-40.

17. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective pediatric premedicant. Paediatr Anaesth 1995;5:293-5.

18. Trabold B, Rzepecki A, Sauer K, Hobbhahn J. A comparison of two different dose of ketamine with midazolam and midazolam alone as oral preanesthetic medication on recovery after sevoflurane anesthesia in children. Paediatr Anaesth 2002;12:690-3.

19. Ghai B, Grandhe RP, Kumar A, Chari P. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Paediatr Anaesth 2005;15:554-9.

20. Turhanoglu S, Kararmaz M, Ozyilmaz MA, Kaya S, Tok D. Effects of different doses of oral ketamine for premedication of children. Eur J Anaesthesiol 2003;20:56-60.

21. Sinner B, Graf BM. Ketamine. In: Schüttler J, Schwilden H, editors. Modern anesthetics. Heidelberg: Springer-Verlag; 2008. p. 313-33.

22. Jankiewizc AM, Nowakowski P. Ketamine and succinylcholine for emergency intubation of pediatric patients. DICP 1991;25:475-6.

23. Kulkarni JA. Oral ketamine for premedication for children. Bombay Hospital Journal 2003;45:424-5.

24. Taira M, Takase M, Sasaki H. Sleep disorder in children with autism. Psychiatry Clin Neurosci 1998;52:182-3.

25. Valicenti-McDermott M, McVicar K, Rapin I, Wershil BK, Cohen H, Shinnar S. Frequency of gastrointestinal symptoms in children with autism spectrum disorders and association with family history of autoimmune disease. J Dev Behav Pediatr 2006;27(2 Suppl):S128-36.

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