Original Article

Effects of premedication of midazolam or clonidine on perioperative anxiety and pain in children

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Summary **The aim of the present study was to compare clinical effects of oral midazolam and clonidine premedication in children. In a prospective randomized double blind trial, 45 children between 2-8 years old received either oral midazolam 0.5 mg/kg (group M) or clonidine at 2 μg/kg (group C_2) or 4 μg/kg (group C_4). The level of sedation, quality of parental separation, mask acceptance and thermodynamics were recorded. Postoperative analgesia, and perioperative side effects were assessed. In comparison to group M, the scores of sedation, parental separation and mask acceptance were significantly higher in group C_2 and group C_4 ($p < 0.05$). Also the level of sedation was significantly better in group C_4 than in group C_2 ($p < 0.05$). However, the rate of postoperative analgesia decreased significantly in group C_2 and C_4 compared to group M. The incidence of shivering was significantly increased in group M compared to group C_2 and C_4. Oral clonidine premedication can therefore provide better preoperative sedation and postoperative analgesia with few adverse effects.**

Keywords: Clonidine, midazolam, children, premedication

1. Introduction

Preoperative anxiety and pain are known to lead to maladaptive behavior in the postoperative period (*1*). A multimodal approach consisting of sedative drugs, parental presence, play therapy, familiar environment and effective pain therapy is necessary to reduce preoperative anxiety (*2,3*).

Oral premedication is widely used in pediatric anesthesia to reduce preoperative anxiety and ensure smooth induction. The benzodiazepine midazolam, an anxiolytic drug, is the most commonly used premedication (*4,5*). Midazolam has a number of beneficial effects when used as premedication in children: sedation, reduction of vomiting, fast onset and limited duration of action (*6,7*). However, it is far from an ideal premedication, having an increased incidence of adverse effects such as postoperative behavior changes, cognitive impairment (*8*), paradoxical reactions, and repiratory depression (*9*). Recently, new drugs such as the alpha 2-agonists have emerged as alternatives for premedication in pediatric anesthesia. Clonidine, a selective centrally acting partial alpha 2-agonist, has been reported to improve perioperative hemodynamic stability, provide analgesic properties, and decrease anaesthetic requirements (*10-12*). However, the reports about administrated dosage of clonidine have remained inconsistent (*13,14*).

The main aim of this study was to evaluate and compare the influence of different premedication regimens on preoperative sedation, separation from parents, and mask acceptance in children. We also compared postoperative analgesia, hemodynamic status, and adverse effects.

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2. Materials and Methods

2.1. *Case selection and study design*

After approval of the Hospital's Ethics Committee

and parental written informed consent, 45 children, ASA status I or II, aged between 2 and 8 years, and undergoing selective ventriculoperitoneal shunt were included in this double-blind, prospective, randomized study. All children exclude abnormal liver function and renal and mental disease.

Children were randomized into the following three groups: group M (n = 15), group C_2 (n = 15), and group C_4 (n = 15) received midazolam 0.5 mg/kg, clonidine 2 μg/kg, and clonidine 4 μg/kg given orally 60 min prior to anesthesia induction, respectively. The premedication was mixed with 5 mL syrup. All children who refused to take the premedication or spat it out were excluded from the study protocol.

2.2. *Assessment and data collection*

Heart rate (HR), blood pressure (BP), pulse oxygen saturation (SPO2), and respiration rate (RR) of children were monitored routinely during perioperation. Ringer's lactate solution was infused according to the child's weight. Preoperative level of sedation was assessed by using a 3-point scale: 1 = crying and struggle, 2 = alert, 3 = drowsy. Parental separation was evaluated by using a 3-point scale: 1 = anxiety and struggle, 2 = anxiety, easily calmed, 3 = drowsy and calm. A 4-point scale was applied for evaluation of mask acceptance (*3*): 1 = combative, angry, 2 = fear of the mask, not easily calmed, 3 = fear of the mask, easily calmed, 4 = calm, cooperative. Assessment was performed by a consultant anesthetist who had no knowledge of the type of premedication.

A strict anesthetic protocol was applied. Anesthesia was induced with inspired isoflurane 2.5% in a fresh gas flow of 3-litre/min. The maintenance of anesthesia was carried out with inspired isoflurane 1.1%~1.5% combined with remifentanyl (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and vecuronium (0.08 $mg \cdot kg^{-1} \cdot h^{-1}$) given intravenously. If children complained of pain, frequent crying, and dysphoria after operation, remedy analgesia was provided by a rectal loading dose of paracetamol of 30-40 mg/kg. All adverse effects including hypotension (SBP < 70 mmHg), bradycardia (HR < 60 beats/min), respiratory depression, nausea/vomiting, and shivering were recorded and administered in the perioperative periods.

2.3. *Statistical analysis*

Results were analyzed using SPSS10.0 software, and all values were reported as mean plus/minus SE. Data analysis for measurement data was performed by unpaired Student's *t*-test to detect the differences between the groups for age, weight, operation time, duration of anesthesia, and various scores. Numerical data was analyzed using the chi-square test. A $p < 0.05$ was considered statistically significant.

3. Results

The three groups were similar with respect to age, weight, gender, operation time and duration of anesthesia (Table 1).

Table 2 summarizes preoperative scores and postoperative analgesia for the three groups. In comparison to group M, the scores of sedation, parental separation and mask acceptance were significantly higher in group C_2 and group C_4 ($p < 0.05$). It is to noted that the level of sedation was significantly better in group C_4 than in group C_2 ($p < 0.05$). However, the rate of remedy analgesia decreased significantly in group C_2 and group C_4 than in group M.

Table 3 shows adverse effects of various groups in the perioperative period. The incidence of shivering was significantly increased in group M than in group C_2 and C_4 ($p < 0.05$). No significant differences were observed between clonidine and midazolam in hypotension, bradycardia, respiratory depression, and nausea/vomiting.

4. Discussion

This study demonstrates clinical advantages of oral clonidine, in both the preoperative sedation and postoperative analgesia, compared with oral midazolam when used as a premedication in children.

Clonidine is experiencing increasing use in the pediatric population as a sedative and analgesic because

Table 1. Patient data

	Group M	Group C_2	Group C_4
Age (year)	5.0 ± 2.1	4.8 ± 1.9	5.2 ± 2.3
Gender (male/femal)	8/7	8/7	9/6
Weight (kg)	17 ± 5	16 ± 6	17 ± 6
Operation time (min)	65 ± 21	62 ± 27	65 ± 22
Anesthesia time (min)	68 ± 28	65 ± 30	68 ± 31

Data are expressed as mean ± SE, $p > 0.05$.

Table 2. Sedation, parental separation and mask acceptance scores and remedy analgesia: midazolam compared with clonidine

Groups	Sedation score	Parental separation score	Mask acceptance score	Remedy analgesia (%)
M	2.1 ± 0.5	1.6 ± 0.5	1.4 ± 0.6	80
C_2	2.4 ± 0.6*	2.1 ± 0.6*	2.8 ± 0.8*	20*
C_4	2.7 ± 0.4*#	2.2 ± 0.6*	2.9 ± 1.0*	20*

Data are presented as mean ± SE; * $p < 0.05$ in comparison with group M; # $p < 0.05$ in comparison with group C_2.

Table 3. Adverse effects of various groups in perioperative period

Groups	Hypotension	Bradycardia	Respiratory depression	Nausea/ vomiting	Shivering
M	0	0	0	3	6
C_2	0	1	0	1	1*
C_4	2	1	0	1	0*

Data are presented as mean ± SE; * $p < 0.05$ in comparison with group M.

of its central alpha2-adrenergic agonist capability (*15-17*). Results of this study indicate that sedation and the anti-anxiety effect of clonidine might contribute to activation of alpha-2 adrenergic receptors in locus coeruleus or in the frontal lobe cortex (*18*).

One major drawback of clonidine used as a sedative premedication is its slow onset of action (*19,20*). So, oral clonidine needs to be administered at least 60 min prior to induction whereas satisfactory sedation can be achieved 30 min after oral midazolam. However, anesthetists may prefer to accept the delay in onset of sedation of clonidine if clinical advantages occur during the perioperative period.

The effect of sedation was found to be related to dosage of clonidine premedication in children for ophthalmic surgery (*21*). Schmidt *et al*. (*22*) reported that children receiving clonidine premedication have similar levels of anti-anxiety and sedation as those receiving midazolam. In contrast, our study demonstrated clonidine premedication provided better levels of sedation and anti-anxiety in children than those given midazolam.

A prospective study of patients undergoing outpatient laparoscopic cholecystectomy indicated patients receiving clonidine (0.15 mg orally 60 min before surgery) required less additional analgesia (*23*). In this study, children given clonidine had less postoperative pain than those given midazolam. However, it remains unclear if this effect is related to activation of postsynaptic α2 receptors in the descending noradrenergic pathway of the spinal cord or related to an anxiolytic effect not measured (*24*).

Mikawa *et al*. showed oral 5 μg/kg clondine premedication led to severe bradycardia, and needed atropine treatment (*25*). The study selected clonidine at a dosage of 2 μg/kg and 4 μg/kg concomitant with atropine intramuscular injection. Only one child in each clonidine group had bradycardia. Likewise, there were no differences in the incidence of hypotension, nausea/vomiting, respiratory depressing between clonidine and midazolam groups. A previous study suggested clonidine was effective treatment for postananesthetic shivering (*26*). In the present study, the incidence of shivering was lower in the clonidine group than in the midazolam group. The mechanism of clonidine preventing shivering was correlated with inhibition of vasoconstriction and a decrease of shivering threshold (*27*).

In conclusion, in this study, premedication with oral clonidine appeared to be superior to oral midazolam. Oral clonidine premedication provided better sedation, anti-anxiety, postoperative analgesia, and prevented postoperative shivering with few adverse effects.

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