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SCIENTIFIC ARTICLE

Effects of ketamine and midazolam on emergence agitation after sevoflurane anaesthesia in children receiving caudal block: a randomized trial☆

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KEYWORDS
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Abstract
Background and objectives: Emergence agitation is a common postanaesthetic problem in children after sevoflurane anaesthesia. We aimed to compare the effects of ketamine and midazolam administered intravenously, before the end of surgery, for prevention of emergence agitation in children who received caudal block for pain relief under sevoflurane anaesthesia.
Methods: 62 American Society of Anesthesiologists patient classification status I children, aged 2–7 years, scheduled for inguinal hernia repair, circumcision or orchidopexy were enrolled to the study. Anaesthesia was induced with sevoflurane 8% in a mixture of 50% oxygen and nitrous oxide. After achieving adequate depth of anaesthesia, a laryngeal mask was placed and then caudal block was performed with 0.75 mL kg^{-1}, 0.25% bupivacaine. At the end of the surgery, ketamine 0.25 mg kg^{-1}, midazolam 0.03 mg kg^{-1} and saline were given to ketamine, midazolam and control groups, respectively. Agitation was assessed using Paediatric Anaesthesia Emergence Delirium scale and postoperative pain was evaluated with modified Children's Hospital of Eastern Ontario Pain Scale.
Results and conclusions: Modified Children's Hospital of Eastern Ontario Pain Scale scores were found higher in control group than in ketamine and midazolam groups. Paediatric Anaesthesia Emergence Delirium scores were similar between groups. Modified Children's Hospital of Eastern Ontario Pain Scale and Paediatric Anaesthesia Emergence Delirium scores showed a significant decrease by time in all groups during follow-up in postanaesthesia care unit. The present study resulted in satisfactory Paediatric Anaesthesia Emergence Delirium scores which are below 10 in all groups. As a conclusion, neither ketamine nor midazolam added to caudal block

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under sevoflurane anaesthesia did show further effect on emergence agitation. In addition, pain relief still seems to be the major factor in preventing emergence agitation after sevoflurane anaesthesia.

PALAVRAS-CHAVE
Bloqueio caudal;
Crianças;
Incidência de agitação;
Anestesia com sevoflurano;
Cetamina;
Midazolam

Efeitos de cetamina e midazolam sobre a incidência de agitação pós-anestesia com sevoflurano em crianças submetidas ao bloqueio caudal: estudo randomizado

Resumo
Justificativa e objetivos: A incidência de agitação é um problema pós-anestésico comum em crianças após a anestesia com sevoflurano. Nosso objetivo foi comparar os efeitos de cetamina e midazolam administrados por via intravenosa, antes do término da cirurgia, para prevenir a incidência de agitação em crianças submetidas ao bloqueio caudal para alívio da dor sob anestesia com sevoflurano.
Métodos: Foram inscritos no estudo 62 pacientes pediátricos, entre 2-7 anos, estado físico classificado de acordo com a Sociedade Americana de Anestesiologistas (ASA: I), programados para correção de hérnia inguinal, circuncisão ou orquidopexia. A anestesia foi induzida com sevoflurano a 8% em uma mistura de oxigênio (50%) e óxido nitroso (50%). Depois de atingir a profundidade adequada da anestesia, uma máscara laríngea foi colocada e, em seguida, o bloqueio caudal foi feito com bupivacaína a 0,25% (0,75 mL kg^{-1}). No fim da cirurgia, cetamina (0,25 mg kg^{-1}), midazolam (0,03 mg kg^{-1}) e solução salina foram administrados aos grupos cetamina, midazolam e controle, respectivamente. A incidência de agitação foi avaliada com a escala *Paediatric Anaesthesia Emergence Delirium* (PAED) e a dor no período pós-operatório avaliada com a escala modificada *Children's Hospital of Eastern Ontario Pain Scale* (mCHEOPS).
Resultados e conclusões: Os escores de dor da escala modificada mCHEOPS foram maiores no grupo controle do que nos grupos cetamina e midazolam. Os escores PAED foram semelhantes entre os grupos. Os escores dessas duas escalas mostraram uma diminuição significativa do tempo em todos os grupos durante o acompanhamento em sala de recuperação pós-anestesia. O presente estudo resultou em escores satisfatórios da escala PAED, que ficaram abaixo de 10 em todos os grupos. Como conclusão, tanto cetamina quanto midazolam, adicionados ao bloqueio caudal sob anestesia com sevoflurano, não mostraram efeitos adicionais sobre a incidência de agitação. Além disso, o alívio da dor ainda parece ser o principal fator na prevenção da incidência de agitação após anestesia com sevoflurano.

Introduction

Emergence agitation (EA) is a common postanaesthetic problem in children after sevoflurane anaesthesia.[1–4] However, the aetiology of EA has not yet been identified clearly. The predisposing factors are preschool age, preoperative anxiety, lack of premedication, type of surgery, awakening in a strange environment.[4,5] The incidence of EA had been reported between 10% and 80% in different studies.[5,6,7] Although EA is also seen in pain-free procedures, pain is thought to be the major contributing factor for EA. In addition to pain treatment, benzodiazepines, opioids, ketamine, alpha-2 agonists and propofol have also been used to prevent EA.[8]

In the present study, we aimed to compare the effects of ketamine and midazolam for prevention of EA after sevoflurane anaesthesia, in children who received caudal block for pain relief.

Methods

The study was approved by the Institutional Ethics Committee of Ankara Research and Training Hospital (Chairperson Assoc Prof Y. Aral) with protocol number 00165 on 13 March 2008. Written informed consents were obtained from parents of the children. Sixty-two ASA I children, aged 2–7 years who were scheduled for inguinal hernia repair, circumcision or orchidopexy were enrolled in the study. Exclusion criteria were mental retardation, physical developmental delay, preoperative agitation and contraindication for caudal block.

The children did not receive any premedication. Anaesthesia was induced with inspired sevoflurane 8% in a mixture of 50% oxygen and nitrous oxide. After loss of consciousness, a peripheral vein was cannulated. ECG, SpO_2, NIBP, temperature, end-tidal CO_2 and anaesthetic gases were monitored during anaesthesia. After achieving adequate

depth of anaesthesia, a laryngeal mask was placed and then children were positioned in the lateral decubitus position for caudal anaesthesia. 0.75 mL kg^{-1}, 0.25% plain bupivacaine was injected using a 20-22 G caudal needle. Thereafter, anaesthesia was maintained with sevoflurane 3% in 50% oxygen–nitrous oxide mixture. No other hypnotic, muscle relaxant or analgesic drug was administered during surgery. Skin incision was made 15 min after caudal block. Caudal block was accepted adequate if heart rate and blood pressure did not increase more than 20% of baseline value after skin incision. The children with failed block were excluded from the study and fentanyl 2 $\mu g\,kg^{-1}$ was administered.

Patients were randomized into 3 groups as control (Group C, $n = 20$), midazolam (Group M, $n = 21$) and ketamine (Group K, $n = 21$) groups. Ketamine 0.25 mg kg^{-1}, midazolam 0.03 mg kg^{-1} and saline at equal volumes were administered intravenously to children approximately 10 min before the end of surgery, in ketamine, midazolam and control groups, respectively in a blinded fashion.[9,10] Then, sevoflurane concentration was reduced, laryngeal mask was removed and inhaled anaesthetics were discontinued. The children were allowed to breathe 100% oxygen for 5 min and then transferred to the postanaesthesia care unit (PACU). Before the transfer to PACU, the caudal blocks were confirmed as functioning by lack of response to toe pinch. Heart rate, NIBP, and SpO_2 were monitored and the children were assessed in the PACU by an anaesthetist blinded to the study groups. Agitation was assessed using PAED (Paediatric Anaesthesia Emergence Delirium) scale at 0, 5, 10 and 30th min and mCHEOPS (modified Children's Hospital of Eastern Ontario Pain Scale) was used to evaluate postoperative pain at 5, 10 and 30th min in the recovery room.[11,12] All agitated children with PAED score more than 10 at the 10th min received 1 mg kg^{-1} propofol, and if the agitation was not controlled in following 10 min, propofol administration was repeated. Children with mCHEOPS score $\geq$6 received morphine 0.05 mg kg^{-1} iv for rescue analgesic. Children were observed 60 min in the PACU and then discharged to the ward. The side effects like nausea, vomiting, bronchospasm, laryngospasm, desaturation, hallucination were also recorded.

Statistical analysis was performed by using Medcalc software programme (Medcalc Software bvba, Mariakerke, Belgium), version 11.3.3.0. To determine the sample size, a pilot study with 10 patients receiving only caudal analgesia, like in control group, was performed. We observed EA in 6 of 10 patients. A 40% reduction in EA was considered to be clinically significant, we calculated 20 patients were required for each group with type I error ($\alpha = 0.05$) and type II error ($\beta = 0.2$). Kolmogorov–Smirnov test was used to analyze the normal distribution of measured variables. Intergroup comparisons were made with ANOVA or Kruskal–Wallis variance test and Friedman test was used for with-in group comparisons. Data are presented as the mean $\pm$ SD and median (minimum–maximum). Chi-square test was used for comparison of categorical data. p Value of less than 0.05 was considered statistically significant.

Results

Sixty-two children were enrolled in the study. Two children were excluded from the study because of inadequate caudal block.

The characteristics of the patients (age, gender, weight), duration of anaesthesia and surgery and types of surgery were similar between groups and shown in Table 1.

Systolic blood pressure values were found similar between groups at all measurement times. Systolic blood pressure was measured lower within ketamine group at the 15th and 30th min following caudal block than at induction ($p = 0.026$).

Heart rates were found similar between groups at all measurement times. Heart rates decreased significantly during anaesthesia within each group.

Pain was evaluated using mCHEOPS scoring system at postoperative 5, 10 and 30 min in PACU. The median values were found below 6 at all measurement times in all groups. Scores were higher in control group than in ketamine and midazolam groups at all measurement times (Fig. 1). When the groups were assessed individually, there were 5, 2 and 3 children at 5th min with mCHEOPS $\geq$6 in control, ketamine and midazolam groups, respectively. At 10th min, there were 1 and 2 patients with mCHEOPS score $\geq$6 in midazolam and control groups, respectively. One patient of the control group also had a higher PAED score at the same measurement time and received propofol. The other two children, one in each group, with mCHEOPS score $\geq$6 received morphine 0.05 mg kg^{-1} iv as rescue analgesic. The mCHEOPS scores of the patients in all groups decreased gradually during follow-up in PACU.

PAED scores were similar between groups at all measurement times (Fig. 2). The median values of PAED scores of the groups were found below 10 except at the arrival of the control group to PACU. There were 11, 6 and 9 children with PAED score above 10 in control, ketamine and

Table 1 The characteristics of the patients, duration of anaesthesia and surgery. Values are expressed as mean $\pm$ SD, median (min-max).

	Control	Midazolam	Ketamine	p Value
Age (years)	5 (2–7)	5 (2–7)	4 (1–7)	0.87
Gender (M/F)	13/7	14/6	14/6	0.86 $\chi^2 = 0.29$
Body weight (kg)	17.3 $\pm$ 3.9	18.6 $\pm$ 6.1	18.1 $\pm$ 5.5	0.74
Duration of surgery (min)	26.8 $\pm$ 11	33.4 $\pm$ 13.3	28.3 $\pm$ 10	0.15
Duration of anaesthesia (min)	53.6 $\pm$ 11.6	57.8 $\pm$ 14.1	53 $\pm$ 12.9	0.41
Types of surgery (IHR/O/C)	11/4/5	10/4/6	11/5/4	0.96 $\chi^2 = 0.62$

IHR, inguinal hernia repair; O, orchidopexy; C, circumcision.

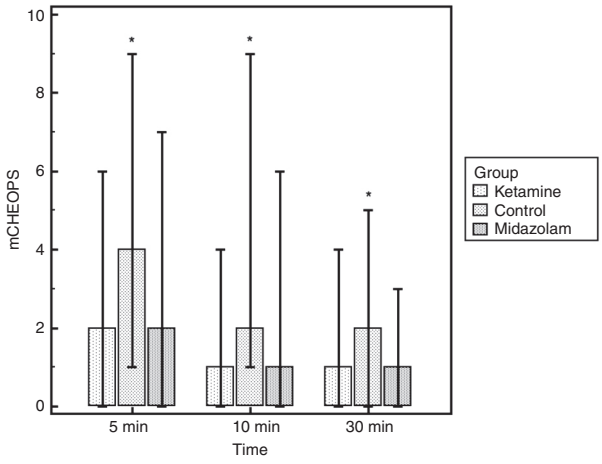

Figure 1 mCHEOPS scores of the groups. *$p < 0.05$ vs ketamine and midazolam groups. (Values are expressed as median (min-max)).

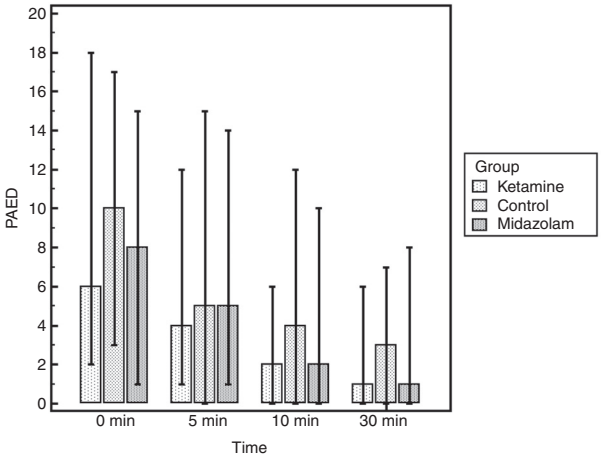

Figure 2 PAED scores of the groups. (Values are expressed as median (min-max)).

midazolam groups, respectively at the arrival. Since EA could show spontaneous resolution, we observed the children for 10 min to administer the rescue drug propofol. In fact, 8, 6 and 8 children with EA showed spontaneous resolution in 10 min in control, ketamine and midazolam groups, respectively. Three patients in control and 1 patient in midazolam groups with PAED score above 10 received 1 mg kg^{-1} propofol, intravenously. Also PAED scores showed a significant decrease in all groups during follow up in PACU.

No side effects like nausea, vomiting, bronchospasm, laryngospasm, desaturation, hallucination were recorded in any patient of the groups.

All patients could be discharged from PACU after 60 min follow-up.

Discussion

In the present study, the effects of ketamine and midazolam on EA were assessed in a group of patients who are at high risk for EA regarding to their age and the used inhaled anaesthetic. The results showed that ketamine or midazolam added to caudal block decreased mCHEOPS scores but did not affect PAED scores in children after sevoflurane anaesthesia.

Pain, rapid emergence in an unknown environment, separation from parents, and preoperative anxiety are major factors contributing to EA.[8]

Different definitions and scales exist for evaluation of EA, but PAED scale is preferred in most of the studies. A score of 10/20 on the PAED scale was reported as the best threshold point for determining the presence of EA.[13] However, Bajwa et al. reported that a PAED score greater than 12 had greater sensitivity than a score of $\geq$10.[14] In our study, we used a score of $\geq$10 on PAED scale for the assessment of EA.

Pain is thought to be the major factor that contributes to EA. In previous studies several analgesics including acetaminophen, ketorolac, fentanyl were administered to prevent EA after sevoflurane anaesthesia. In most of these studies, addition of analgesics reduced the incidence of EA.[1,15,16] Caudal block is another preferred technique for pain relief in children. Aouad et al. had shown that the incidence of EA and pain scores in patients receiving caudal block were significantly lower compared to those receiving intravenous fentanyl under sevoflurane anaesthesia for inguinal hernia repair.[6] However, Aono et al. reported EA in 40% of children with caudal block following sevoflurane anaesthesia for minor urologic surgery.[17] We used mCHEOPS scoring system to evaluate and to exclude pain as a contributing factor of EA.

Although pain is thought to be important in aetiology, EA is also seen in pain free procedures.[2,3] This may due to rapid emergence in an unknown environment with altered cognitive function which is another risk factor for EA. It is difficult for the children to cooperate to a strange environment upon rapid emergence following anaesthesia. Therefore, agents that provide sedation at the time of emergence may be helpful in prevention of EA.[17–19] This point was one of the reasons to establish this study.

Low doses of midazolam and ketamine are safely used for sedation. Chen et al. found that 0.05 mg kg^{-1} midazolam in combination with 0.5 μg kg^{-1} of fentanyl at the end of surgery was effective in reducing the incidence and severity of EA.[19] Ozcengiz et al. found 0.5 mg kg^{-1} oral midazolam, given for premedication, very effective in reducing EA.[20] Kararmaz et al. had shown that oral ketamine reduced the incidence of EA after desflurane anaesthesia without delaying recovery.[21] Abu-Shahwan showed that administration of 0.25 mg kg^{-1} iv ketamine at the end of anaesthesia reduced significantly the incidence and severity of EA in children undergoing dental repair.[22] Dalens et al. administered 0.25 mg kg^{-1} ketamine, 0.1 mg kg^{-1} nalbuphine and saline in three groups of patients, and they found significantly lower EA in ketamine and nalbuphine groups compared to control without a delay in awakening and discharge.[9] In contrary to literature, ketamine and midazolam did not affect EA in children in whom pain was relieved by caudal block in the present study.

Parental presence may be another important factor that influences the incidence of EA. Arai et al. studied the effect of parental presence on EA and found that parental presence during induction of anaesthesia enhanced the effect of oral midazolam on EA of children compared with midazolam and

parental presence alone groups.[23] In our study, parents were present at the arrival to PACU.

In children it is difficult to assess pain and also it can be confusing to differentiate pain and EA. In the present study, although the PAED scores were similar, mCHEOPS scores were statistically different among groups. Since all the caudal blocks were functioning and all patients were considered to be free of pain, sedation caused by ketamine and midazolam might have reduced the mCHEOPS scores in these groups. This may due to the parameters of mCHEOPS which are not specific for pain and may be related with sedation.[12,24]

In this study, we accepted parents to PACU and provided effective pain relief with caudal block in all groups. This resulted in satisfactory PAED scores which are below 10 in all groups. As a conclusion, neither ketamine nor midazolam added to caudal block under sevoflurane anaesthesia did show further effect on EA. In addition, pain relief still seems to be the major factor in preventing EA after sevoflurane anaesthesia.

Conflicts of interest

The authors declares no conflicts of interest.

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