Clinical Investigation

Effect of caudal clonidine on emergence agitation and postoperative analgesia after sevoflurane anaesthesia in children: Randomised comparison of two doses

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ABSTRACT

Background and Aims: Sevoflurane, a popular inhalational anaesthetic for children, has been associated with significant emergence agitation in the recovery phase. This study was intended to compare two doses of caudal clonidine added to ropivacaine 0.2% in order to decide on the optimal dose for prevention of sevoflurane induced emergence agitation (EA) and to get a meaningful prolongation of postoperative analgesia with minimal side effects. **Methods:** Sixty-one children aged 1–7 years (American Society of Anaesthesiologists physical status I-II) received standardized general anaesthesia with inhaled sevoflurane and caudal epidural block with 0.2% ropivacaine 1 ml/kg for sub-umbilical surgeries. They were assigned randomly to two groups: (I) clonidine 1 μg/kg added to caudal ropivacaine; (II) clonidine 2 μg/kg added to caudal ropivacaine. EA and postoperative analgesia were assessed using pain/discomfort scale score and face, legs, activity, cry, consolability (FLACC) score respectively. **Results:** EA was observed in 8 children (26.6%) in group I when compared to only 2 children (6.4%) in group II after first 15 min postoperatively. Incidences of EA at 15 min, as well as total incidence of agitation, were both significantly lower in group II when compared to group I with $P < 0.05$. Duration of analgesia in group I (12 [8–20] h) and group II (16 [8–20] h) was statistically comparable ($P > 0.05$). There was no difference in the incidence of sedation or complications. **Conclusion:** Caudal clonidine 2 μg/kg added to 0.2% ropivacaine 1 ml/kg is suggested to be the optimal dose, for prevention of EA and meaningful prolongation of postoperative analgesia with minimal side-effects.

Key words: Caudal clonidine, emergence agitation, optimal dose, postoperative analgesia, sevoflurane

INTRODUCTION

Sevoflurane has evolved as a popular inhalational anaesthetic for general anaesthesia in children. It is characterised by a lower blood/gas partition coefficient, less irritation to the airway, less cardiodepressive effect, and less toxicity to the liver and kidney as compared with other volatile anaesthetics. However, concern has been raised over propensity of sevoflurane for significant excitatory emergence features in the immediate recovery phase.[1]

First described in the early 1960's, emergence agitation (EA) is characterised by a variety of presentations including crying, excitation, agitation, and delirium occurring during the early stage of emergence from anaesthesia in children.[2]

Emergence agitation is a major source of dissatisfaction for parents, nurses, and others taking care of these children. The irritable, uncooperative, incoherent child who is inconsolably crying, moaning, kicking, or thrashing is at risk for injury and requires extra nursing

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care and supplemental sedative and/or analgesic medications, which may delay patient discharge from hospital.[3,4] It has been observed that age and physical status of the patient, the preanaesthetic medications, the general anaesthetic agents, the operation and the preoperative psychological status all contribute to the EA.[5,6]

Effective analgesia and many pharmacological measures have been described to prevent and treat EA. Of them, ketamine, propofol, fentanyl and alpha-2 agonists have been found to be useful.[7]

Caudal epidural block is one of the most popular, reliable, and safe techniques in the paediatric anaesthesia that can provide analgesia for a variety of infra- and supra-umbilical surgical procedures. Although versatile, one of the major limitations of the single-shot technique is the relatively short duration of postoperative analgesia. The most frequently used method to further prolong postoperative analgesia following caudal is to add different drugs to the local anaesthetic solution.

Clonidine, an alpha-2 agonist has been studied as an adjuvant in caudal block for prevention of EA in children,[8,9] besides prolonging the duration of analgesia of single-shot caudal.[10,11]

Since both these parameters are to be assessed in different time frames, we planned to study the prevention of sevoflurane induced EA in the first postoperative hour and the prolongation of caudal analgesia in the next 24 h.

METHODS

After obtaining clearance from the Ethics Committee, the study was carried out in seventy healthy children of American Society of Anaesthesiologists (ASA) physical status I and II aged 1–7 years, undergoing sub-umbilical surgeries including inguinal hernia repair, orchidopexy, circumcision, hypospadias repair, suprapubic cystolithotomy, posterior urethral valve repair and cystoscopic procedures. The children were block randomised and allocated by envelope method to one of two groups having 35 children each. Criteria for exclusion were history of developmental delay or mental retardation, which could make observational pain intensity assessment outside the norm, history of preoperative agitation, any known or suspected coagulopathy or any signs of infection at the site of proposed caudal block or spinal deformity. This was a randomised, double-blind, parallel study.

Careful preanaesthetic examination was performed, and parental informed consent was taken. No premedication was given. In the operating room, after connecting to Schiller® multi-parameter monitor, haemodynamic parameters like heart rate (HR) and blood pressure were recorded. Induction was carried out using 8% sevoflurane in N_2O-O_2 (50:50) and fresh gas flow of 5 L/min, through Jackson-Rees' modification of Ayre's T-piece. Trachea was intubated after a single dose of atracurium 0.4 mg/kg, and the lungs ventilated manually. Anaesthesia was maintained with sevoflurane 2–3%. Caudal anaesthesia was performed in the lateral position with 25 gauge hypodermic needle using the standard technique, and one of the two different mixtures described below were administered.

Random assignment of children to one of the two groups and preparation of caudal solution was done by a senior resident who was not involved in the intervention and postoperative data collection. Children in group I received 1 ml/kg of ropivacaine 0.2% + clonidine 1 μg/kg (1 ml) and those in group II received 1 ml/kg of ropivacaine 0.2% + clonidine 2 μg/kg (1 ml). No further analgesic or sedative was given.

Heart rate, mean arterial pressure (MAP) and SpO_2 were recorded before induction, after induction and then every 5 min after caudal anaesthesia.

During the surgery, adequate analgesia was defined by hemodynamic stability as indicated by the absence of an increase in MAP or HR of >10% compared with baseline values obtained just before the surgical incision. Patients in whom HR or MAP increased by >10% were administered fentanyl 2 μg/kg and were excluded from the study.

During the surgery, children received Ringer's solution 5 ml/kg/h. At the beginning of skin closure, sevoflurane and nitrous were turned off, and the child's lungs were ventilated with 100% oxygen at a fresh gas flow rate of 6 L/min. Extubation was performed following return of adequate spontaneous respiration and the gag reflex, after clinically excluding any residual neuromuscular block. The time from the cessation of gas to the eye-opening (emergence time) was noted.

The child was transferred to the recovery room for 1 h, where HR, SpO_2, blood pressure was monitored half hourly. All children had at least one parent in attendance during recovery. Thereafter, the child was moved to the paediatric ward, where the rest of the observations were taken for 24 h.

We defined the primary end-point of observation as the appearance of postanaesthetic agitation. The pain/discomfort scale [Table 1] was used to determine agitation. This scale evaluates postoperative pain or discomfort in children.[12] Due to the technique used, we can exclude pain as the cause of agitation in the first postoperative hour. We noted the maximum score during the 1st h and scores at four fixed end points: 15, 30, 45 and 60 min after administration of inhalational anaesthetic ceased. The scores for movement, agitation and posture on the pain/discomfort scale (items 3–5) were used to assess the postanaesthetic agitation as reported in previous studies.[8,9] As in other studies, we define a total score of ≥ 3 at any time - point for items 3–5 of the pain/discomfort scale as an indication of postanaesthetic agitation.

To assess the intensity of pain we used the paediatric observational face, legs, activity, cry, consolability (FLACC) pain scale [Table 2]. After being shifted to the paediatric ward, the child was observed every 4 h for the first 24 h after operation. If the FLACC pain scale score was noted any time to be 4 or more, rectal suppository paracetamol 40 mg/kg, was used as rescue analgesic. The duration of adequate caudal analgesia (from the time of caudal injection to the 1st time the FLACC pain scale score is noted to be 4 or more) was also recorded.

Side-effects like bradycardia, hypotension, respiratory depression and urinary retention were taken into consideration. Bradycardia and hypotension were defined as the fall in HR or blood pressure by >20%. Respiratory depression was defined as unable to maintain SpO_2 of ≥ 95%.

A four-point sedation scale was used in first postoperative hour to assess sedation half hourly, where score of 1, 2, 3, and 4 refers to sleeping-not arousable by verbal command, arousable by verbal command, drowsy- not sleeping and alert/awake respectively.

The data of the present study were recorded and after its proper validation, check for error, coding and decoding were compiled and analysed using the software IBM SPSS 20 for Windows. Appropriate univariate and bivariate analysis were carried out using the Student's *t*-test for the continuous variable (age) and two-tailed Fisher exact test or Chi-square test for categorical variables. The FLACC score were compared using Mann–Whitney U-test a nonparametric test. All means are expressed as mean ± standard deviation.

Table 1: Pain/discomfort scale score

Items	Scoring		
	0	1	2
Blood pressure	±10% of preoperative level	>20% of preoperative level	>30% of preoperative level
Crying	Not crying	Crying but responds to tender loving care	Crying and does not respond to tender loving care
Movement	None	Restless	Thrashing
Agitation	Patient asleep or calm	Mild	Hysterical
Posture	No special posture	Flexing legs and thighs	Holding scrotum or groin
Complaints of pain (when appropriate by age)	Asleep, or states no pain	Cannot localise	Can localise

Table 2: FLACC pain scale

Categories	Scoring		
	0	1	2
Face	Smile or no particular expression	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Leg	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moved easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or talking to, distractible	Difficult to console

FLACC – Face, legs, activity, cry, consolability

The critical levels of significance of the results were considered at 0.05 levels, that is, $P < 0.05$ was considered as significant. According to a power analysis, the sample size of thirty patients in each group was sufficient to detect a reduction in agitation from 40% to 20%, with an alpha risk of 0.05 and a power of 0.8. Assuming an attrition rate of 15%, initial sample size in each group came out to be 35.

RESULTS

The caudal block failed in four children in group I and three in group II. One child each in group I and II did not satisfy the protocol as nurse in the ward administered paracetamol suppository as soon as the child reached the ward.

Hence, the number of cases for which analysis was done in group I was 30 and in group II it was 31.

There was no difference between the groups with respect to age, sex, weight, ASA classification, type and duration of surgery or emergence time [Table 3].

Eight out of thirty (26.6%) children in group I experienced EA as compared to only two out of thirty-one (6.4%) children in group II at 15 min after emergence (Fisher exact $P = 0.0302$). At 30 min after emergence 3 children in group I and none in group II experienced EA (Fisher exact $P = 0.1128$). Incidences of EA at 15 min, as well as total incidence of agitation, were both significantly lower in group II when compared to group I with $P < 0.05$ [Table 4].

Median time of maintaining adequate caudal analgesia (FLACC scale score <4) without the need for paracetamol for group I was 12 (8–20) h and for group II is 16 (8–20) h. There was no statistically significant difference between the two groups as regards the analgesia time ($P = 0.535$) [Table 5].

Eight out of thirty children in group I and 10 out of 31 children in group II showed sedation score of 2 at 30 min after emergence. At 60 min after emergence, 10/30 children in group I and 11/31 children in group II showed a sedation score of 2. Sedation score of 2 meant that child was asleep, but arousable by verbal command. No child was sedated beyond that score. Median sedation score in both groups at both times was 3 [Table 6].

There was no incidence of respiratory depression, hypotension, bradycardia or urinary retention.

DISCUSSION

In our study, we have shown that incidence of sevoflurane induced EA is effectively reduced by clonidine 2 μg/kg as compared to clonidine 1 μg/kg when added to caudal ropivacaine 0.2% (1 ml/kg) in children of 1–7 years of age undergoing sub-umbilical surgeries. Duration of postoperative analgesia provided by both the doses was similar, and no significant sedation was observed in any case.

Our study aimed to come up with an optimal dose of caudal clonidine (as an adjuvant) that would lead to prevention of EA and meaningful prolongation of

Table 3: Patient characteristics, duration of anaesthesia and emergence time

Parameters	Group I (1 μg/kg) (*n*=30)	Group II (2 μg/kg) (*n*=31)
Age (years)	4.16 (1-7)	4.51 (1-7)
Sex (male:female)	27:3	26:5
Weight (kg)	16.73 (±4.28)	18.48 (±4.75)
ASA I	30	31
Duration of anaesthesia (min)	41.83 (16.21)	40.96 (15.35)
Emergence time (s)	564 (46.20)	567 (47.34)

ASA – American Society of Anaesthesiologists

Table 4: Incidence of emergence agitation at different time interval after surgery

Groups	Time after emergence			
	15 min	30 min	45 min	60 min
Group I	8	3	0	0
Group II	2	0	0	0
Fisher's exact *P*	0.0302	0.1128		

Table 5: Children maintaining adequate caudal analgesia for different time interval

Time interval from caudal block/duration of analgesia (h)	Number of children showing FLACC ≥4	
	Group I (*n*=30)	Group II (*n*=31)
0	0	0
4	0	0
8	2	3
12	15	12
16	12	13
20	1	3

FLACC – Face, legs, activity, cry, consolability

Table 6: Sedation score of children at 30 min and 60 min after emergence

Sedation score	Group I		Group II	
	At 30 min	At 60 min	At 30 min	At 60 min
2	8	10	10	11
3	11	16	9	16
4	11	4	12	4

postoperative analgesia with minimal side-effects. We evaluated the child in first postoperative hour for EA and in the next 24 h for the duration of postoperative analgesia.

All the children were healthy; no event of desaturation, hypercapnia, hypotension or bradycardia occurred. Fluid therapy was adequate. Four children in group I and three in group II showed signs of failed caudal block and were ruled out of study. Rest of the cases had effective caudal block. Hypoxia, metabolic disturbances, urinary retention and pain were excluded as a cause of agitation.

Certain drugs such as atropine, scopolamine, midazolam that are found to be associated with EA were avoided.[5]

During surgery adequate depth was maintained using sevoflurane 2–3% in 50% nitrous and oxygen, to achieve amnesia and tube tolerability, as the caudal analgesia was effective.

Ropivacaine is reported to be safer than bupivacaine in terms of central nervous system and cardiac toxicities.[13] In the light of a pharmacokinetic study demonstrating the safety of caudal ropivacaine 0.2% (1 ml/kg) in 1–8 years old children[14] and other studies supporting the efficacy of this dose,[15,16] we considered the same dose in our study.

Clonidine reduced post sevoflurane agitation in many studies and in two studies the effect of caudal clonidine on EA has been studied.

The first one (Bock *et al*.) was a randomized controlled trial conducted on 72 children.[8] In this study, clonidine was administered either intravenous (i.v.) or as an adjunct to a caudal block with local anaesthetic. It was reported that caudal clonidine 1 μg/kg did not reduce EA. Our study also produced similar results where clonidine 2 μg/kg was found to reduce the incidence of EA more as compared to clonidine 1 μg/kg.

Ghosh *et al*. being concerned about dose-dependent side-effects of caudal clonidine compared lower doses (1 μg/kg and 0.75 μg/kg) with placebo.[9] In contrast to our study, they found that clonidine 0.75 μg/kg effectively reduced agitation. A possible explanation to this difference could be that they had used a lower concentration of sevoflurane in their study, and moreover, we did not have any placebo control group.

Justification for the use of α2-agonists for prevention of EA stems from the fact that they reduce secretion of noradrenaline from the locus ceruleus, facilitating release of inhibitory neurons, such as those of the gamma-aminobutyric acid system.[17,18]

Clonidine 2 μg/kg reduced the incidence of EA without prolonging the emergence time or increasing sedation, when compared with clonidine 1 μg/kg, which suggest that this effect on EA is not related to its sedative property. In contrast to our results, Malviya *et al*.[17] and Sharpe *et al*.[19] found that arousal time was increased with clonidine 2 μg/kg. This difference could be due to shorter duration of surgeries in both studies. Emergence time remained similar on addition of clonidine 2 μg/kg in the study conducted by Kulka *et al*.[20]

There is no documented maximum safe dose for caudal clonidine as an adjuvant. Many studies have been performed taking into account doses between 1 μg/kg and 2 μg/kg. The major side-effects of concern were bradycardia, hypotension, respiratory depression and urinary retention.The most undesirable of them are bradycardia and hypotension. Previous studies have reported statistically, but not clinically significant differences in these hemodynamic variables in children who received 2–3 μg/kg of clonidine i.v. or caudally.[8,11,20] Klimscha *et al*. compared clonidine 1 and 2 μg/kg as adjuvant to bupivacaine with plain bupivacaine. There was a significant decrease from baseline MAP in all groups (range 13–23%) observed 5–20 min after injection. However, there were no significant intergroup differences in MAP. Conversely, a decrease in HR from baseline was not observed. None of the patients required drug therapy to correct hypotension or bradycardia.[21] Clonidine inhibits sympathetic preganglionic neurons; therefore, the degree of clonidine-induced hypotension is also related to the spinal site of injection. Thoracic epidural administration of clonidine closer to the origin of sympathetic neurons causes a more pronounced MAP decrease than lumbar clonidine administration.[22] Thus, more distant caudal site of injection might favour a moderate haemodynamic response to clonidine. Furthermore, hypotension is an uncommon complication in children <7 years of age.[23]

With this background in mind and support of previous studies, 2 μg/kg appears to be a safe dose in terms of haemodynamic stability.

We did not observe significant sedation or respiratory depression in any of the cases. Klimscha *et al*. and Malviya *et al*. also reported that, as sedation made the children look more comfortable, it was actually appreciated by parents, and was not regarded as an adverse side-effect.

In this study, we found that the time of adequate caudal analgesia (FLACC scale score <4) without the need for paracetamol for group I was 12 (8–20) h and for group II is 16 (8–20) h (P = 0.535). These results are similar to those reported by Klimscha *et al*. They concluded that although there was no significant difference between the two doses, there were fewer rescue interventions required with 2 μg/kg clonidine added to 0.75 mL/kg 0.25% bupivacaine, compared with 1 μg/kg clonidine group, which suggests that this dose provides greater benefit to the child at no additional risk.[21] We could not appreciate this benefit as we didn't observe 24 h analgesic requirement postoperatively.

We used Pain Discomfort Scale score for assessment of EA. The scores for movement, agitation and posture on the PDS (item 3–5) were used as reported in the previous studies.[8,9]

For the assessment of pain, we used FLACC scale that has been validated by Minas *et al*. for assessing pain, especially in preverbal children and has been used in many studies.[24]

The newer alpha 2-receptor agonist, dexmedetomidine, that possesses an eightfold greater degree of specificity for the α2-versus the α1-receptor and has a shorter half-life compared with clonidine (2–3 h vs. 12–24 h, respectively), may be associated with less postoperative sedation. While the pharmacologic profile of dexmedetomidine might suggest an improved risk/benefits ratio over clonidine for the prolongation of analgesia, few studies have suggested no additional advantage of dexmedetomidine over clonidine.[10,11]

CONCLUSION

Clonidine 2 μg/kg was more effective in preventing EA as compared to clonidine 1 μg/kg, without significant change in duration of analgesia with clonidine 2 μg/kg in children undergoing sub-umbilical surgeries under sevoflurane anaesthesia, with minimal side-effects.

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Announcement

CALENDAR OF EVENTS OF ISA - 2014

Certain important dates are given here for the members. All the applications should be sent by registered post (with Acknowledgement Due)

Date	Name of the Award/Post	Application has to be sent to
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