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CLINICAL REEARCH

Intraoperative clonidine to prevent postoperative emergence delirium following sevoflurane anesthesia in pediatric patients: a randomized clinical trial

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Abstract
Introduction and objective: Emergence Delirium (ED), particularly in children, is characterized by mental confusion, irritability, disorientation, and inconsolable crying. ED prolongs the time required in the Post-Anesthesia Care Unit (PACU) and increases concern and anxiety in parents. The present study aimed to determine the effectiveness and safety of low-dose clonidine in preventing ED in children receiving sevoflurane anesthesia for tonsillectomy/adenotonsillectomy.
Methods: A randomized, double-blind clinical trial was conducted between November 2013 and January 2014. Sixty-two children aged 2–12 years, scheduled to undergo tonsillectomy/adenotonsillectomy, and classified as American Society of Anesthesiologists (ASA) physical status I/II were included, with 29 being randomized to receive 1 $\mu g.kg^{-1}$ clonidine intravenously, and 33 allocated to a control group that received no clonidine. Anesthesia was induced and maintained with sevoflurane. Children with altered state of consciousness, neurological deficit, history of allergy to dipyrone, or receiving other drugs such as preanesthetic agents were excluded from the study. The primary outcome was the presence of ED in the initial 20 minutes in the PACU according to the Pediatric Anesthesia Emergence Delirium (PAED) scale. The Chi-Square test and Fisher's two-tailed exact test were used for statistical analysis, as applicable. Significance level was set at 5%, and Risk Ratios (RR) and their 95% Confidence Intervals (95% CI) were calculated.

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Results: The frequency of ED was significantly decreased in the group of children who received clonidine (17.2% vs. 57.6%; RR = 0.30; 95% CI 0.13–0.70; p = 0.001). There was no difference between groups with respect to the frequency of postoperative self-harm (falls and bruises), dislodged catheters, and for most of the other adverse events evaluated.
Conclusions: The use of 1 $\mu g.kg^{-1}$ intravenous clonidine during anesthesia induction can effectively reduce the incidence of ED in children undergoing elective tonsillectomy/adenotonsillectomy under general inhalation anesthesia with sevoflurane.
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What is already known

The incidence of postoperative emergence delirium (ED) in children receiving general anesthesia with sevoflurane for tonsillectomy or adenotonsillectomy is high. Studies suggest that intraoperative clonidine administration may minimize this phenomenon.

What this article adds

There is a reduction in the incidence of postoperative emergence delirium (ED) in children undergoing elective tonsillectomy or adenotonsillectomy under inhalation anesthesia with sevoflurane when clonidine (1 $\mu g.kg^{-1}$) is also used, as compared to when it is not used; moreover, there is no increase in adverse events with the use of clonidine.

Implications for translation

Clonidine (1 $\mu g.kg^{-1}$) can be used during anesthesia induction to prevent postoperative agitation in children receiving inhalation anesthesia with sevoflurane. Nevertheless, before its use is standardized in clinical practice, further randomized, double-blind clinical trials should be conducted with larger samples of children.

Introduction

Emergence Delirium (ED) is a well-documented clinical phenomenon, particularly in children, and is characterized by mental confusion, irritability, disorientation, and inconsolable crying. ED prolongs the time an individual has to remain in the Post-Anesthesia Care Unit (PACU), thus increasing hospital costs. The confused state not only generates anxiety among staff members and parents regarding the child's clinical status, but in rare cases it may result in accidental self-harm.[1]

The highest incidence of ED is reported to occur in the first 30 minutes following the patient regaining consciousness. The duration of the phenomenon is generally limited, lasting between 10 and 45 minutes, and in most cases resolving spontaneously. Nevertheless, prolonged episodes of ED lasting up to 2 days have also been reported.[2] In a previous study, ED occurred in approximately 5.3% of all patients; however, in the pediatric population, this incidence may reach 10–80%, depending on the type of anesthesia, the child's age and the type of surgery.[2–9]

Clonidine, an alpha-2-adrenergic agonist, was initially introduced as an adjuvant anesthetic. In the 1990s, European anesthesiologists adopted clonidine as a preanesthetic agent in both general and spinal anesthesia on the basis of its sedative, hypnotic, and analgesic properties.[10–13] In an attempt to reduce the degree of ED, the intraoperative use of different doses has been proposed.[12–14] High doses of clonidine such as 2–3 $\mu g.kg^{-1}$ effectively prevented adverse effects in children receiving sevoflurane anesthesia as shown in placebo-controlled studies in which adjuvant clonidine was administered intravenously following the induction of anesthesia.[12,15,16]

The objective of the present study was to assess the efficacy of a low dose of clonidine (1 $\mu g.kg^{-1}$) administered during anesthesia induction with sevoflurane in reducing the incidence and severity of ED in preschool and school-aged children undergoing tonsillectomy or adenotonsillectomy. Secondary outcomes were the incidence of postoperative self-harm, the need for ED treatment, parents' satisfaction, and the frequency of adverse events in the PACU including nausea, vomiting, bradycardia, dizziness, hypotension, pruritus, and somnolence.

Methods

The present randomized, double-blind clinical trial was conducted at the pediatric surgical center of the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) between November 2013 and January 2014. IMIP's internal review board approved the study protocol (CAAE 16056213.3.0000.5201). In all cases, children were only admitted to the study if parents or guardians agreed to their participation and signed an informed consent form.

Children 2–12 years of age, who were scheduled to undergo outpatient tonsillectomy/adenotonsillectomy for recurrent infection and obstruction, and who were classified as physical status I/II according to the American Society of Anesthesiologists (ASA) were admitted to the study.[17] Exclusion criteria consisted of altered states of consciousness, neurological deficits, use of any preanesthetic agent, and allergy to dipyrone, precluding its administration as an intraoperative analgesic.

A statistician who did not otherwise participate in the study generated a randomization list using the Random Allocation software program, version 1.0 (Isfahan, Iran) and prepared sequentially numbered, opaque envelopes containing the letters ''C'' (clonidine) or ''NC'' (no clonidine). After an attending anesthesiologist not directly involved in the study opened the envelope, the patients allocated to the clonidine group received 1 $\mu g.kg^{-1}$ clonidine, while the patients allocated to the control group did not.

In the operating room, children were monitored using capnography, cardioscopy, pulse oximetry and noninvasive blood pressure monitoring (mmHg). General anesthesia was induced with incremental sevoflurane up to 8% in a mixture of 33% oxygen and 66% nitrous oxide, and then maintained with sevoflurane up to 2–3% in 33% oxygen and 66% nitrous oxide. As soon as the children were asleep, intravenous access was obtained in the upper limb. Alfentanil at a dose of 2 $\mu g.kg^{-1}$ and propofol at a dose of 2–4 $mg.kg^{-1}$ (depending on the patient's age) were administered. The children in the clonidine group also received 1 $\mu g.kg^{-1}$ clonidine intravenously. To blind the PACU nurse and anesthesiologist, the children and their parents, no entries were made on patient charts regarding whether clonidine was used or not. To prevent postoperative nausea and vomiting, dexamethasone was administered at a dose of 0.15 $mg.kg^{-1}$ after intubation and ondansetron was administered at a dose of 0.15 $mg.kg^{-1}$ thirty minutes prior to extubation. For postoperative analgesia, 50 $mg.kg^{-1}$ dipyrone and 1 $mg.kg^{-1}$ tramadol were administered intravenously during surgery. At the end of surgery, sevoflurane was discontinued, extubation was performed, and children were transferred to the PACU. Parents were allowed to accompany the patient in the PACU in order to keep their child calm during the period of anesthesia recovery.

Sociodemographic characteristics, including the patient's age, parents' ages, and family income, were recorded. The duration of anesthesia, the amount of time the patient remained in the PACU, and the time interval between return to consciousness at the end of anesthesia and the beginning of ED evaluation, as conducted using the Pediatric Anesthesia Emergence Delirium (PAED) scale, were all recorded in minutes. The primary outcome was the presence of ED in the first 20 minutes of the child's stay in the PACU.

After the child had regained consciousness, previously trained evaluators assessed the presence or absence of ED every 5 minutes for 20 minutes using the 5-item PAED scale. The evaluator applying the instrument in the PACU was blinded with respect to the nature of the intervention.[6] After rating each criterion of the scale, partial scores were obtained, which, when added together, generated a total score indicative of the degree of ED. For the purposes of statistical analysis, total PAED scores $\geq$ 10 were considered indicative of the presence of ED.[10,11]

Parents' satisfaction was assessed at the time of the child's discharge from the PACU. At that point, the parents were simply asked whether they were satisfied with the care provided to their children during the time they spent in the sector. Possible answers were unsatisfied, slightly satisfied, satisfied, and very satisfied. For the purpose of analysis, parents were considered satisfied when the answer given was satisfied or very satisfied. The secondary outcomes consisted of the incidence of accidents in the PACU such as postoperative self-harm (falls and bruises) or dislodged venous catheters, as well as the need for drugs in the PACU to reduce the occurrence of adverse events such as nausea, vomiting, dizziness, hypotension, pruritus, somnolence, excessive somnolence, and bradycardia.

The sample size was calculated using the STATCALC module of Epi-Info, version 3.5.4 (Centers for Disease Control and Prevention, Atlanta, GA, USA). The expected frequency of ED was previously estimated in a pilot study as 17% for the clonidine group and 57% for the control group. For a significance level of 5% and a power of 80%, 54 patients would be required. To compensate for any possible losses, this number was increased to 60 children.

Statistical analysis was conducted using Epi-Info, version 3.5.4 and the R software, version 2016 (R Core Team, 2016, Vienna, Austria). Tables were built to determine the association between the independent variables and the outcomes assessed, using the Chi-Square test or Fisher's exact test, as applicable. The significance level was set at 5%. Risk Ratios (RR) and their 95% Confidence Intervals (95% CI) were calculated, as well as the Number Needed to Treat (NNT) and the Number Needed to Harm (NNH), along with their respective 95% CI. To determine whether the variables were normally distributed, the Kolmogorov-Smirnov test was applied. Student's *t*-test was used to compare means, if normally distributed, and the Mann-Whitney test was used to compare medians when distribution was not normal.

Results

A total of 77 children were screened for this study. Of these, 3 were excluded because they were allergic to dipyrone and another child was excluded due to neurological dysfunction. Of the 73 remaining patients, 11 did not participate in the study because their surgeries were canceled. Therefore, 62 children were enrolled and randomized to one of the two groups, with 29 children being assigned to the clonidine group and 33 children to the control group (Fig. 1).

The demographic characteristics were similar in both groups. The mean age of patients was 68.9 $\pm$ 30.1 months. No significant differences were found between the groups with respect to the frequency of patients classified as ASA physical status I at enrollment to the study, the mean duration of anesthesia, the amount of time the patient remained in the PACU, or in the time between the end of anesthesia and the beginning of ED evaluation (Table 1).

The overall incidence of ED in the 62 children was 38.7%, with this frequency being significantly lower in the clonidine group: 17.2% (n = 5) vs. 57.6% (n = 19) in the controls (RR = 0.30; 95% CI 0.13–0.70; p = 0.001; NNT = 3; 95% CI 1.6–5.4). The median scores for all but one of the PAED criteria were significantly lower in the clonidine group. The median of the total score for the clonidine group was 6 (range 3–9) compared to 13 (range 6–15) for the control group (p = 0.007) (Table 2). In the PACU, fewer children in the clonidine group required drugs to reduce ED compared to the control group: 3.4% vs. 21.2%, respectively (RR = 0.16; 95% CI 0.02–1.24; p = 0.04; NNT = 6; 95% CI 3.0–43.2).

No significant difference was found between the groups insofar as the frequency of postoperative self-harm (falls

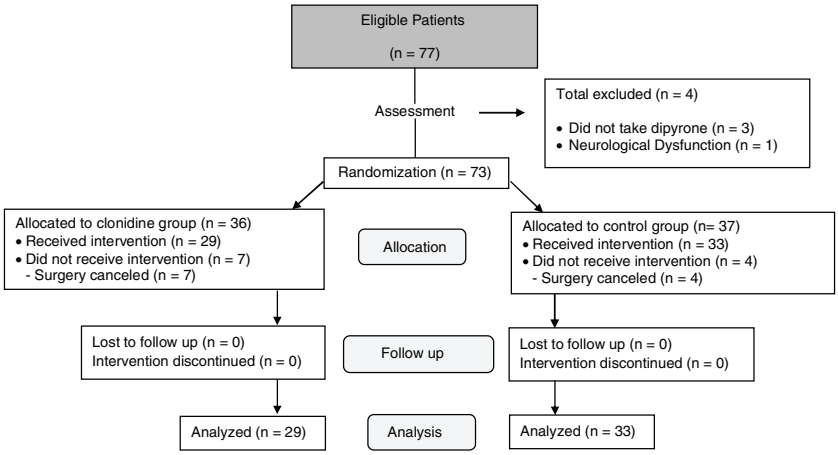

Figure 1 CONSORT flowchart showing the enrollment of participants in the study.

Table 1 Characteristics of the participants according to the study group (clonidine or control).

Characteristic	Clonidine group (n = 29)		Control group (n = 33)		*p*-value
		Range		Range	
Age of children (months), mean ± SD	65.8 ± 27.0	33–137	71.6 ± 32.8	28–140	0.45[a]
ASA I score, n (%)	25 (46.3)	–	29 (53.7)	–	0.57[b]
Duration of anesthesia (min), mean ± SD	49.4 ± 13.6	18–75	45.5 ± 13.9	15–80	0.27[a]
Time from the end of anesthesia to beginning of assessment, awake (min), mean ± SD	17.7 ± 5.4	7–30	17.8 ± 7.2	5–30	0.95[a]
Duration patient remained in the PACU (min), mean ± SD	29.7 ± 11.9	17–65	31.0 ± 11.3	17–60	0.67[a]

ASA, American Society of Anesthesiologists; PACU, Post-Anesthesia Care Unit; SD, Standard Deviation.
[a] Student's *t*-test.
[b] Fisher exact test.

Table 2 The Pediatric Anesthesia Emergence Delirium (PAED) scale criteria and the scores obtained in the study groups.

Behavior	Clonidine group		Control group		*p*-value[a]
		Min–Max		Min–Max	
PAED 1, median (IQR)	2 (1–2)	0–4	2 (2–3)	0–4	0.29
PAED 2, median (IQR)	1 (1–2)	0–4	2 (1–3)	0–4	0.02
PAED 3, median (IQR)	1 (1–2)	0–4	2 (1–3)	0–4	0.01
PAED 4, median (IQR)	1 (0–2)	0–4	3 (1–4)	0–4	0.0008
PAED 5, median (IQR)	0 (0–2)	0–4	3 (1–4)	0–4	0.002
Total PAED, median (IQR)	6 (3–9)	0–19	13 (6–15)	0–20	0.007

IQR, interquartile range; PAED 1, child makes eye contact with the caregiver; PAED 2, child's actions are purposeful; PAED 3, child is aware of his/her surroundings; PAED 4, child is restless; PAED 5, child is inconsolable; Min, Minimum; Max, Maximum.
[a] Mann Whitney test.

and bruises) or dislodged catheters were concerned. The frequency of somnolence was higher in the children in the clonidine group: 65.5% vs. 33.3% (RR = 1.96; 95% CI 1.13–3.40; p = 0.01; NNH = 4; 95% CI 1.8–13.8). Conversely, the groups were similar with respect to the other adverse events investigated (dizziness, nausea, vomiting, excessive somnolence, and pruritus). No cases of hypotension or bradycardia occurred in this study (Table 3).

Parents' satisfaction was greater in the clonidine group compared to the controls: 86.2% vs. 51.5%, respectively (RR = 1.67; 95% CI 1.16–2.40; p = 0.003) (Table 3).

Discussion

In the present study, the frequency of ED in children undergoing tonsillectomy/adenotonsillectomy under gen-

Table 3 Incidence of emergence delirium, adverse events, and parents' satisfaction.

Secondary outcomes	Clonidine group		Control group		RR	95%CI	*p*-value
	n	%	n	%			
Postoperative lesions (falls, bruises), dislodged catheters	3	10.3	6	18.2	0.57	0.16–2.07	0.31[b]
Somnolence	19	65.5	11	33.3	1.96	1.13–3.40	0.01[a]
Dizziness	2	6.9	1	3.0	2.27	0.22–23.8	0.45[b]
Nausea	2	6.9	4	12.1	0.57	0.11–2.88	0.40[b]
Vomiting	2	6.9	0	0	–	–	0.21[b]
Excessive somnolence	7	24.1	7	21.2	1.14	0.45–2.86	0.78[a]
Pruritus	1	3.4	0	0	–	–	0.47[a]
Need for drugs in the PACU to reduce ED	1	3.4	7	21.2	0.16	0.02–1.24	0.04[b]
Parents' satisfaction	25	86.2	17	51.5	1.67	1.16–2.40	0.003[a]

PACU, Post-Anesthesia Care Unit.
[a] Chi-Square test.
[b] Fisher's exact test.

eral inhalation anesthesia with sevoflurane was significantly lower when clonidine was administered intraoperatively at an intravenous dose of 1 $\mu g.kg^{-1}$. The results are consistent with those of a previous study in which ED was reported in 22% of patients who received clonidine intravenously at a dose of 2 $\mu g.kg^{-1}$ compared to 41% in the control group.[14] Other studies have compared the use of 0.5 $\mu g.kg^{-1}$ of midazolam and 2 and 4 $\mu g.kg^{-1}$ of clonidine as oral preanesthetic agents administered to reduce ED in children, with results showing that the higher dose of clonidine was more effective in reducing the incidence of ED compared to the other options used.[18] Similarly, 3 $\mu g.kg^{-1}$ of clonidine significantly reduced the incidence of ED compared to a dose of 1 $\mu g.kg^{-1}$, suggesting a possible dose-dependent mechanism of action.[19] Another study reported that a 1.5 $\mu g.kg^{-1}$ dose of clonidine failed to prevent ED.[20]

Although some investigators have demonstrated an actual reduction in ED with the use of clonidine, anesthesiologists have opted not to administer the drug because of adverse events.[21] The most commonly reported adverse events include somnolence, nausea, vomiting, headache, bradycardia, and hypotension. Hypotension is the most concerning side effect, as it requires immediate treatment, and the response is not dose dependent. In the present study, except for the incidence of somnolence, which was higher in the clonidine group, no significant difference was observed between the groups with respect to the incidence of any of the other adverse events, and neither hypotension nor bradycardia was detected in any child. However, the sample size in this study may have been too small to show statistically significant differences between the groups regarding side effects. On the other hand, the dose of clonidine of 1 $\mu g.kg^{-1}$ administered in this study could have been too low to trigger any side effects.

Previous studies have failed to find any significant differences among groups evaluated in terms of nausea, dizziness, or hypotension.[14] In a study that compared clonidine to placebo for the reduction of ED, two patients in the control group vomited compared to none in the clonidine group; however, one patient in the clonidine group complained of nausea. There were no cases of hypotension and/or bradycardia.[12] Other studies have reported that the incidence of vomiting alone was significantly lower in the group that used clonidine compared to the placebo group.[20]

Another study showed an increase in the incidence of somnolence in the clonidine group when compared to the control group,[14] while yet another study reported the occurrence of excessive somnolence following discharge from hospital in children who received clonidine rectally.[22] The difficulty involved in evaluating these events is relevant given somnolence is a subjective symptom, and this may have contributed to the differences in these findings.

In the present study, no significant difference was found in the mean amount of time spent by the patient in the PACU. Conversely, an earlier randomized, double-blind clinical trial reported that the patients in the clonidine group remained in the PACU for a longer period of time (57 minutes) compared to those in the control group (46 minutes).[14] One explanation for this difference may be that the dose of clonidine used in that clinical trial was twice the one used in the present study.

In this study, we sought to potentially identify a drug to reduce the incidence of ED that would be inexpensive and could be used at a low dose with few side effects. Severe episodes of ED are known to lead to an increase in hospital costs.[1] Furthermore, seeing their child in a state of ED can be stressful for parents or guardians. In the present study, no significant difference was found between the two groups with regard to postoperative self-harm, although this complication was reported in another similar study.[14] Nevertheless, the frequency of this outcome was low in the present sample, and the sample size may have been too small to detect a significant difference between the groups.

ED has been investigated in children through the use of various diagnostic criteria. Nevertheless, until recently, investigators had no reliable, valid evaluation scale with which to measure the phenomenon in children. The PAED scale was established to minimize measurement errors.[6] PAED was selected for this study because it has been shown to be a reliable and valid tool with which to measure the degree of ED in children in clinical practice.[6] Certain differ-

ences in relation to the degree of ED between the present study and other previous studies can be explained by the fact that the previously used scales were not specifically designed to evaluate ED. Therefore, further studies using the PAED scale, a tool that has already been consolidated for the evaluation of ED, are required.

The limitations of the present study include its small sample size and the fact that pain was not evaluated, although some patients diagnosed with ED may experience pain. However, ED may occur during painless procedures such as imaging, and the fact that all the patients in the present study were treated with dipyrone and tramadol during surgery must be taken into consideration. Hence, further randomized clinical trials are required to confirm the efficacy and safety of the use of clonidine in anesthesia induction as a means of preventing ED, and to exclude other causes of ED including systemic hypotension, pain, hypoglycemia, hypoxia, and upper airway obstruction.[23]

In conclusion, the findings of the present study show a reduction in ED in children undergoing elective tonsillectomy/adenotonsillectomy under general inhalation anesthesia with sevoflurane. This reduction was obtained by administering the low dose of 1 $\mu g.kg^{-1}$ clonidine during anesthesia induction.

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Conflicts of interest

The authors declare no conflicts of interest.

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