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Efficacy of Oral Clonidine Premedication in Children

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Background: **Clonidine, an α_2-adrenoceptor agonist, has been shown to be effective as a preanesthetic medication in adults. The current study was designed to investigate the efficacy of two doses of oral clonidine as a premedicant preceding oral atropine in children.**

Methods: **In a prospective, randomized, double-blind, controlled clinical trial, 105 children, aged 4–12 yr, undergoing elective ophthalmologic surgery received 0.4 mg/kg diazepam, 2 μg/kg clonidine, or 4 μg/kg clonidine orally. These agents mixed with apple juice were administered 105 min before the estimated time of induction of anesthesia, and were followed by treatment with 0.03 mg/kg oral atropine 60 min before anesthesia. A blinded observer noted the children's level of sedation, quality of separation from parents, and degree of acceptance of mask application during inhalation of nitrous oxide used for establishment of venous access. Anesthesia was induced with 5 mg/kg thiamylal, and tracheal intubation was facilitated with 0.2 mg/kg vecuronium. Hemodynamic changes after tracheal intubation were compared among the three groups.**

Results: **Clonidine produced significant sedation, and the effect was dose related. Clonidine, 4 μg/kg, provided better quality of separation and acceptance of mask than the two other regimens. This dose of clonidine attenuated the increases in blood pressure and heart rate after tracheal intubation. No clinically significant perioperative hypotension or bradycardia was observed.**

Conclusions: **These data indicate that, even in pediatric surgery, the combination of 4 μg/kg and 0.03 mg/kg oral clonidine is an effective premedication. However, the safety and optimal dose of clonidine in this setting remain to be determined. (Key words: Anesthesia: pediatric. Premedication: oral. Sympathetic nervous system, α_2-adrenoceptor agonist: clonidine.)**

ALTHOUGH clonidine, an α_2-adrenoceptor agonist, was introduced into clinical practice as an antihypertensive medication approximately 20 yr ago,[1] its application has been limited because of untoward side effects, including sedation. However, these properties are partially responsible for a new enthusiasm for use of this drug in anesthesia. It has recently been shown to be an effective premedicant in adults, providing preoperative sedation,[2,3] postoperative analgesia,[4,5] perioperative hemodynamic stability,[6–8] and reduction in the volatile anesthetic requirement. We undertook the current study to investigate the effectiveness of oral clonidine in children as a preanesthetic medication, and its efficacy in attenuating the cardiovascular responses to tracheal intubation. To assess these effects, we compared sedation, separation, mask acceptance, and hemodynamic changes associated with tracheal intubation between patients receiving clonidine and those given diazepam.

Materials and Methods

Subjects

After institutional approval of Kobe University School of Medicine and parental informed consent, we initiated the trial, which involved 105 children (ASA physical status 1 inpatients) ranging in age from 4 to 12 yr, to evaluate oral clonidine as a preanesthetic medication. The children were randomly assigned to one of three groups (35 children per group): 0.4 mg/kg diazepam, 2 μg/kg clonidine, or 4 μg/kg clonidine in 0.15 ml/kg apple juice. These agents were administered 105 min before estimated induction of anesthesia. All children also received 0.03 mg/kg atropine *p.o.* in 0.2 ml/kg apple juice 60 min before estimated induction of anesthesia.

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Assessment of Efficacy of Premedication

The level of sedation was assessed using a three-point sedation scale (1 = tearful/combative; 2 = alert/aware; and 3 = drowsy/sleeping) at the time of preanesthetic medication and every 30 min thereafter until entry into the operating room. Just before separation from their parents, the children's behavior was also evaluated, using a different three-point rating scale (1 = poor (anxious/combative); 2 = good (anxious/easily reassured); and 3 = excellent (sleeping/calm)). A minimum interval of 90 min was allowed between oral preanesthetic medication and entry into the operating room, where all children received 3 l/min N_2O and 3 l/min O_2 *via* a mask for 3 min to provide analgesia during venous cannulation.[9] Next, the quality of mask acceptance was immediately evaluated with a four-point rating scale (1 = poor (afraid, combative, and crying); 2 = fair (fearful and not easily calmed); 3 = good (slightly fearful and easily calmed); and 4 = excellent (unafraid and cooperative)).

Anesthesia and Hemodynamic Measurements during Anesthetic Induction

After establishment of venous cannulation, nitrous oxide was discontinued and the children breathed 100% O_2 for 5 min. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) monitoring with an automatic noninvasive blood pressure (BP) monitor (Pulsemate BX-5; Nippon Colin, Tokyo, Japan) was begun. Heart rate (HR) was monitored from lead II of the electrocardiogram. Immediately before induction of anesthesia, SBP, DBP, and HR were recorded by independent observers. Anesthesia was then induced with 5 mg/kg thiamylal followed by 0.2 mg/kg vecuronium to facilitate tracheal intubation. Direct laryngoscopy was attempted 2 min after thiamylal and maintained for 30 s. The endotracheal tube was placed exactly within the last 5 s of laryngoscopy. All intubations were performed by the same individual, who was blinded to the nature of the experimental treatment. From the administration of thiamylal until 5 min after induction, ventilation was assisted or controlled with 1.5% halothane and 50% N_2O in oxygen, and end-tidal P_{CO_2} was maintained between 4.1 and 5.0 kPa (30.8 and 37.5 mmHg, respectively). This variable was measured using a Datex Capnometer (Helsinki, Finland) *via* a catheter placed in the nostril, from immediately after sleep until commencement of laryngoscopy. After insertion of the endotracheal tube, expired gas was sampled from a T-piece connected to the tube. Further automatic hemodynamic measurements were obtained by the independent observers at 2, 3, 4, and 5 min after administration of thiamylal.

Anesthesia was maintained with 0.5–2% halothane and 60% N_2O in oxygen. Intraoperative muscle relaxation was obtained with intermittent administration of 0.02 mg/kg vecuronium, if necessary, to maintain 70% twitch depression. After surgery, each patient's trachea was extubated in the operating room after residual neuromuscular blockade had been antagonized with 0.05 mg/kg neostigmine and 0.02 mg/kg atropine. Criteria for extubation included: (1) regular and adequate respiratory rate and depth of respiration; (2) an end-tidal P_{CO_2} of less than 50 mmHg; (3) fully reversed neuromuscular blockade (as assessed by sustained tetanic contraction with 50 Hz); and (4) intact airway protective reflexes. The time from administration of the preanesthetic medication to induction of anesthesia (premedication time), and from induction of anesthesia until extubation of the trachea (anesthesia time), were recorded.

Postoperative Parental Questionnaire

Twenty-four hours after surgery, each child's parents were asked to complete a followup questionnaire. They were asked to evaluate their child's preoperative experience (1 = unpleasant, 2 = acceptable, and 3 = pleasant). The parents asked the child to assess his or her own surgical experience (1 = unpleasant, 2 = acceptable, and 3 = pleasant). The child was also asked if he or she remembered the application of the face mask.

Preoperative and Postoperative Vital Signs and Adverse Effects

The incidences and times of occurrence of vomiting were recorded while patients were in the ward before the operation, while patients were in the operating room, and during the first 24 h after operation. Any other adverse reactions and side effects (*e.g.*, hypotension (SBP < 70 mmHg), rebound hypertension (SBP > 140 mmHg), bradycardia (HR < 60 beats/min), respiratory depression (RR < 12 breaths/min), and hypoxemia (arterial hemoglobin oxygen saturation (Sp_{O_2}) < 90% for 15 s)) during the perioperative period were also recorded. To accomplish this, Sp_{O_2} was continuously recorded with a DPX 3740 recorder system connected to a pulse oximeter (Biox 3740 pulse oximeter, Ohmeda, Madison, WI) from premedication until 24 h after surgery. Nurses or anesthesiologists

were also watching the pulse oximeters from premedication until transfer to the operating room, and from completion of anesthesia until 1 h after anesthesia. The BP, HR, and RR were measured by a standard manual pediatric pressure cuff, radial artery palpation, and observation of the chest wall, respectively, every 10 min during the preanesthetic evaluation period until the child was transferred to the operating room. Furthermore, these variables were also measured by an independent nurse and an anesthesiologist blinded to the treatment, every 10 min during the initial 2-h period after termination of surgery, every 20 min for the ensuing 3 h (2–5 h postanesthesia), and at 30-min intervals during the subsequent 5 h (from 5 to 10 h postanesthesia).

Statistics

Statistical analysis of data was performed using ANOVA for continuous variables, followed by multiple *t* test with Bonferroni correction when indicated, and using Kruskall-Wallis Rank test, and chi-squared test for discrete variables. Differences were considered statistically significant when $P < 0.05$.

Results

Assessment of Quality of Sedation, Separation, and Mask Acceptance

Patients in the three groups, all of whom underwent elective ophthalmologic surgery, mostly for strabismus with minimal blood loss, were comparable with respect to age, weight, premedication time, and anesthesia time (table 1). Figure 1 shows that there were no differences in sedation scores at the time of pretreatment evaluation among the three groups. The group receiving 4 μg/kg clonidine showed increased sedation at the 30, 60, and 90 min after premedication compared with the diazepam group. Figure 2 shows that 4 μg/kg, but not 2 μg/kg, clonidine produced better quality of separation from parents than diazepam. The quality of mask acceptance was significantly improved in the 4 μg/kg clonidine-treated group (excellent: 74, 51, and 43% of children receiving 4 or 2 μg/kg clonidine, and diazepam, respectively; $P < 0.05$). However, if the "good" and "excellent" groups are combined, there is no difference between the three groups (91, 74, and 72% of children receiving 4 or 2 μg/kg clonidine, and diazepam, respectively; $P < 0.05$). Thus, there is little clinical significance in the quality of mask acceptance.

Table 1. Patient and Surgery Data

	Diazepam 0.4 mg·kg^{-1}	Clonidine 2 μg·kg^{-1}	Clonidine 4 μg·kg^{-1}
n	35	35	35
Age (y)	6.6 ± 0.4	6.9 ± 0.5	6.8 ± 0.4
Weight (kg)	21 ± 1.4	25 ± 1.6	22 ± 1.4
Premedication time (min)	106 ± 2	103 ± 2	104 ± 2
Anesthesia time (min)	83 ± 4	76 ± 3	81 ± 4
Type of surgery			
Strabismus	29	30	29
Eyelid(s)	6	5	6

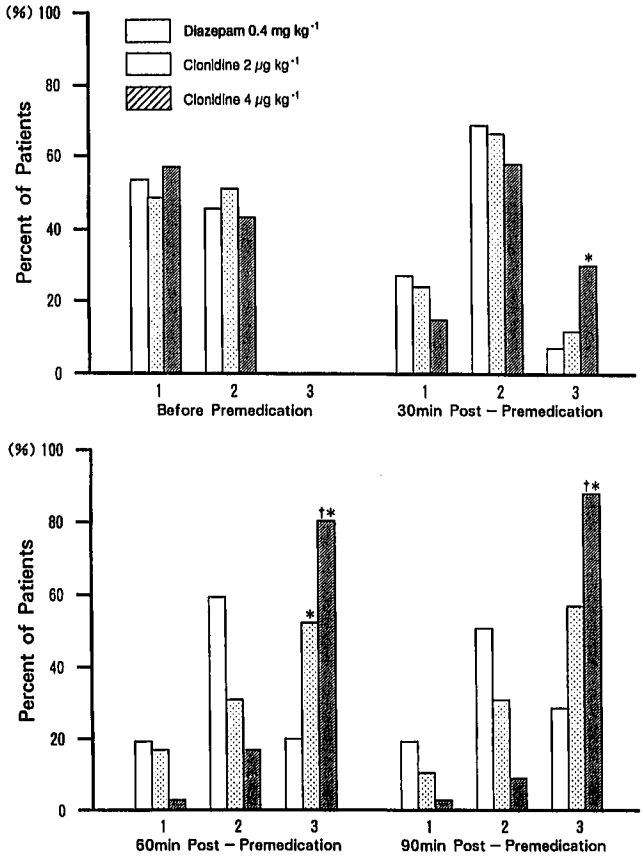

Fig. 1. Preoperative sedation scores. Values are expressed as percent of patients (n = 35 for each group). See text for explanation of separation scale. *$P < 0.05$ compared with diazepam; †$P < 0.05$ compared with 2 μg/kg clonidine.

Hemodynamic Measurements Associated with Tracheal Intubation

Figures 3 and 4 show that 4 μg/kg clonidine attenuated the BP and HR increases associated with tracheal

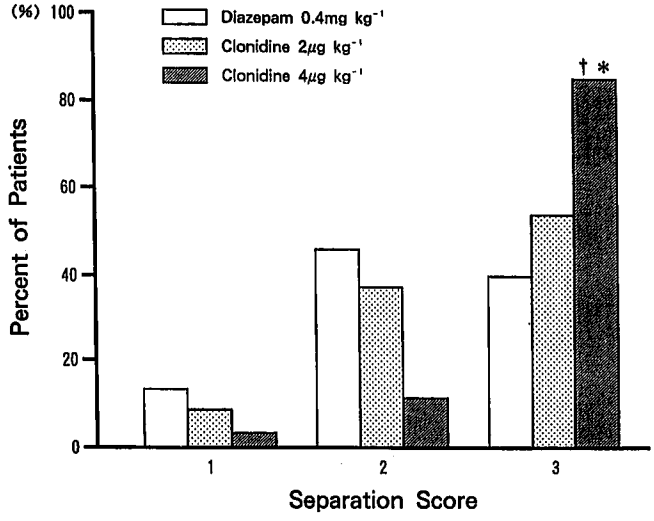

Fig. 2. Preoperative separation score. Values are expressed as percent of patients (n = 35 for each group). See text for explanation of separation scale. *$P < 0.05$ compared with diazepam; †$P < 0.05$ compared with 2 μg/kg clonidine.

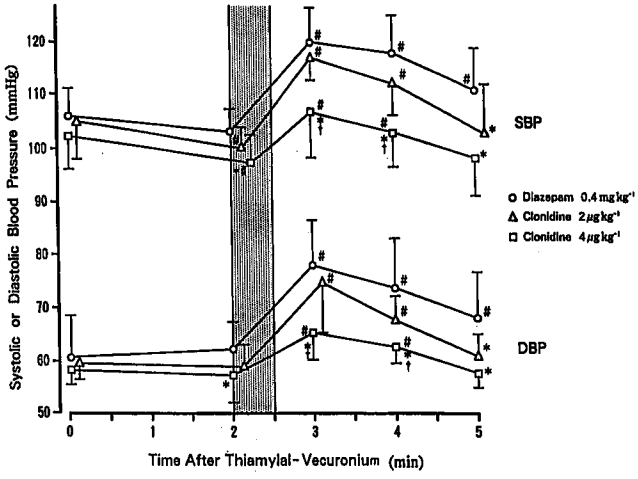

Fig. 3. Changes in blood pressure (mean ± SD) after thiamylal and in response to tracheal intubation with oral clonidine or diazepam (n = 35 for each group). The stippled area denotes the duration of laryngoscopy and tracheal intubation. *$P < 0.05$ *versus* diazepam; †$P < 0.05$ for 2 μg/kg *versus* 4 μg/kg clonidine; #$P < 0.05$ *versus* preinduction value (time = 0) within groups.

intubation. In contrast, 2 μg/kg clonidine failed to attenuate these hemodynamic changes. The percent change in the average maximum SBP, DBP, or HR associated with tracheal intubation was significantly less in the 4 μg/kg clonidine group than in the 2 μg/kg clonidine and the diazepam groups.

Postoperative Parental Questionnaire

Sixty-six percent of the parents of children in the high-dose clonidine group reported that their child's experience was pleasant, while only 11% of those in the diazepam group did ($P < 0.05$). In the 4 μg/kg clonidine group, a significantly larger number of children felt that their experience was pleasant compared with those in the 2 μg/kg clonidine or the control group (60, 23, and 23%, respectively; $P < 0.05$). Amnesia for face-mask application was most common after 4 μg/kg clonidine premedication than after 2 μg/kg clonidine or diazepam (51, 23, and 17%, respectively; $P < 0.05$).

Preoperative and Postoperative Vital Signs and Adverse Effects

There were no significant differences among the three groups in preoperative vital signs (SBP, DBP, HR, and RR) or Sp_{O_2}. Postoperative minimum BP, HR, and RR were lowered statistically in the 4 μg/kg clonidine group than in the diazepam group until 10 h after surgery. These values in the 4 μg/kg clonidine group increased with time. Children receiving 2 μg/kg clonidine postoperatively had lower minimum vital signs,

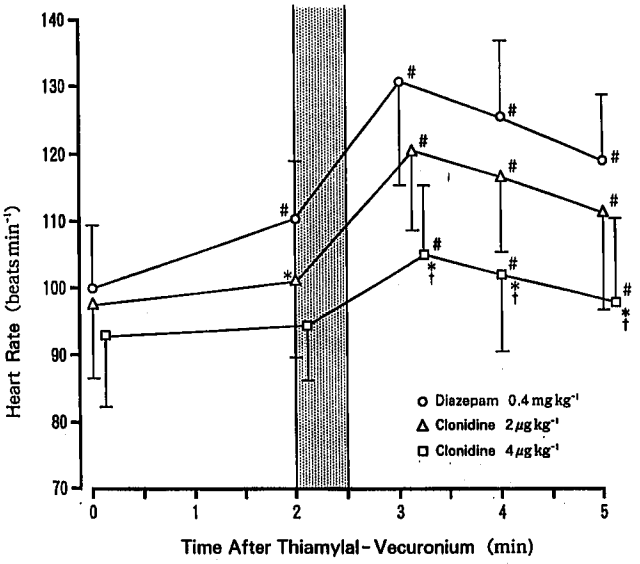

Fig. 4. Changes in heart rate (mean ± SD) after thiamylal and in response to tracheal intubation with oral clonidine or diazepam (n = 35 for each group). *$P < 0.05$ *versus* diazepam; †$P < 0.05$ for 2 μg/kg *versus* 4 μg/kg clonidine; #$P < 0.05$ *versus* preinduction value (time = 0) within groups.

except RR, than those receiving diazepam until 8 h after anesthesia. However, no children in the clonidine groups had postoperative hypotension or bradycardia requiring treatment within 10 h after surgery (lowest SBP = 75 mmHg and lowest HR = 66 beats/min). Furthermore, no children in the clonidine groups had rebound hypertension, respiratory depression, or hypoxemia (highest SBP = 134 mmHg, lowest RR = 12 breaths/min, and lowest Sp_{O_2} = 93%) during the period of postoperative observations.

Discussion

Clonidine, 4 μg/kg *p.o.*, 105 min before intravenous induction of anesthesia in children provided preoperative anxiolysis and cooperation, and attenuated the hypertensive response to tracheal intubation. It was superior in both regards to 2 μg/kg clonidine or 0.4 mg/kg diazepam. Clonidine, 0.2 mg or 2.5–5 μg/kg, provides preoperative sedation and perioperative hemodynamic stability in adults.[2–8,#] In our preliminary study, one of the four children receiving 5 μg/kg clonidine had hypotension and bradycardia requiring drug therapy in the operating room, whereas none of the five children who received 4 μg/kg clonidine had these complications. Clonidine, 150 $\mu g/m^2$ (estimated dose of approximately 4–5 μg/kg), produces no side effects other than drowsiness in children aged 3–17 yr.[10,11] Thus, the doses (2 and 4 μg/kg) of the drug used in the current study were chosen to ensure a safe approach to the initial evaluation of clonidine's effects in children. However, the optimal dose of clonidine remains unknown in this clinical setting. The rationale for the timing of clonidine treatment was based on another preliminary study of ten children, in whom assessment of the sedative effect of clonidine at 15-min intervals (until 180 min after treatment) led us to conclude that the maximal sedative effect occurred 105–120 min after treatment. Other investigators administered clonidine to adult patients 90–120 min before anesthesia.[2,12] Diazepam has been recommended for treatment 60–120 min before anesthesia.[13–15]

Sedation Produced by Clonidine

The sedative effect of clonidine was dose related, in agreement with findings in adult patients,[2,3,6,7] and was superior to diazepam, which is the preoperative sedative in routine use in our practice. Midazolam, which is becoming a more popular premedication in children,[16,17] may not prove to have the same superiority over diazepam as does clonidine. Further studies should compare these agents.

Attenuation of the Cardiovascular Responses to Tracheal Intubation by Clonidine

Consistent with previous results in adults,[2,18,19] 4 μg/kg clonidine effectively attenuated the cardiovascular responses to tracheal intubation in children undergoing intravenous induction. Although intravenous induction is probably most commonly used in children older than 8–10 yr of age, and inhalational induction is more common for younger children, the use of EMLA cream (eutectic mixture of local anesthetics) is likely to increase the popularity of intravenous inductions in younger children. Although the use of anticholinergic premedication in pediatric anesthesia is decreasing, we believe that all hemodynamic measurements in the current study may be ameliorated by oral atropine (as a second premedicant). Atropine was administered to prevent the oculocardiac reflex, and the hemodynamic effect of clonidine may have been attenuated by atropine, because atropine is an effective antidote to the bradycardia and hypertension of a clonidine overdose.[20,21] Thus, our results may not be applicable to children who are not premedicated with atropine.

Hypertension and tachycardia after tracheal intubation are of little clinical importance for healthy children. Blunting the hemodynamic changes associated with tracheal intubation by clonidine would be beneficial in children at risk for cerebral vascular accidents and cardiac dysrhythmias. Such pediatric patients include children with hypertension from renovascular disease or renal failure, those with cerebral arteriovenous malformations or aneurysms, and those with myocardial disease or aortic insufficiency.

Complications

Perioperative hypotension has been demonstrated in adults receiving 0.3 mg clonidine. It is noteworthy that no clinically significant side effects on hemodynamics (*e.g.*, perioperative hypotension, rebound hypertension, and bradycardia) were observed throughout the study. However, the effect of clonidine on hemodynamic changes during slow induction with inhalational anesthetics deserves study. Studies in humans have confirmed that the effects of clonidine on respiration

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is minor compared with those of opioids.# In the current study, RR and Sp_{O_2} were not different among the three groups throughout the study period. However, the limited number of children available in the current study precluded a proper safety assessment of clonidine.

We have shown that the combination of 4 μg/kg oral clonidine and 0.03 mg/kg atropine is an effective and safe premedication in healthy children undergoing ophthalmologic surgery. Further studies are required to determine the optimal dose and assess the safety of clonidine in other clinical settings, or in younger children.

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