Original Article

Consequence of dexmedetomidine on emergence delirium following sevoflurane anesthesia in children with cerebral palsy

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Abstract: Children with cerebral palsy can demonstrate irritability following emergence from general anaesthesia. As well, an elevated rate of emergence delirium (ED) in children has been associated with the application of sevoflurane. The current study’s intent is to administer dexmedetomidine, in a single dosage administration, at the initial phase of sevoflurane based anesthesia with regard to the occurrence and severity of ED in children afflicted with cerebral palsy. Participating in the study (American Society of Anesthesiologists I-II) are eighty children ranging in ages two through twelve years. They would be anaesthetised with sevoflurane based anesthesia while undergoing lower limb surgical procedures. The participants were equally distributed to either Group c or Group D. Group C was administered 10 ml saline 0.9%, and Group D was administered dexmedetomidine 0.5 μg•kg⁻¹. Five minutes prior to commencement of the surgical procedures, the participants received the prescribed pharmaceutical dosages under the anesthesia of sevoflurane. In order to sustain the BIS values in a range of 45 and 55, at 60 second increments, endtidal sevoflurane concentrations (ETsev) were modified. After conclusion of the surgical procedures, in post anesthesia care unit (PACU), the frequency of ED was gauged with Aonos four point scale and the severity of ED was gauged with pediatric anesthesia emergence delirium scale upon admission (T0), after intervals of five minutes (T5), fifteen minutes (T15) and thirty minutes (T30). Extubation time, emergence time and length of at stay at the PACU were assessed. Relative to Group C, participants of Group D exhibited noticeably shortened times of emergence, extubation and PACU duration of stay. Prior to surgical incision, ETsev was elevated in the control group, (1.9±0.2 vs 1.6±0.3; P = 0.023) and amid the initial 20 minutes following the surgical incision (1.6±0.2 vs 1.1±0.2; P = 0.016). At intervals of commencement, T0, of five minutes (T5) and fifteen minutes T15, Group D exhibited lower occurrences and severity of ED than those participants in Group C. Dexmedetomidine, given as a bolus dose post induction, was effective in reducing the occurrence and severity of emergence delirium in children with cerebral palsy who were undergoing lower limb surgical procedures under sevoflurane anaesthesia.

Keywords: Dexmedetomidine, emergence delirium, sevoflurane, children, cerebral palsy

Introduction

When emerging from anesthesia, children afflicted with cerebral palsy (CP) often demonstrate irritability. Those enduring emergence delirium (ED) after being subjected to sevoflurane anesthesia with a reported incidence near 80% [1] demonstrate visible signs of despondent emotions, confusion, delusion, cognitive impairment and memory retention issues [2]. Children with ED do not endure any after-effects as it is short in terms of duration though it can pose post-surgical injury to the patient, resulting in the necessity for additional after-care and financial expenditure [3].

To assist in a smooth transition from the emergence of sevoflurane anesthesia, pharmaceutical drugs such as propofol, α2-adrenoreceptor agonists, midazolam, and ketamine have been utilized [4, 5]. Dexmedetomidine, which is far selective than clonidine (α2/α1 = 220/1), is a definitive α2-adrenoreceptor agonist (α2/α1 = 1620/1) that offers sedative and analgesic characteristics without respiratory depression at clinical dosages [6, 7].
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The administration of dexmedetomidine, after sevoflurane anesthesia in non-surgical procedures and pediatric surgery in inpatient [8, 9]/outpatient [10, 11] situations has demonstrated significant reductions in the occurrence of ED. To address the consequence of single dose dexmedetomidine given post induction but pre-surgery on the incidence and severity of ED, requirement for sevoflurane in the midst of surgery and subsequent emergence, a double-blinded randomized prospective study was initiated utilizing CP children undergoing lower limb surgery.

Material and methods

This trial was registered at www.ClinicalTrials.gov, NCT02244515. The eighty non-quadriplegic (mono-, di-, hemiplegic) children with CP, ranging in age from two to twelve, that were scheduled for elective Achilles-tendon lengthening procedure had been screened and approved, (Guangzhou Women and Children's Medical Center, Guangzhou, China), with American Society of Anesthesiologists (ASA) physical status I or II in a double blind, randomized prospective controlled program. A computer generated randomization table was employed to distribute program participants into (Group C) and dexmedetomidine group (Group D). Participants that displayed symptoms of sinus bradycardia and atrio-ventricular block, non-communicative severe developmental delay, seizure disorders, and treatment with seizure medications were disqualified from the program.

Participants were required to fast for a minimum of 8 hours and were administered 0.5 mg•kg⁻¹ oral midazolam 30 minutes prior to being separated from their parents’ custody. Display of agitation and combative actions while being induced with anesthesia despite pre-medication with midazolam was recorded with each participant.

Prior to the administering of anesthesia, all participants are attached to a noninvasive arterial blood pressure monitor and electrocardiogram. A pediatric BIS sensor (Aspect Medical Systems) was placed on the child’s forehead which recorded, using Aspect 2000 BIS XP monitors (Aspect Medical Systems) the mean BIS values (Aspect Medical Systems) in five minute increments. As well, in five minute increments, systolic blood pressure (SBP), diastolic blood pressure (DAP), heart rate (HR), and end tidal sevoflurane concentration (ETsev) were also recorded. By means of a face mask, 6 l•min⁻¹ of O₂ with 8.0% sevoflurane of general anesthesia was administered. Sufentanil 0.3 μg•kg⁻¹ and rocuronium 0.6 mg•kg⁻¹ was administered upon confirmation of a venous access. Sevoflurane in oxygen, maintaining an end-tidal CO₂ of 4.6±0.5 kPa (35±4 mmHg) with controlled ventilation was sustained for the performance of orotracheal intubation.

For intra-operative and post-operative analgesia prior to surgical procedures, participants were recipients of caudal block, which were performed utilizing a 23-gauge needle using aseptic method.

Participants were administered a caudal solution comprised of 0.7 ml•kg⁻¹ of 1.0% lidocaine containing epinephrine 5 μg•ml⁻¹ ml (up to a maximum of 20 ml) [12, 13]. Successful caudal block were confirmed according to way of Orme RM et al. report [14].

The Objective Pain Scale (OPS) utilized in the post-anesthetic care unit (PACU) is a critical indicator of the success of the caudal block [15]. Blood pressure, crying, movement, posture, and agitation are variables of the OPS scoring system. A participant that receives a score of score of ≥ 4 but ≤ 10 is deemed to be suffering from pain was administered iv fentanyl (0.5-1.0 μg•kg⁻¹) and classified as a non-successful caudal block. Data, from non-successful caudal blocks, not conforming to established parameters and standards was rejected.

Five minutes prior to the commencement of the surgical procedure, Group D participants were administered dexmedetomidine 0.5 μg•kg⁻¹ diluted in 10 ml NaCl 0.9% while Group C participants received 10 ml NaCl 0.9% over 2 min. At five minute intervals, pharmaceutical drugs were intravenously administered. Those above two IV agents were drawn up and concealed from view of the participants and administered by the first anesthetist. The second anesthetist observed, confirmed and recorded all variables of the participants.

A 4 l•min⁻¹ of a mixture of 60% air in oxygen and sevoflurane was administered as a means of
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Table 1. Pediatric anesthesia emergence delirium scale

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Not at all</th>
<th>Just a little</th>
<th>Quite a bit</th>
<th>Very much</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Make eye contact with caregiver</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Actions are purposeful</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Aware of surrounding</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Restless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Inconsolable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

1 - Calm; 2 - Not calm but could be easily consoled; 3 - Moderately agitated or restless and not easily calmed; 4 - Combative, excited, thrashing around.

Table 2. Patients’ criteria and anesthetic details

<table>
<thead>
<tr>
<th></th>
<th>Group C (N = 40)</th>
<th>Group D (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>6.3±2.2</td>
<td>6.1±1.9</td>
</tr>
<tr>
<td>Weight (kg) (mean ± SD)</td>
<td>22±8</td>
<td>21±6</td>
</tr>
<tr>
<td>Sex (M:F) (N)</td>
<td>28/12</td>
<td>27/13</td>
</tr>
<tr>
<td>Operation time (min) (mean ± SD)</td>
<td>39±10</td>
<td>42±12</td>
</tr>
<tr>
<td>Anesthesia time (min) (mean ± SD)</td>
<td>59±23</td>
<td>63±21</td>
</tr>
<tr>
<td>Incidence of agitation before induction (%)</td>
<td>10.5</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, number or percent; *Significant difference between group C and group D; P < 0.05 is significant.

sustaining the anesthesia. The sevoflurane concentration is variably adjusted 0.1-0.5% every sixty seconds in order to assure a range of 45 to 55 for BIS values. With the caudal block completed, a minimum period of fifteen minutes must elapse prior to a surgical incision. With the procedure concluded and the cessation of sevoflurane, the administration of neostigmine 0.05 mg·kg⁻¹ and atropine 0.02 mg·kg⁻¹ iv initiated the onset of the reversal of residual muscle relaxation.

Upon restoration of the participants gag reflex, the demonstration of facial movements and the rate of train of four (TOF) was higher than 0.8 by a nerve stimulator (TOF-Watch®, Organon, Ireland), was extubation performed.

Upon admission to the post anesthesia care unit (PACU), children were permitted to have one parent stay with them until they were discharged. Utilizing the Aonos four point scale [16] 1 = calm; 2 = not calm but could be easily consoled; 3 = moderately agitated or restless and not easily calmed; 4 = combative, excited, or disoriented, thrashing around, medical professionals were able to assess the incidence of ED. Scores of three and four were deemed as evidence of the presence of ED, while one and two would considered as non-existence of ED. A pediatric anesthesia emergence delirium (PAED) scale crafted by Sikich et al. [2] (Table 1), a five-point rating scale with five grades for each item was employed to the determine the participants ED severity. At intervals of PACU admission (T0) and at 5 min (T5), at 15 min (T15) and at 30 min (T30) in the PACU, the severity and occurrence of ED was gauged. A reading equal to or greater than 15/20 or higher indicated severe agitation in the participant.

Episodes of the participant experiencing of hypotension, bradycardia, laryngospasm, bronchospasm and oxygen desaturation were recorded. As well, time intervals for the following occurrences were recorded; (a) time to complete surgical procedure (b) time from application of sevoflurane anesthesia to removal of face mask, (c) extubation time, from the discontinuation of sevoflurane to the removal of endotracheal tube, emergence time, from end of sevoflurane to the first response to a verbal command and length of PACU stay, from arrival to discharge. Children that registered a modified aldrete score that was more than nine without agitation were transferred to a ward instead of the PACU.

Statistical analysis

Shapiro-Wilk W tests were employed to assess baseline variables distribution. It was determined that forty participants were necessary for each group (for a level of significance of 0.05 and a power of 0.80) under the assumption that incidence of postoperative agitation of 30% or greater after sevoflurane anesthesia was previously reported [17, 18], and a 50% decrease in ED was deemed to be clinically significant.

Arithmetic mean and standard deviation values for dissimilar variables were calculated and statistical analysis were performed for all groups utilizing Statistical Program for Social Science
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**Figure 1.** Changes in the end-tidal concentration of sevoflurane. Data are expressed as mean ± SD. After induction was defined as after endotracheal tube insertion but before dexmedetomidine infusion. Before incision was defined as 5 min after dexmedetomidine but before start of surgery. After 5, 10, 15, and 20 min was defined as 5, 10, 15, and 20 min after start of surgery. *P < 0.05 compared between group C and group D, ΔP < 0.05, compared with after induction within each group.

**Table 3.** Incidence of emergence agitation, pediatric anesthesia emergence delirium scale, modified children’s hospital of eastern ontario pain scale and recovery characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group C (N = 40)</th>
<th>Group D (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of emergence agitation (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>21Δ</td>
<td>6*Δ</td>
</tr>
<tr>
<td>T5</td>
<td>17</td>
<td>3*</td>
</tr>
<tr>
<td>T15</td>
<td>12</td>
<td>1*</td>
</tr>
<tr>
<td>T30</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PAED (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>13.5±4.8Δ</td>
<td>9.6±3.2*Δ</td>
</tr>
<tr>
<td>T5</td>
<td>8.1±4.6</td>
<td>5.7±2.7*</td>
</tr>
<tr>
<td>T15</td>
<td>5.3±3.9</td>
<td>4.1±2.1*</td>
</tr>
<tr>
<td>T30</td>
<td>4.1±1.6</td>
<td>3.2±1.8</td>
</tr>
<tr>
<td>Patients with PAED score &gt; 15 (N)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Extubation time (min)</td>
<td>8.9±2.5</td>
<td>7.2±2.3*</td>
</tr>
<tr>
<td>Emergence time (min)</td>
<td>12.6±3.5</td>
<td>10.3±2.9*</td>
</tr>
<tr>
<td>Duration of PACU stay (min)</td>
<td>41.3±6.1</td>
<td>37.5±5.6*</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD, number or percent; *P < 0.05 compared between group C and group D; ΔP < 0.05 compared within each group; PAED - Pediatric anesthesia emergence delirium; PACU - Post anesthesia care unit.

**Results**

There were no variation in participant characteristics in either of the study groups, nor severity and occurrence prior to administration of anesthesia or surgical procedure and anesthesia times (Table 2).

None of the children exhibited symptoms of nausea and vomiting, laryngospasm, bronchospasm, hypo-tension, bradycardia and oxygen desaturation episodes. Group D HR, SBP and DBP exhibited insignificant differences with each time point during surgical procedures in comparison to Group C (P > 0.05).

The ETsev necessary to sustain a range of 45-55 of BIS values was insignificant amongst the control group and the dexmedetomidine group after induction of anesthesia (2.1±0.2 vs 2.2±0.4; P = 0.773), though it should be noted that the control group required significantly higher ETsev before surgical incision (1.9±0.2 vs 1.6±0.3; P = 0.023) and during the first 20 min after surgical incision (1.6±0.2 vs 1.1±0.2; P = 0.016) (Figure 1).

There was a shorter duration for Group D in comparison to Group C for emergence time, extubation time and stay at the PACU. The severity and occurrence of ED also was lower in comparison to Group C.
at T0, T5 and T15 as well as the amount of those that developed severe ED (PAED > 15). As time progressed with each group, the Aonos four point scale and PAED scale saw dramatic reduction (Table 3).

Discussion

Children afflicted with cerebral palsy will often experience irritability upon emergence from anesthesia. Professionals struggle with what the root cause is towards such irritability while eliminating documented symptoms. Many elements are associated with the cause of irritability, such as unfamiliar surroundings upon awakening and visual and cognitive impairment [19]. The placement of a parent with the child upon awaking can be helpful towards reducing such irritability.

The administration of sevoflurane seem to trigger more occurrences of ED than halothane in an assessment of 23 randomized controlled trials [20]. Prior to the trial it was deemed a phenomenon that individuals woke rapidly after the administration of sevoflurane anesthesia [21], however our results yielded data that indicated that as a result of less usage of sevoflurane in Group D in comparison to Group C, the use of dexmedetomidine with less sevoflurane anesthesia, has rapid emergence properties, and is associated with low incidence of ED.

Data from Group C indicated longer PACU stays, extubation time and emergence time in comparison to Group D and not consistent with prior research [22, 23] suggesting that the period to awake correlates in a negative manner with ED data. The reason may related to less use of sevoflurane during the surgery.

Group D, concerning the severity and occurrence of ED was considerably lower than that of Group C. The incidence of ED after sevoflurane anesthesia is reduced in children as a result of dexmedetomidine’s sedative and analgesic effects according to prior research [8, 11, 24]. In a research conducted by Guler et al. [9], a base of 60% N2O in oxygen with 1.5-2% sevoflurane along with muscle relaxants was administered to children undergoing adenotonsillectomy. Observations from administering dexmedetomidine five minutes prior to the completion of surgery revealed that there was a noticeable reduction in agitation with prolongation of extubation and emergence times. According to research conducted by Ibacache et al. [8], those anesthetized with 1-3% sevoflurane in 50% N2O in oxygen and a single iv dose of dexmedetomidine 0.15 and 0.3 μg•kg⁻¹ for enduring lower abdominal surgery exhibited a reduction of postoperative agitation from 37% in the control group to 17% and 10%, respectively. Historical and contemporary research have yielded the fact that ED resolution can be achieved without the introduction of pharmacology over a period of time [1, 25].

There is widespread belief that the sense of pain is an ignition source of the occurrence of ED but this does not suggest that the absence of pain will offer a calm waking from sevoflurane anesthesia [1]. Where MRI was required, nearly half of all pediatric patients demonstrated symptoms of ED after sevoflurane anesthesia [10]. There was no established link between the effectiveness of ketamine, a2-agonists, or fentanyl in postoperative pain relief and the reduction of ED [4]. In our trial, we adopted caudal anesthesia for intraoperative and postoperative analgesia, excluded the influence of pain on emergence agitation.

In the range between BIS Values of 45-55, dexmedetomidine lowered the sevoflurane requirements by nearly thirty percent in children undergoing Achilles-tendon lengthening surgery with CP. Prior research confirms its consistency in reducing inhalational/intravenous anesthetic requirements after dexmedetomidine infusion within the post-incision period [26].

Dose-dependent HR and BP reduction can be achieved with the administration of Dexmedetomidine [7, 27]. Ibacache et al. [8] and Guler et al. [9] reported absence of hemodynamic effects at a 0.3-0.5 μg•kg⁻¹ reported bolus dose with no hemodynamic effect in a comparable research study. However, a higher dose dexmedetomidine (1 μg•kg⁻¹ followed by 0.1 μg•kg⁻¹•h⁻¹) may associate with bradycardia and hypotension [28].

In conclusion, dexmedetomidine reduced sevoflurane mandates during surgery, thereby decreasing extubation time, emergence time and shortened the period of time in PACU. In the comparable study, evidence of the reduction of the severity and occurrence was attain-
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...ed with dexmedetomidine 0.5 μg•kg⁻¹ when administered five minutes prior to the commencement of surgical procedures of children afflicted with cerebral palsy under the influence of sevoflurane anesthesia.

Disclosure of conflict of interest

None.

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References

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