Original Article

Effect of caudally administered clonidine on sevoflurane induced emergence agitation—A randomized trial

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Abstract

Background and Aims: Emergence agitation (EA) is an unpleasant problem encountered in children following anesthesia with Sevoflurane. We studied the effectiveness of caudal epidural block (CEB) with ropivacaine 0.2% and clonidine two microgram per kilogram (mcg/kg) on the incidence of EA, with respiratory depression and hemodynamic variables as secondary end points.
Material and Methods: Ninety children aged one to eight years undergoing infra umbilical surgeries were randomly allocated into two groups: Group RS: Ropivacaine 0.2% one ml/kg + Saline one ml and Group RC: Ropivacaine 0.2% one ml/kg + Clonidine two mcg/kg made to one ml. They were then administered general anesthesia with endotracheal intubation followed by CEB using test drugs. Post surgery, EA was evaluated by Modified Richmond Agitation Scale at 15-minute intervals for one hour. The results were then analyzed using mean and standard deviation (SD), Chi square test, and Independent t test.
Results: EA was significantly lower in group RC when compared to group RS ($P < 0.0001$).Group RC had 12 (28.5%) children with EA at 15 minutes compared to 35 (83.3%) children in Group RS. At 30 minutes, it was seen in five (11.3%) and 27 (64.2%) children in group RC and RS, respectively. No significant respiratory depression was noted in both groups. A significant decrease in heart rate was seen in Group RC ($P < 0.001$) but was not significant clinically. No adverse events were recorded in both the groups.
Conclusion: Addition of clonidine (2mcg/kg) to ropivacaine 0.2% offers an advantage over 0.2% ropivacaine alone in decreasing the incidence of sevoflurane induced EA in children undergoing lower abdominal surgery without any adverse effects.

Keywords: Caudal anesthesia, clonidine, emergence agitation, ropivacaine, sevoflurane

Introduction

Sevoflurane is a popular inhalational anesthetic used in pediatric population. Though the rapid and smooth induction due to lower blood/gas partition co-efficient and low irritation to airways is impressive on one hand, the equally rapid awakening from anesthesia is also a cause for worry since it results in post anesthetic emergence agitation (EA).[1,2] EA is a significant problem in children recovering from anesthesia with a reported incidence of 10-80%[3-6] and manifests as restlessness, disorientation, crying, excitation, and agitation during emergence and may cause injury to the child, disruption of the surgical site and dressing, drains, or even removal of intravenous catheters. This necessitates extra nursing care and supplemental sedation and/or analgesics, which may delay discharge from hospital.[7]

Pain, anxiety, and rapid return to consciousness in an unfamiliar environment have been thought to provoke EA. Recent studies have also pointed towards sevoflurane as a cause for EA.[8] Though ketamine, propofol, fentanyl and

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alpha-2 agonists have been found to be useful to prevent and treat EA, their intravenous use may result in undesirable post-operative adverse effects like respiratory depression.[1,9]

Caudal epidural block (CEB) is not only a popular and reliable regional technique in children, but also a proven safe method for prolonging post-operative analgesia, especially when combined with adjuvants. Clonidine, as an adjuvant allows a lower concentration of the local anesthetic to be used to achieve the same level of anesthesia thereby increasing the margin of safety. It also increases the duration of analgesia.[10] The combination of ropivacaine-clonidine for CEB in pediatric patients has been found to be effective and safe in various studies.[11-13] These studies mention the analgesic efficacy of this combination. Studies evaluating the efficacy of this combination in preventing EA, especially in Indian population is scarce. This study intents to evaluate the usefulness of CEB with ropivacaine 0.2% and clonidine 2 mcg/kg in preventing EA in patients receiving sevoflurane general anesthesia (GA).Incidence and severity of emergence agitation was the primary outcome studied. Hemodynamic parameters and incidence of respiratory depression were the secondary outcomes of our study.

Material and Methods

This randomized clinical trial was conducted at a tertiary care hospital in south India. This study was conducted from November 2018 to June 2019. Children aged between one to eight years of both gender posted for elective infra umbilical surgeries lasting between 45 minutes to one hour (surgeries for hernia, hydrocele, undescended testis, cystoscopies) and belonging to American Society of Anesthesiologists physical status (ASA-PS) I and II were enrolled. Children with developmental delay/mental retardation, previous history of agitation, infection at injection site, coagulopathy, spinal deformity and known allergy to study drugs were excluded from the study.

The patients were randomly allocated into two groups by simple random sampling using shuffled closed sealed envelope technique: the control group—GROUP RS received Ropivacaine 0.2% 1ml/kg + Normal saline 1ml and the intervention group—GROUP RC received Ropivacaine 0.2% 1ml/kg + Clonidine 2mcg/kg made to 1ml.The study drug was prepared by the same anesthesiologist who was involved in randomization but not in observation and postoperative data collection.

Premedication with oral midazolam 0.3mg/kg was given one hour prior to surgery. Standard monitoring included pulse oximeter (SpO2), non-invasive blood pressure, electrocardiography and end tidal carbondioxide (EtCO2). Induction was done with propofol 2mg/kg and atracurium 0.5mg/kg and tracheal intubation was done with appropriate size endotracheal tube and position confirmed by bilaterally equal air entry, adequate chest rise, and EtCO2 graphs. Anesthesia was maintained with sevoflurane 2-3%, N2O-O2 (50:50) and intermittent dose of atracurium 0.1mg/kg.After intubation, patients were placed in lateral decubitus position and a single dose CEB was performed under sterile conditions by another anesthesiologist who was blinded to the drug that was injected.

The surgical incision was made after ten minutes of caudal placement. The caudal block was considered to have failed if the patient had an increase in heart rate/mean arterial pressure (MAP), or both, of more than 15% compared with baseline just before the surgical incision. In such instances, the patient was withdrawn from the study and treated with 1–2 mcg/kg of fentanyl. Heart rate, MAP, SPO2 were recorded before induction, after induction and then every 15 min after caudal block and throughout surgery.The time from cessation of sevoflurane to opening of eyes was taken as mean time of awakening.At the end of surgery, neuromuscular block was reversed with neostigmine (0.05 mg/kg) and glycopyrolate (0.01 mg/kg). After extubation patients were shifted to PACU, and observed for the following:

1. The severity of post anesthetic agitation measured by Modified Richmond Agitation Scale (0 = calm, 1 = restless, 2 = slightly agitated, 3 = very agitated, 4 = combative), every 15 minutes for one hour.
2. Heart rate, MAP, SpO2 for first four hour
3. Respiratory depression.

Respiratory depression was defined as a decrease in SpO2 to less than 94% or respiratory rate less than ten per minute requiring oxygen supplementation or assisted ventilation. Bradycardia was defined as heart rate 20% below the baseline value and was treated with atropine 20mcg/kg intravenously. Hypotension was defined as systolic blood pressure 20% below the baseline value and was treated with injection ephedrine. Hypertension was defined as systolic blood pressure 20% above the baseline value.Tachycardia was defined as heart rate 20% above the baseline value.

The study was approved by institutional ethical committee and informed parental consent was taken from one or both parents prior to enrolment in the trial. With an assumed incidence of 60%EA in control group and to detect a reduction in EA by 50% with a power of 80% and alpha error of 5%, we needed 41 cases in each group. To compensate for dropouts we took 45 cases in each group.

All the data were entered in pre-formed Microsoft excel data sheet and was analyzed using SPSS version 19.0. Per protocol analysis of data was done and children who required additional analgesia with injection fentanyl were excluded from analysis. Nominal data was analyzed with Chi square test and t test was used for numerical data. Mann Whitney U test was used to study the ordinal outcomes. A P value of <0.05 was considered as statistically significant.

Results

Ninety children were enrolled in the trial and were randomized equally into two groups.Group RC received ropivacaine 0.2% 1 ml/kg with clonidine 2 mcg/kg made to one milliliter and group RS received ropivacaine 0.2% 1ml/kg with saline 1ml. One patient from RC and three from RS were excluded from the study due to failure of CEB[Figure 1].There was no statistical difference with respect to demographic parameters like age, sex, body weight and duration of surgery[Table 1].

EA was significantly reduced in group RC when compared to group RS. At 15 minutes, 12 children (28.5%) in group RC had EA compared to 35 (83.3%) in Group RS. At 30 minutes, it was 5 (11.3%) and 27 (64.2%) in RC and RS , respectively with P value of 0.01. The median score was significant at both 15 and 30 minutes (Mann Whitney U test P value of < 0.001 at both 15 and 30 minutes). There was no EA in both the groups after 45 minutes[Table 2].

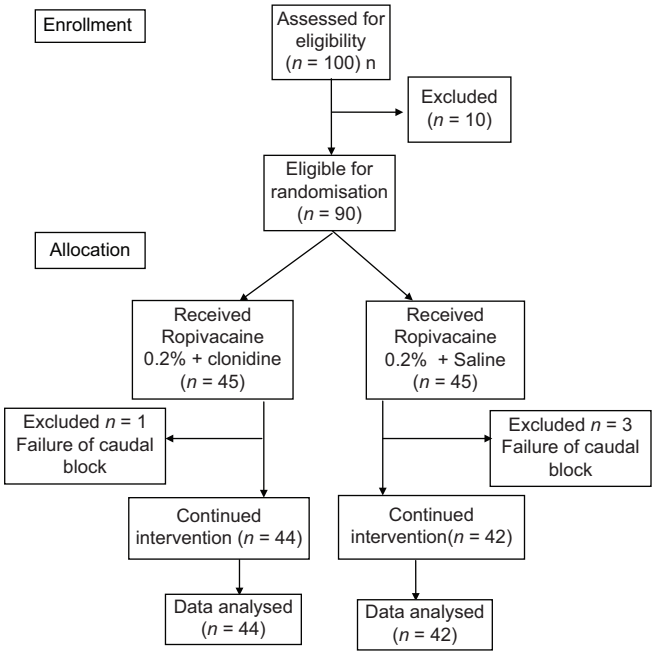

Figure 1: Consort flow chart

Group RC showed a decrease in heart rate compared to Group RS. This was statistically significant from 45 minutes after induction upto four hours (Student t test, $P < 0.001$). But no child in Group RC required treatment for bradycardia[Table 2, Figure 1]. Mean time of awakening[Table 2] and MAP[Table 2, Figure 2] were comparable in both groups with no statistical significance. There was no case of respiratory depression in both the groups.

Table 1: Comparison of baseline variables between Groups

Parameter	Group RC (n=44)	Group RS (n=42)	P
Age (years)	3.21 (2.0)	3.42 (2.2)	0.64
Sex (Male :Female)	4:1	4:1	
Bodyweight (kg)	11.3 (2.8)	11.8 (3.2)	0.44
Average duration of surgery (minutes)	45 (6.0)	48 (5.0)	0.5

Table 2: Comparison of outcome parameters between Groups RC and RS

	Group RC (n=44)	Group RS (n=42)	p
Median MRAS			
15 minutes	0	1	<0.001
30 minutes	0	1	<0.001
45 minute	0	0	
60 minutes	0	0	
Incidence of agitation n (%)			
15 minutes	12 (28.5)	35 (83.3)	0.38
30 minutes	5 (11.3)	27 (64.2)	0.01
45 minute	0	0	
60 minutes	0	0	
Mean Blood pressure			
60 minutes	76.2 (8.2)	75.5 (8.2)	0.68
Heart Rate			
60 minutes	109.4 (6.8)	121.9 (6.3)	<0.001
Mean time to awakening in seconds	160 (25)	156 (32)	0.86

MRAS=Modified Richmond Agitation Score

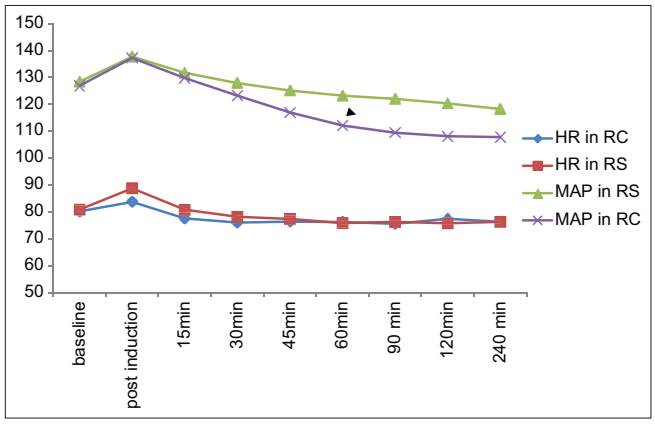

Figure 2: Changes in heart rate (HR) and Mean arterial pressure (MAP) in groups RC and RS

Discussion

Post anesthetic EA is a major cause of concern related to the use of sevoflurane, occurring more frequently with sevoflurane than with other inhalational agents like halothane, as reported by several studies. Its predilection to cause EA has even prompted some authors to suggest further studies to evaluate the safety profile of sevoflurane.[1]It thus becomes imperative to find an effective means to continue the use of sevoflurane which has many distinct advantages in pediatric anesthesia, but without the dreaded problem of EA.

Clonidine, an alpha 2 adrenoreceptor agonist is used as a sedative and analgesic.[14] The effect of clonidine on reducing EA has been a matter of interest lately and has been attributed to its ability to reduce noradrenaline release from locus ceruleus. This facilitates the release of inhibitory neurotransmitters like gamma amino butyric acid.[15]

Bock *et al.* studied the effect of clonidine on EA by administering it as an adjuvant both caudally (with bupivacaine) and intravenously. They observed that it is effective in reducing the incidence of EA in both routes when given in a dose of three mcg/kg as compared to one mcg/kg. They also noticed that clonidine is more effective in reducing pain when given through epidural route than intravenously.[1]Saxena *et al.* reported clonidine as an effective caudal adjuvant with ropivacaine in a dose of two mcg/kg for prevention of EA.[2]Hence we used clonidine in a dose of 2 mcg/kg and preferred the caudal route of administration to give the patients the added benefit of better analgesic effect compared to intravenous route as was demonstrated in the study by Bock *et al.*[1]

In our study we found that the sevoflurane induced agitation on emergence was significantly less in ropivacaine-clonidine group than the ropivacaine-saline group.A median score of zero was seen at both 15 and 30 minutes in Group RC compared to a score of one in Group RS at both these time intervals. Similar findings of reduced EA with the use of clonidine as an adjuvant to bupivacaine has been reported by Bock *et al.*[1] Our findings are also in concordance with the study by Saxena *et al.* where they compared two different doses of clonidine- 1mcg/kg and 2mcg/kg given caudally with 0.2% ropivacaine and found that clonidine 2mcg/kg had lesser incidence of EA and also provided longer duration of analgesia.[2]

In our study we did not observe significant respiratory depression in both the groups. The mean time to awakening was comparable in both the groups. Similar findings have been reported in various other studies.[2,10,11]

When given neuraxially, clonidine dampens the preganglionic sympathetic impulse generation resulting in parasympathetic predominance. This is clinically seen as bradycardia and hypotension- the two disturbing side effects of clonidine.[16] The degree of hypotension depends on the spinal site of administration, with thoracic epidural administration causing a more pronounced fall in MAP than the more distal lumbar clonidine injection.[17] In our study, there was a fall in heart rate in Group RC, with a statistically significant decrease seen from 45 minutes after induction. However, no child required treatment with atropine. There was no significant difference in MAP in both the groups. This can probably be explained by the more distal administration of clonidine and also by the finding that hypotension is uncommon in children less than seven years of age.[18]

There is also another advantage of caudal clonidine administration with a local anesthetic-that of providing an enhanced pain relief and also prolonging the duration of post-operative analgesia provided by the CEB. Several studies have already been carried out to assess the efficacy of caudal clonidine for post-operative analgesia and also to find the optimum dose for the same.[10-13] This excellent analgesic profile also probably adds to its effect on reducing EA since pain is one of the implicated factors for causing EA.

We have used the Modified Richmond Agitation Score for assessing the severity of emergence agitation since it is the score routinely used as per the institution protocol. However there are validated and specific scores mentioned in literature for assessing EA, like the pediatric anesthesia emergence delirium scale (PAEDS) score. This probably is a limitation in our study and further studies using specific scoring systems might throw more light on the efficacy of caudally administered clonidine in reducing incidence and severity of sevoflurane induced EA.

Conclusion

Sevoflurane induced emergence agitation is a disturbing complication in the post-operative period. Caudal epidural block with 0.2% ropivacaine and clonidine 2 mcg/kg is effective in alleviating this problem without causing any significant respiratory depression, hemodynamic disturbances, or any other adverse effects. We therefore conclude that caudal clonidine administration is a safe and effective means of preventing sevoflurane induced emergence agitation in children.

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Conflicts of interest

There are no conflicts of interest.

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