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Research Paper

Efficacy of Dexmedetomidine in Reducing Emergence Agitation After Sevoflurane Anaesthesia in Indian Paediatric Populatio

Medical Science

KEYWORDS : Paediatric anaesthesia, Emergence agitation, Sevoflurane, Dexmedetomidine

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ABSTRACT

Background: Emergence agitation is an undesirable, yet a very common phenomenon after sevoflurane anaesthesia in paediatric patients. Aim of the present study was to find out the effect of dexmedetomidine infusion on the incidence and severity of emergence agitation following sevoflurane anaesthesia in paediatric population.

Materials & Methods: Eighty four children aged 2-7 years undergoing infraumblical surgeries under sevoflurane based anaesthesia were included in this randomized prospective study. Children were allocated in two groups to receive either 0.5 µg. kg-1. dexmedetomidine or normal saline as slow infusion over a period of 10 minutes before termination of anaesthesia.

Statistical Analysis: The numerical variables were compared using Student's unpaired T-test and other variables were compared using Mann-Whitney u test. Statistical analysis was done using standard statistical software : Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001], SPSS Statistics version 17 [Illinois, Chicago: SPSS Inc., 2008],Graph Prism version 4 [San Diego, California: GraphPad Software Inc., 2005].

Results & Conclusion: Only 12% children in the dexmedetomidine group developed emergence agitation as compared to 57% in the control group. Agitation scores were significantly lower in dexmedetomidine group compared to control group (1.69±0.92 vs 2.7±1.1). Single dose dexmedetomidine was found to be effective in reducing emergence agitation after sevoflurane anaesthesia in paediatric patients.

Introduction:

Emergence agitation has been described as a state of nonpurposeful restlessness and inconsolability that is often accompanied by thrashing, screaming, prolonged crying and disorientation. Children exhibiting emergence agitation appear to be unaware of their surroundings and are unable to be consoled by parents and care-givers. Patients suffering from emergence agitation may harm themselves during periods of inconsolability and may **dislodge drains, intravenous catheters or other medical devices essential for their care [1].**

Sevoflurane is rapidly becoming the most popular inhalational anaesthetic in paediatric anaesthesia due to its rapid induction and rapid recovery profile. Further it is pleasant, nonpungent and nonirritant to airways. However quick recovery after sevoflurane has been associated with increased emergence agitation. Certain studies report the incidence of emergence agitation to be as high as 67%[2]. A number of analgesics and sedatives have been used to treat emergence delirium, but they usually prolong recovery and delay discharge[3].

Early reports suggest that dexmedetomidine, an alpha2 agonist, reduces emergence agitation[4]. Hence present study was designed primarily to find out the efficacy of single dose dexmedetomidine for attenuation of emergence agitation in Indian paediatric population. Secondary outcome measures include estimation of incidence of emergence agitation.

Review of Literature

Emergence agitation was reported as early as 1961 by Eckenhoff JE et al. They were the first to report the signs of hyperexcitation in patients emerging from ether, cyclopropane, or ketamine anesthesia, particularly when administered for tonsillectomy, thyroidectomy, and circumcision[8].

Welborn LG, Hannallah RS, Norden JM, et al. compared emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients and found the incidence of emergence delirium to be more with the newer insoluble anaesthetics than with halothane[7]. Their studies were supported with the findings by Davis PJ et al [9].

A study was conducted by Cravero J and his colleagues in the year 2000 comparing the incidence of emergence delirium after sevoflurane and halothane anaesthesia in patients undergoing bilateral myringotomy and grommet tube insertion. The study included 43 children who received either sevoflurane or halothane as sole anaesthetic agent.They did not receive any premedication and received rectal acetaminophen for postoperative pain control. They found the incidence of emergence agitation to be higher in the sevoflurane group-57% vs 27%.[12]

In a recent commentary on the diagnosis of delirium in pediatric patients, Martini addressed the role of brain maturation in the genesis of this phenomenon. He pointed out that the pediatric brain is almost a mirror image of a normal age-related regressive process with a consequent decline in norepinephrine, acetylcholine, dopamine and gamma amino butyric acid (GABA). The findings of Martini et al were published in J Am Acad Child Adolesc Psychiatry in 2005[20].

Several drugs have been used with variable success for the prevention and treatment of emergence agitation. Most notable amongst them are midazolam, fentanyl, ketamine , propofol ,alfentanil.,remifentanyl, clonidine and dexmedetomidine.

Tesoro S and his colleagues conducted their study in 169 children .They found clonidine in a dose of 2 mcg/kg to be effective in prevention of emergence agitation after sevoflurane anaesthesia [13].

Dexmedetomidine , a novel alpha 2 agonist , with sedative and analgesic properties was found to be effective in reducing emergence agitation after sevoflurane anaesthesia. Mauricio E Ibbacache et al conducted their study in 90 children posted for superficial lower abdominal and genital surgeries under sevoflurane anaesthesia. They concluded that dexmedetomidine in a dose of 0.3 mcg/kg significantly reduced sevoflurane induced emergence agitation in children with no adverse effects [4].

Manaa EM,Abdelhaleem AA,Mohamed EA compared the effects of fentanyl and dexmedetomidine in reducing emergence agitation after sevoflurane anaesthesia.They conducted their study in 60 children aged 3-6 years.They found fentanyl at a dose of 1 mcg/kg and dexmedetomidine in a dose of 0.3 mcg/kg to be equally effective in reducing the incidence of emergence agitation after sevoflurane anaesthesia [16].

Materials & Methods:

After approval of Institutional ethical committee this randomized, prospective, double blind study was carried out in Department of

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Anaesthesiology at a tertiary care hospital. All paediatric patients aged between 2 and 7 years, of ASA physical status I and II who were scheduled for elective infra-umbilical surgeries were included in the study. The exclusion criteria were lack of parental consent, known adverse effect to any of the drugs used in the study, mental retardation, developmental delay, known neurological or psychiatric illness (cerebral palsy, seizures etc), failure of caudal block (rise of heart rate or MAP >10% from pre-incisional values after giving surgical incision), patients with history of chronic or acute intake of sedative or analgesic drugs, patients with history of acute respiratory illness and bronchial asthma.

Written informed consent from the parents of all the patients was obtained before the study. Total of 84 children were included in the study. The children were randomly allocated into two groups using a random number table. Ten minutes before end of anaesthesia each child received one of the study solutions intravenously over a period of 10 minutes. Administration of the study solutions and collection of data were done by two independent anesthesiologists who were blinded of the study design.

Patients were also blinded to which drug they received.

None of the patients were given any solid food overnight, but each was encouraged to take clear fluids until 2 hours before induction of anaesthesia. All the patients were given premedication with oral midazolam at a dose of 0.5 mg /kg body weight

On arrival in the operation room, monitors were attached and baseline parameters were recorded. All patients were induced with sevoflurane 8% in 100% oxygen using transparent face mask and Jackson Rees modification of Ayer's T-piece breathing system. After loss of consciousness, intravenous cannulation was done and Ringer lactate solution was infused for perioperative fluid therapy.

When adequate depth of anaesthesia was reached, a laryngeal mask airway of appropriate size for the age and weight of the child was inserted and the patient was allowed to breathe spontaneously. Thereafter anaesthesia was maintained by sevoflurane with 60% N_2O in oxygen. Concentration of sevoflurane was adjusted to maintain adequate depth of anaesthesia which was assessed clinically as well as BIS monitoring.BIS levels were kept between 40 and 60. Analgesia was achieved by 0.75 ml kg^{-1} of 0.25% preservative free bupivacaine deposited in caudal epidural space. Normocapnia was maintained and End tidal carbon dioxide was kept at around 35±4 mm Hg.

Ten minutes before end of anaesthesia, children were randomly allocated into two groups to receive one of the study solutions intravenously over a period of 10 minutes.

Group S – Normal saline (10 ml)
Group D – Dexmedetomidine (0.5μg kg^{-1}) diluted in 10 ml normal saline.

All syringes with study drugs and placebo were prepared by the investigator. Administration of study drugs or placebo and intraoperative data collection was done by other two anaesthesiologists blinded to the study drugs.

At the end of the procedure anaesthetic gases were discontinued and patients were allowed to breathe oxygen having a fractional inspiratory concentration (F_i) 1.

LMA was removed when patient opened his eyes to verbal command. Gentle suctioning was done during removal of airway. Patient was transferred to recovery room for monitoring of vital signs. The duration of anaesthesia, surgery and emergence time (time from termination of anaesthesia to eye opening on command) were noted down. The quality of emergence was evaluated by using 4 point Watcha Scale [5].

Children who had a Watcha score of more than 2 were considered to have emergence agitation. They were treated with rescue fentanyl citrate at incremental doses of 0.3 μg. $kg.^{-1}$. The total amount of rescue drug required in both the groups was noted. In the post-anaesthetic care unit parents were allowed to stay with child. One anaesthesiologist blinded to patients group stayed with the patient and recorded vital parameters, Watcha score[5], Modified Aldrete score[6], Hanallalah Objective Scale[7] every 10 minutes until discharge to ward (Modified Aldrete score 9). Time required for the need of rescue analgesic was noted.

Analysis-- The sample size was taken to be 42 per group. A reduction of 30% in the incidence of emergence agitation was considered to be statistically significant. The confidence level was assumed to be 95% with 5% probability of Type I error.

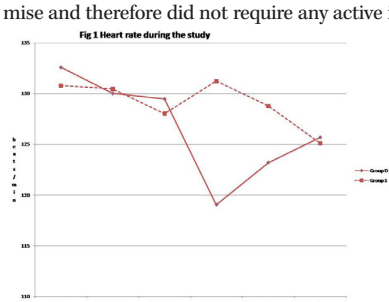
Statistical Analysis:
The numerical variables were compared using Student's unpaired t-test and other variables were compared using Mann – Whitney 'u' test. Statistical Analysis was done with standard statistical softwares: Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001], SPSS Statistics version 17 [Illinois, Chicago: SPSS Inc., 2008], Graph Prism version 4 [San Diego, California: GraphPad Software Inc., 2005]. A p value of <0.05 was considered significant.

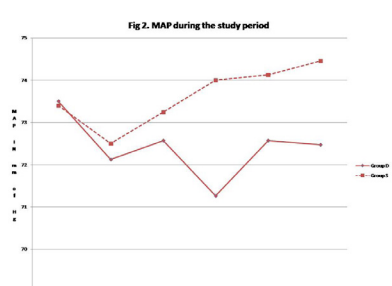
Results:
The children in both the groups were comparable in terms of their age, sex distribution, weight, type of surgery and duration of surgery. (Table I)

Table I- Comparison of demographic parameters between two groups

Parameters	Group D	Group S	P value
Age (years)	4.9±1.2	4.02±1.7	P>0.05
Weight (kg)	16.85±6.0	16.05±6.03	P>0.05
Duration of surgery (in minutes)	44.14±16.61	38.81±17.45	P>0.05

Fall in heart rate was observed after infusion of dexmedetomidine. However, it was not associated with any haemodynamic compromise and therefore did not require any active intervention (Fig 1, 2).





The time of emergence was taken as the time from discontinuation of anaesthesia to the time the when the child opened eyes on command. It was significantly more dexmedetomodine group (Table II).

Table II: Time of emergence (in minutes)

Group	Mean	Standard deviation	95% interval Confidence		Minimum time taken for emergence after discontinuation of anaesthesia (in min)	Maximum time for emergence after discontinuation of anaesthesia (in min)	P Value
			Upper limit	Lower limit			
Gr D	5.48	1.58	4.98	5.97	10	3	P<0.05
Gr S	3.05	1.01	2.73	3.37	5	1	

Incidence of emergence agitation in group S was found to be 57% while in group D it was only 12%. The children in dexmedetomidine group had uniformly low Watcha scores which meant that the children in this group were calmer all throughout the period of observation. In the initial 10 minutes after emergence, the patients in group S had very high emergence agitation scores. Rescue fenatanyl citrate was administered at dose of 0.3μkg^{-1} if the children had Watcha score>2. Incremental doses of 0.3μkg^{-1} were repeated every 10 minutes if the children continued to be agitated with Watcha score more than 2, up to a maximum dose of 1.8 μkg-^{1} over 60 minutes (Table III).

Table III: Comparison of Watcha Scores (Postoperative emergence)

Post operative period	Group D [Mean±S.D]	Group S [Mean± S.D]	P Value
10 minutes	1.69±0.92	2.7±1.1	P<0.05
20 minutes	1.69±0.60	1.98±0.69	P>0.05
30 minutes	1.67±0.48	1.64±0.48	P>0.05
40 minutes	1.55±0.50	1.69±0.56	P>0.05
50 minutes	1.57±0.50	1.67±0.58	P>0.05
60 minutes	1.55±0.50	1.69±0.52	P>0.05

More than 50% patients developed emergence agitation and required rescue fentanyl citrate in control group. Requirement of fentanyl was as high as 1.5 μg kg-1 in 10% of patients (Table IV).

Table IV: Incidence of Emergence Agitation and Requirement of rescue fentanyl citrate

	Group D	Group S
Watcha score> 2	5/42 (12%)	24/42 (57%)
Fentanyl citrate dose		
0.3 mcg/kg	3 (7%)	6 (14%)
0.6 mcg/kg	2 (5%)	9 (21%)
0.9 mcg/kg		5 (12%)
1.2 mcg/kg		
1.5 mcg/kg		4 (10%)

Although, 57% patients required fentanyl citrate during postoperative period for treatment of emergence agitation, pain was significantly more in control group (Table V).

Table V: Postoperative Pain Scores

Post operative period	Group D Mean±S.D	Group S Mean± S.D	P Value
0 minutes	2.62±1.45	4.55±1.37	P<0.05
30 minutes	2.31±0.95	3.48±1.08	P<0.05
60 minutes	2.02±0.56	2.62±1.29	P<0.05

The criteria for discharge from PACU were decided using modified Aldrete score. A score of more than 9 was considered sufficient for discharge. We have found that this score was reached by a period of 40 minutes in both the groups (Table VI).

Table VI: Discharge from PACU (Modified Aldrete Score)

	Group D	Group S	P Value
10 minutes	7.57±0.91	7.71±0.81	P>0.05
20 minutes	8.26±1.01	8.33±0.57	P>0.05
30 minutes	8.83±0.88	8.86±0.35	P>0.05
40 minutes	9.23±0.66	9.05±0.38	P>0.05
50 minutes	9.45±0.55	9.43±0.50	P>0.05
60 minutes	9.55±0.55	9.59±0.49	P>0.05

Discussion:

Emergence agitation is distressing phenomenons for the children experience it, for the nursing personnel taking care of these patients and also for the parents witnessing it. Efforts to control emergence agitation have been hampered by the confusion regarding its exact definition and underlying causative factors. This makes it difficult to draw valid conclusions from the various clinical studies done on this subject.

Despite much work related to emergence delirium in paediatric anaesthesia, its exact cause remains obscure. Many factors related to anaesthesia, surgery, the patient and adjunct medication have been suggested. They include rapid emergence from anaesthesia, intrinsic property of the anaesthetic, type of surgery, age of the patient, preoperative anxiety, child temperament, postoperative pain and use of any adjunct medication.[8]

Meta analysis of 23 randomized control trials revealed that emergence agitation was more common with sevoflurane than halothane.[9] Rapid recovery after sevoflurane anaesthesia was considered as a cause of higher incidence of emergence anaesthesia. However, propofol, another agent with rapid recovery property does not increase emergence agitation. Infact propofol has been used to reduce emergence agitation.[10, 11] Hence rapid recovery cannot be the only cause of emergence agitation.

Pain is a major contributor for agitation after emergence from anaesthesia. Therefore all the patients included in this study population received a successful caudal block, to provide adequate pain relief during immediate post operative period. Inspite of that pain score was consistently high in control group compared to dexmedetomidine group. Propable reason may be the type of pain scale used for assessment of severity of pain. The objective pain scale, commonest pain scale used in preschool children is based on changes in systolic blood pressure, crying, movement, agitation and complaints of pain. This scale has got certain criteria commonly seen in agitated child. Therefore, in spite of optimum pain relief, pain score remained high in control group due to overlapping criteria in Hanallah objective pain scale[7] and Watcha scale[5].

The time required for emergence from anaesthesia was significantly longer in dexmedetomidine group compared to control group. This is consistent with previous study[16]. The statistically significant difference between the two groups is of small magnitude and is not clinically significant. The delayed emergence from anaesthesia did not delay discharge from PACU.

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Dexmedetomidine produces dose dependent fall in heart rate and blood pressure.[17, 18] However, Ibacache ME et al[4] and Guler G et al[19] reported no haemodynamic effects at a 0.3-0.5 μg kg^{-1} bolus dose. Present study had used 0.5 μg kg^{-1} dexmedetomidine as slow infusion and observed statistically significant bradycardia. However, this bradycardia was clinically insignificant and did not cause haemodynamic instability. The drop in mean arterial pressure was never more than 30% from the baseline values.

Limitations

Few randomized controlled studies have been conducted in Indian children regarding efficacy of dexmedetomidine in reducing emergence agitation after sevoflurane anesthesia and present study has shown significant results in this regard. The cause for the increased incidence of emergence agitation in indian as compared to western countries needs to be investigated.

However small sample size and single centre design are its limitations.

Further larger multicentre randomized controlled trials are necessary to recommend use of dexmedetomidine routinely for reducing emergence agitation after sevoflurane anesthesia.

Conclusion:

This study shows that administration of single dose dexmedetomidine before end of anaesthesia was effective in reducing incidence of emergence agitation after sevoflurane anaesthesia. Administration of dexmedetomidine led to calmer children, with less pain scores without prolonging the duration of stay and without significant adverse effects. Of special note was that the incidence of emergence agitation after sevoflurane anaesthesia is quite high (57%) in Indian paediatric population.

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