

Oral Clonidine Premedication Does Not Change Efficacy of Simulated Epidural Test Dose in Sevoflurane-anesthetized Children

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Background: **Caudal epidural anesthesia is often used as an adjunct to general anesthesia and for postoperative pain relief in children. In anesthetized children, epinephrine and isoproterenol are reliable indicators to detect accidental intravascular injection of a test dose. Oral clonidine, a useful premedicant in pediatric anesthesia, modifies hemodynamic responses to sympathomimetics, including catecholamines. The aim of the current study was to determine whether oral clonidine premedication alters the efficacy of a simulated intravascular test dose containing epinephrine or isoproterenol in sevoflurane-anesthetized children.**

Methods: **One hundred twenty children (aged 1–7 yr) were randomly divided into six groups; control–saline, control–epinephrine, control–isoproterenol, clonidine–saline, clonidine–epinephrine, and clonidine–isoproterenol. The three clonidine groups received oral clonidine 4 mg/kg as premedication, whereas the three control groups did not receive any premedication. Anesthesia was maintained with sevoflurane at a level of 1.2 minimum alveolar concentration. After hemodynamics were stable, 0.1 ml/kg of 1% lidocaine containing epinephrine 0.5 mg/kg or isoproterenol 75 ng/kg was intravenously given to the two epinephrine or isoproterenol groups, respectively, to simulate intravascular injection of a test dose. The saline groups received saline alone instead of the test dose. Heart rate, blood pressure, and T-wave amplitude of electrocardiogram were recorded before and after administration of study drugs for subsequent analysis.**

Results: **Test solution containing epinephrine increased heart rate, systolic blood pressure, and T-wave amplitude. Oral clonidine had no effect on elevation of these variables in response to epinephrine. The isoproterenol-containing test dose produced a prominent increase in heart rate and a less pronounced increase in systolic blood pressure and T-wave amplitude. Oral clonidine also failed to modify isoproterenol-induced hemodynamic and T-wave changes. Calculated sensitivity and specificity of epinephrine or isoproterenol were all 100% based on a new heart rate criterion (positive if ≥ 10 beats/min) and were unaltered by oral clonidine premedication.**

Conclusions: **Epinephrine or isoproterenol is a reliable marker to detect accidental intravascular injection of a test dose with 100% sensitivity and specificity based on a new heart rate criterion in sevoflurane-anesthetized children. These data suggest that oral clonidine premedication does not alter the efficacy of a simulated epidural test dose containing epinephrine or isoproterenol. (Key words: Electrocardiograph; hemodynamics; lidocaine.)**

COMBINED epidural and general anesthesia is a popular technique for provision of anesthesia and postoperative analgesia in pediatric patients undergoing abdominal or thoracic surgery.[1] Inadvertent intravascular injection of local anesthetics intended for epidural anesthesia can result in serious cardiovascular and central nervous system toxicity.[2] To avoid these life-threatening adverse complications, administration of an epinephrine-containing epidural test dose that causes an increase in heart rate (HR) and blood pressure (BP) is a common clinical practice.[3] Isoproterenol is available as an alternative marker for epidural test dosing in children receiving sevoflurane anesthesia.[4] In children, regional anesthetic techniques are frequently applied during general anesthesia with sevoflurane to minimize discomfort and allow safe performance of the procedure.[5]

Clonidine, a useful premedicant for pediatric anesthesia,[6] has been shown to decrease HR and BP,[6,7] to attenuate atropine-induced tachycardia, and to mitigate pressor and tachycardiac responses to tracheal intubation in children. Thus, oral clonidine premedication may reduce the efficacy of a simulated epidural test dose by attenuating epinephrine–isoproterenol-induced increase in HR and BP. If so, this would be a disadvantage of clonidine premedication. To test this hypothesis, we determined the sensitivity and specificity of an epidural test dose containing epinephrine or isoproterenol using hemodynamic and electrocardiographic (T-wave amplitude) criteria.

Methods

One hundred twenty children, aged 18–90 months (American Society of Anesthesiologists status I), with a normal sinus rhythm assessed by preoperative electrocardiography were enrolled in the current study after obtaining institutional approval and informed parental consent. The patients, who were scheduled to undergo minor surgery, were randomly assigned to one of six groups (n = 20 each) according to a combination of their premedicants and catecholamine for simulation of epidural test dose as follows: control–saline, children did not receive any premedicant but received intravenous saline; clonidine–saline, children received oral clonidine premedication followed by intravenous saline; control–

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Table 1. Hemodynamic and Electrocardiographic Changes before and after Test Dose

	CONT-SAL	CLON-SAL	CONT-EPI	CLON-EPI	CONT-ISP	CLON-ISP
Hemodynamics						
At ward (before premedication)						
SBP (mmHg)	106 ± 15	103 ± 13	99 ± 14	104 ± 17	104 ± 15	101 ± 14
DBP (mmHg)	61 ± 10	59 ± 9	58 ± 8	61 ± 11	62 ± 10	59 ± 10
HR (beats/min)	100 ± 17	102 ± 18	101 ± 16	99 ± 17	103 ± 18	98 ± 17
Preinduction*						
SBP (mmHg)	107 ± 17	98 ± 12‖	103 ± 15‖	101 ± 14‖	106 ± 18	98 ± 13‖
DBP (mmHg)	63 ± 12	57 ± 9	62 ± 9‖	57 ± 8‖	62 ± 12	58 ± 9
HR (beats/min)	118 ± 25‖	96 ± 12§‖	113 ± 21‖	94 ± 14§‖	114 ± 19‖	90 ± 12§‖
TWA (mV)	0.49 ± 0.19	0.46 ± 0.17	0.44 ± 0.16	0.48 ± 0.15	0.51 ± 0.17	0.46 ± 0.18
Postinduction (before atropine)†						
SBP (mmHg)	102 ± 14	97 ± 11‖	100 ± 13	97 ± 11‖	103 ± 14	96 ± 10‖
DBP (mmHg)	60 ± 9	57 ± 8	60 ± 8	56 ± 8‖	59 ± 10	56 ± 8
HR (beats/min)	101 ± 15	96 ± 14‖	100 ± 17	94 ± 13‖	99 ± 18	91 ± 13‖
TWA (mV)	0.46 ± 0.15#	0.43 ± 0.15#	0.41 ± 0.13#	0.46 ± 0.14#	0.47 ± 0.17#	0.44 ± 0.16#
Hemodynamics						
Pretest dose (after atropine; time 0)‡						
SBP (mmHg)	103 ± 13	98 ± 13‖	102 ± 14	99 ± 12‖	105 ± 16	97 ± 13‖
DBP (mmHg)	62 ± 8	58 ± 8	63 ± 9	59 ± 9‖	62 ± 10	58 ± 10
HR (beats/min)	109 ± 18	99 ± 16‖	109 ± 19	98 ± 17‖	103 ± 18	94 ± 14‖
TWA (mV)	0.45 ± 0.14#	0.43 ± 0.14#	0.40 ± 0.13#	0.44 ± 0.15#	0.45 ± 0.15#	0.42 ± 0.17#
Mean maximal increase in HR (beats/min)	—	—	24 ± 7	25 ± 7	23 ± 6	25 ± 6
Time to measured HR increase of 10 beats/min greater than postinduction (time 0) (sec)	—	—	18 ± 3	17 ± 3	24 ± 4	23 ± 3
Time to maximal increase in HR (sec)	—	—	33 ± 7	32 ± 8	48 ± 11	46 ± 9
Duration of time for increased HR ≥ 10 beats/min (sec)	—	—	42 ± 9	46 ± 11	101 ± 33	107 ± 29
Mean maximal increase in SBP (mmHg)	—	—	29 ± 11	31 ± 12	14 ± 9	12 ± 8
Mean maximal increase in TWA (%)	—	—	71 ± 37	67 ± 40	26 ± 18	32 ± 21
Time to maximal increase in TWA (sec)	—	—	21 ± 5	20 ± 4	36 ± 9	38 ± 9

Data are mean ± SD.

* Measured immediately before induction of sevoflurane-anesthesia in the operating room.

† Measured 10 min after induction of sevoflurane-anesthesia and immediately before intravenous atropine.

‡ Measured 10 min after injection of atropine and immediately before intravenous test dose or saline (time 0 in fig. 1). At this time, hemodynamic variables and end-tidal concentrations of sevoflurane were stable.

§ $P < 0.05$ for CLON-groups vs. CONT-groups.

‖ $P < 0.05$ *vs.* hemodynamics at ward.

# $P < 0.05$ *vs.* TWA at preinduction.

CLON-EPI = children received clonidine premedication followed by intravenous test dose containing epinephrine; CLON-ISP = children received clonidine premedication followed by intravenous test dose containing isoproterenol; CLON-SAL = children received clonidine premedication followed by intravenous saline; CONT-EPI = children did not receive any premedication but received intravenous test dose containing epinephrine; CONT-ISP = children did not receive any premedication but received intravenous test dose containing isoproterenol; CONT-SAL = children did not receive any premedication but received intravenous saline; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; TWA = T-wave amplitude; — = Data on hemodynamic responses to test dose in CONT-SAL and CLON-SAL groups were omitted because HR, SBP, and TWA were essentially unchanged in these groups.

epinephrine, children did not receive any premedicant but received an intravascular test dose of lidocaine containing epinephrine; clonidine–epinephrine, children received oral clonidine premedication followed by an intravascular test dose of lidocaine containing epinephrine; control–isoproterenol, children did not receive any premedicant but received an intravascular test dose of lidocaine containing isoproterenol; and clonidine–isoproterenol, children received oral clonidine premedication followed by an intravascular test dose of lidocaine containing isoproterenol.

In the three clonidine groups, children received clonidine 4 mg/kg 90–110 min before induction of anesthesia with a small amount of water. All children were prohibited from eating solid food or drinking milk products after midnight, but were instructed to ingest clear fluid 3 h before induction of anesthesia. Table 1 shows the demographic data of the six groups. Monitoring included pulse oximetry, respiratory gas analysis, automated noninvasive oscillometric BP device, and electrocardiography. Anesthesia was induced with sevoflurane and nitrous oxide (70%) in oxygen using a semiclosed circle system. After loss of consciousness, venous access was obtained on a forearm peripheral vein for injection of study drugs and intraoperative infusion. Atropine 0.01 mg/kg was intravenously given to all patients 10 min after induction of anesthesia. End-tidal concentration of sevoflurane for anesthetic maintenance was 3.0% (in control groups)[8] or 1.6% (in clonidine groups)[9] measured with AS/3 (Datex-Ohmeda, Helsinki, Finland), corresponding to 1.2 minimum alveolar concentration (MAC). Ventilation of the lungs was first assisted and

thereafter controlled to obtain end-tidal carbon dioxide tensions of 32–39 mmHg.

We confirmed that hemodynamics in each patient were stable for 10 min after injection of atropine, then the control–epinephrine or clonidine–epinephrine group received an intravenous test dose consisting of 1% lidocaine with 1:200,000 epinephrine solution 0.1 ml/kg (= lidocaine 1 mg/kg plus epinephrine 0.5 mg/kg), the control–isoproterenol or clonidine–isoproterenol group received that consisting of 1% lidocaine with 3:4000,000 isoproterenol solution 0.1 ml/kg (= lidocaine 1 mg/kg plus isoproterenol 75 ng/kg), and the control–saline or clonidine–saline group received saline 0.1 ml/kg. The test solutions were prepared by the second author (K.N.) and injected by a blind observer (M.S.) over 5 s. The data were recorded and analyzed by the observer who was blinded to the group assignment. HR and BP were recorded before premedication at the hospital ward, immediately before induction of anesthesia, 10 min after induction of anesthesia and immediately before intravenous atropine, 10 min after intravenous atropine and immediately before injection of the test solutions or saline (time 0 in figures), and subsequently at 15-s (for HR continuously monitored) and 30-s (for BP) intervals for 5 min.

Morphologic changes of T wave continuously recorded in a strip chart were analyzed at preinduction, postinduction, and pretest dose points by the blinded observer (K.M.). Furthermore, the maximal values of HR, BP, and T-wave amplitude after the test dose or saline were recorded. Time to measured HR increase of 10 beats/min greater than pretest dose value, time to maximal increases in HR and T-wave amplitude from injection of the test solutions, and duration of time for increased HR $\geq$ 10 beats/min were obtained. All measurements were completed before surgical skin incision. Oxygen saturation assessed by pulse oximeter was $\geq$ 97% in all children during the study. No children had arrhythmia during the study.

Criteria for definition of positive hemodynamic responses included HR increase $\geq$ 20 beats/min and systolic BP (SBP) increase $\geq$ 15 mmHg, occurring within 2 min after administration (conventional criteria).[10] These criteria were determined from data in unmedicated, awake adult volunteers.[10] Thus, a new HR criterion for positive test dose in anesthetized children was advocated: positive if $\geq$ 10 beats/min HR increase.[11–13] Furthermore, a T-wave criterion was proposed: positive if $\geq$ 25% increase in amplitude.[12,13] Use of the new HR and T-wave criteria has been shown to provide better sensitivity.[12,13] In the current study, sensitivity (true positive/[true positives + false negatives]) and specificity (true negatives/[true negatives + false positives]) were calculated on the basis of these traditional and new criteria.

Statistics

Data are expressed as mean values ± SD. Data were statistically analyzed by two-way analysis of variance to compare changes in hemodynamics and T-wave amplitude between groups. When a significant difference was identified, this was followed by an unpaired Student *t* test. Changes in hemodynamics and T-wave amplitude over time within each group were analyzed using repeated-measures analysis of variance, followed by a paired Student *t* test. Statistical significance of nonparametric data (*e.g.*, sensitivity, specificity) was determined using the Fisher exact probability test. For all comparisons, $P < 0.05$ was considered significant. The sample size of the current study is sufficient to detect large differences (effect size = $(\text{mean}_1 - \text{mean}_2)/\text{SD} = 0.7–1.0$) in variables at a significance level of 0.05 and a power of 0.7–0.85.[14]

Results

Mean (± SD) age, weight, and height were 53 ± 25 months, 18 ± 7.0 kg, and 105 ± 18 cm, respectively, and

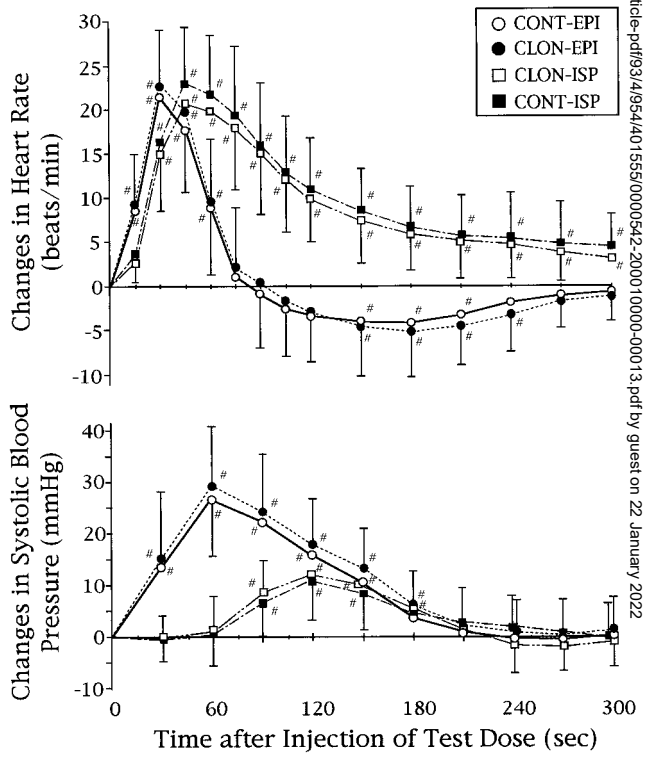

Fig. 1. Heart rate changes and systolic blood pressure changes (mean ± SD) after intravenous injection of the test dose containing epinephrine 0.5 mg/kg or isoproterenol 75 ng/kg. Some SD bars are omitted for clarity. Data in control–saline (CONT-SAL) and clonidine–saline (CLON-SAL) groups were also omitted because heart rate and systolic blood pressure was essentially unchanged in these groups. #$P < 0.05$ *versus* pretest dose (time 0) values within groups. $P > 0.05$ between the two epinephrine groups and between the two isoproterenol groups.

Table 2. Sensitivity and Specificity of Epidural Test Dose Containing Epinephrine or Isoproterenol

	CONT-EPI	CLON-EPI	CONT-ISP	CLON-ISP
Conventional HR criterion (20 beats/min increase)[10]				
Sensitivity (%)	75 [15/20]	85 [17/20]	80 [16/20]	85 [17/20]
Specificity (%)	100 [20/20]	100 [20/20]	100 [20/20]	100 [20/20]
New HR criterion (10 beats/min increase)[11]				
Sensitivity (%)	100 [20/20]	100 [20/20]	100 [20/20]	100 [20/20]
Specificity (%)	100 [20/20]	100 [20/20]	100 [20/20]	100 [20/20]
SBP criterion (15 mmHg increase)[10]				
Sensitivity (%)	100 [20/20]	100 [20/20]	40 [8/20]	55 [11/20]
Specificity (%)	100 [20/20]	100 [20/20]	100 [20/20]	100 [20/20]
TWA criterion (25% increase)[12,13]				
Sensitivity (%)	90 [18/20]	90 [18/20]	30 [6/20]	40 [8/20]
Specificity (%)	100 [20/20]	100 [20/20]	100 [20/20]	100 [20/20]

Data are expressed as percent [proportion]. $P > 0.05$ between the two -EPI groups and between the two -ISP groups.

CLON-EPI = children received clonidine premedication followed by intravenous test dose containing epinephrine; CLON-ISP = children received clonidine premedication followed by intravenous test dose containing isoproterenol; CONT-EPI = children did not receive any premedication but received intravenous test dose containing epinephrine; CONT-ISP = children did not receive any premedication but received intravenous test dose containing isoproterenol; HR = heart rate; SBP = systolic blood pressure; TWA = T-wave amplitude.

were comparable in the six groups. Table 1 shows that there was no significant difference in hemodynamics at the hospital ward and HR increased before induction of anesthesia in the control groups. However, BP and HR at postinduction and pretest dose (time 0) points did not differ between the clonidine and control groups. The T-wave amplitude was similar at any point among the groups (table 1).

There were no significant difference in timing, duration, or degree of HR increase produced by epinephrine or isoproterenol between the control and clonidine groups (fig. 1). Oral clonidine premedication had no effect on maximal increase in SBP induced by epinephrine or isoproterenol (fig. 1 and table 1). T-wave amplitude was increased in all children receiving epinephrine or isoproterenol, although the degrees were different. Clonidine did not modify the maximal increase T-wave morphologic changes or time to the peak value from injection of these catecholamines (table 1).

In the saline groups, intravenous injection of saline did not essentially change HR, SBP, or T-wave amplitude (data not shown). Thus, specificities of epinephrine or isoproterenol based on four types of criteria were all 100% (table 2). Sensitivities of epinephrine or isoproterenol according to the new HR criterion were all 100% (table 2). However, sensitivities of epinephrine or isoproterenol were 75–85% based on the conventional HR criterion. Sensitivities of epinephrine based on SBP criterion were 100% in the two epinephrine groups (table 2). Sensitivities of epinephrine based on T-wave criterion were 90% in both of the groups. However, sensitivities of isoproterenol based on SBP and T-wave criteria were lower than those of epinephrine (table 2). Oral clonidine premedication did not alter the sensitivities of epinephrine or isoproterenol based on these hemodynamic and T-wave criteria (table 2).

Discussion

Much has been shown about modulation of clonidine on hemodynamic responses to exogenously administered drugs acting on the cardiovascular system.[6,15,16] Oral clonidine attenuates the bradycardia-reversing effect of intravenous atropine in awake children.[17] In adults, oral clonidine enhances the pressor response to ephedrine[15] and phenylephrine.[16] On the other hand, oral clonidine does not alter the efficacy of a simulated intravenous test dose containing epinephrine in awake adults.[18] Another study found that the same dose of clonidine enhances the hemodynamic responses to epinephrine-containing test solutions.[18,19]

In agreement with previous reports,[12,13] the epinephrine-containing test dose did not provide 100% sensitivity on the basis of conventional HR criteria. In sevoflurane-anesthetized children, the new HR criterion would be useful. T-wave amplitude is advocated as a novel, reliable guide for detecting intravascular injection of a test dose containing epinephrine in sevoflurane-anesthetized children with 100% sensitivity and specificity.[12,13] However, shortcomings of this indicator include age limit for successful application. Elevation of T-wave amplitude to epinephrine is inversely proportional to age, and the upper age limit where this increase is detectable is estimated at 92 months as calculated from extrapolation of linear fitted line to zero of T-wave morphologic change.[13] Another drawback of this marker is that T-wave positive response to intravenous epinephrine requires atropine pretreatment.[20] We were unable to confirm completeness of this marker: sensitivity was 90% despite the use of atropine pretreatment. Our failure may be a result of the use of some older children (aged 85–90 months) in the current study. Furthermore, intravenous treatment with atropine before epinephrine prolongs duration of the HR positive response and augments

SBP increase sufficiently to ameliorate sensitivity for detection of intravascular injection of test dose.[11] Atropine may be used in children scheduled to undergo epidural anesthesia to improve efficacy of simulated epidural test dose containing epinephrine.

Hemodynamic responses to epinephrine or isoproterenol vary from several clinical situations, including inhalational anesthetics. Sevoflurane inhibits pressor and tachycardic responses to epinephrine in children.[11–13] Although sevoflurane at concentrations of 1–2 MAC has no effect on HR and causes dose-dependent reduction of BP in adults,[21] the effects of the volatile anesthetic on HR and BP in infants and children vary from age.[22] Inhalation of sevoflurane at 1 MAC has no effect on HR in neonates, infants, and children aged less than 3 yr, whereas the anesthetic (1 MAC) increases HR in children older than 3 yr.[22] In children aged 1–3 yr or 5–12 yr, SBP is not changed by inhalation of 1 MAC sevoflurane. However, SBP decreases in children aged 3–5 yr receiving sevoflurane.[22] Halothane is also known to suppress hemodynamic responses to epinephrine.[23] Halothane per se slows HR through reduction of cardiac sympathetic activity with a consequent vagal predominance and direct slowing of sinoatrial nodal discharge.[24] A decreased chronotropic responses to isoproterenol was found in sevoflurane-anesthetized children compared with halothane-anesthetized children at 1 MAC.[4] Thus, our data obtained in 1.2 MAC sevoflurane-anesthetized children cannot be extrapolated to pediatric patients receiving halothane or other concentrations of sevoflurane.

We have found that isoproterenol caused SBP increase and T-wave morphologic change in all of the children. However, because we have also observed a great individual variation in degree of increases in these guides, sensitivities based on SBP and T-wave criteria were as low as 30–55%. Thus, when isoproterenol-containing test solution is used in children, a new HR criterion rather than conventional HR, SBP, or T-wave criteria is a useful indicator with 100% sensitivity. In this point, isoproterenol may be inferior to epinephrine as a marker for detection of accidental intravascular injection of epidural test dose.

In conclusion, we have shown that oral clonidine did not change the efficacy of a simulated epidural test dose containing epinephrine or isoproterenol in sevoflurane-anesthetized children as assessed by a new HR criterion. Conventional HR and T-wave criteria may be limited to application of epinephrine–isoproterenol-containing test solution. Epinephrine was also reliable based on SBP criterion.

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