Original Article

ORAL ATROPINE PREMEDICATION IN INFANTS ATTENUATES CARDIOVASCULAR DEPRESSION DURING HALOTHANE ANAESTHESIA

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ABSTRACT

Objectives: To evaluate the effect of oral atropine premedication in infants attenuates cardiovascular depression during halothane anaesthesia.

Methodology: **Design and setting**: Tertiary care teaching hospital. **Subjects**: A double blind study was conducted on 60 patients of paediatric age group of ASA Grade I were divided into Group A(4-9 months) & Group B(10-15 months). Patients of both the groups were randomly placed into premedication subgroups: subgroup I (Placebo), subgroup II (Lo Dose, 0.02mg/kg), subgroup III (Hi Dose, 0.04mg/kg) with 10 patients in each group.

Results: Oral atropine given one hour before the induction of anaesthesia in the doses of 0.02mg/kg and 0.04mg/kg is effective in attenuating cardiovascular depression caused by halothane which is the most commonly used inhalational anaesthetic agent in paediatric patients.

Conclusion:Oral atropine given one hour before the induction of anaesthesia was effective in attenuating cardiovascular depression caused by halothane which was the most commonly used inhalational anaesthetic agent in paediatric patients.

Key words: Oral atropine, Premedication, Halothane Anaesthesia, Cardiovascular depression.

INTRODUCTION

The exposure of the strange and the unfamiliar environment of operation theatre is invariably a rare experience in ones life and that too under some compulsion caused by some ailment. Where as adult patients can be psychologically prepared by reassurance and drug supplements, the paediatric patients refuse outrightly to accept any explanation. Children imagine and feel the pain of injection, distress of black anaesthesia, face masks & operation in their own way. The drugs play a major role to cause dullness of senses so that the child's reaction is both acceptable and manageable. A promise, nor mere assurance, that patient will get a sweet syrup rather than a painful prick may be of help. Thus the development of a reliable premedicant is desirable. In addition to quitening the patient, there are few other aims which should be achieved while selecting a premedicant. These are production of amnesia, soothening and facilitation of induction, maintenance & recovery from anaesthesia, reduction of secretions in oral cavity and respiratory tract, supression of undesirable autonomic reflexes and prevention of post-op vomiting, which has contributed to mortality caused by pulmonary aspiration

The drugs commonly used prior to anaesthesia are opiates, benzodiazepines, atropine and phenothiazines. Phenothiazines use is associated with salivary suppression, antiemesis and amnesia but it caused muscle tremors, restlessness, post-op pallor and delayed recovery from anaesthesia. Incidence of restlessness & dizziness is more with benzodiazipines but advantage is that it does not delay the recovery and is often followed by a period of amnesia and provides post-op comfort. Belladona alkaloids have been used in anaesthesia for many centuries. Out of these, atropine is most widely used. Though belladona drugs can be used orally, the oral use of atropine is not much in vogue. It is usually

admitted by s.c, i.m, i.v routes, though it is completely absorbed from gatrointestinal tract (small intestine). The gastrointestinal absorption of atropine has also been studied [2] and observed that atropine sulphate is completely ionised upto pH of 7.5 & poorly lipid soluble, High alkalanity of duodenum and small intestine favour rapid absorption. Oral atropine has been used as premedication in children and found to be as effective as atropine given parenterally. [7,12]

Inhalation of halothane, N_2O, and O_2 is the most common method of inducing GA in paediatric patients, but incidence of bradycardia and myocardial depression is almost a consistent finding in dose related fashion. Because the ventricles of young infant's heart are not so compliant and the cardiac output is highly dependent on H.R. Blood pressure depends on both C.O. & S.V.R. Infants require increased alveolar concentration of halothane to block the response to a surgical stimulus; thus more prone to cardiovascular depression effects of halothane. Keeping all these points in mind, we need to have a premedicant that can attenuate this cardiovascular depression during halothane anaesthesia. Atropine administration supports cardiac output by increasing H.R. and supports B.P. by maintaining cardiac output. Its antisialagogue and antiemetic actions help in reducing the secretions of saliva & mucous from respiratory tract & prevent post-op nausea & vomiting, thus allowing smooth induction, maintenance & recovery from anaesthesia.

MATERIAL AND METHODS

A double blind study was conducted in 60 ASA grade I paediatric patients, undergoing elective surgery & who had been fasting for minimum of 4 hours. Patients were divided into 2 groups depending upon their ages as Group A (4 to 9 months) & Group B (10 to 15 months). Patients of both these groups were randomly placed into premedication subgroups: subgroup I (Placebo), subgroup II (Lo Dose, 0.02mg/kg), subgroup III (Hi Dose, 0.04mg/kg) with 10 patients in each group.

No other sedative premedication was administered. As it was a double blind study, it was desirable to administer same volume of syrup with varying concentration of atropine to all the 3 groups.

Before administering premedication, baseline measurements of heart rate, systolic B.P. and mean arterial pressure were done . Serial measurements of heart rate, systolic B.P. & mean arterial pressure were recorded at 5 minute interval from premedication to transport of patient to operating room. Measurements during this time were used to determine the onset of action of oral atropine which was defined as the time from premedication until the development of sustained heart rate 15% above the baseline. In O.T. this noninvasive monitoring was continued and preinduction levels of heart rate, SBP & MAP were recorded. Further measurements were made at 1 min interval starting immediately before the induction of anaesthesia and continued until the onset of surgical stimulation.

Induction of anaesthesia was done using Halothane in increasing inspired conc. Upto 3% in the mixture of 60% N_2O + 40% O_2 at a flow rate of 5ml/ min using a Jackson Rees circuit with assisted ventilation. Immediately after induction, I.V catheter was inserted and 10ml/kg body weight of isolyte p was infused. Tracheal intubation was performed under deep Halothane anaesthesia (3% Halothane). After intubation the inspired concentration of Halothane was decreased to 1.5 to 2% & maintained . I.V Atropine was administered when required between induction and surgical stimulation if SBP decreased 50% below preinduction level. Onset of time of action was noted. Lowest values of H.R, SBP & MAP obtained during induction were determined. Antisialagogue effects were observed & graded as: Dry - Grade 2, Moist - Grade 1 and Wet - Grade 0.

These were recorded at the end of study and subjected to statistical analysis. Side effects like flushing, irritability and increase in body temperature were observed post-op in the recovery room.

STATISTICAL ANALYSIS: After conducting the study, the collected data was analysed by analysis of variance (ANOVA), in the 3 medication groups.

Inter group comparisons were made using Scheffe F test. The placebo groups in 2 age ranges were compared with each other using a two-tailed unpaired student t-test to evaluate the effects of Halothane anaesthesia on SBP. Chi-squire analysis was used to compare the incidence of heart rate less than 100 beats/min and SBP decrease of more than 50% in the oral atropine groups(high and low dose) versus placebo groups. Statistical significance was assumed when $p < 0.05$.

Group	Sub group	Mean ± S.D.	Mean Difference	S.E	t	p value
GROUP A (4-9 Mths.) GROUP B (10-15 Mths.)	I Placebo I Placebo	---- ----	---- ----	---- ----	---- ----	---- ----
GROUP A GROUP B	II Low Dose 0.2mg/kg II Low Dose 0.2mg/kg	39.50 ± 9.55 38.0 ± 6.74	1.5	3.69	0.40	>0.05 N.S.
Group A Group B	III Hi Dose0.4mg/kg III Hi Dose0.4mg/kg	36.50 ± 4.55 37.50 ± 3.75	1.0	1.28	0.78	>0.05 N.S.

Onset of action of atropine in min in all the groups (Table no. 1)

There was no increase in H.R. in placebo groups of group A & B whereas in low group of group A the mean onset of action was 39.5± 9.55 min & that in Group B was 38.0± 6.74 min. In high dose of group A it was 36.5± 4.55 min & in group B it was 37.5± 3.75 min. So both low & high dose of oral atropine have same onset of action irrespective of age & weight of patient as the difference in readings of low & high dose was statistically insignificant.

Group A						Group B					
Sub Group	No. of cases	Mean± S.D.	S.E	t	p value	Sub Group	No. of cases	Mean ± S.D.	S.E	T	p Value
I Placebo	10	124.70 ±11.24	I & II 6.65	1.90	>0.05 N.S.	I Placebo	10	128.0 ± 13.09	I & II 5.32	1.07	>0.5 N.S.
II Lo dose	10	137.40 ±17.81	I & III 4.97	3.42	<0.01 H.S.	II Lo dose	10	133.70 ± 10.61	I & III 6.36	1.02	>0.05 N.S.
III Hi dose	10	141.70 ±11.01	II & III 6.57	0.65	>0.05 N.S.	III Hi dose	10	134.50 ± 15.29	II & III 5.89	0.11	>0.1 N.S.

H.R. at the time of induction in Group A & Group B (Table no. 2) Heart rate(H.R.):-

Mean HR in subgroup I, II and III of group A was 124.70 ± 11.24,137.40 ± 17.81 and 141.70±11 respectively. It was non significant in subgroup I and III and highly significant in subgroup II.

Mean HR in subgroup I, II and III of group B was 128 ± 13.09,133.70±10.61 and 134.50±15.29 respectively. It was non significant in all the subgroup I ,II and III.

Group A						Group B					
Sub Group	No. of cases	Mean ± S.D.	S.E	T	P value	Sub Group	No. of cases	Mean ± S.D.	S.E	T	P Value
I placebo	10	53.0 ±2.82	I & II 3.18	1.22	>0.5 N.S.	I placebo	10	62.50 ± 4.83	I & II 2.36	1.00	>0.1 N.S.
II Lo dose	10	56.90 ± 9.66	I & III 1.81	8.10	<0.001 H.S.	II Lo dose	10	60.10 ± 5.72	I & III 2.15	0.13	>0.05 N.S.
III Hi dose	10	61.10 ± 4.99	II & III 3.43	4.20	>0.5 N.S.	III Hi dose	10	62.20 ± 4.83	II & III 2.36	0.88	>0.05 N.S.

Mean arterial pressure(MAP) in both Group A & Group B (Table no. 3)

MAP in subgroup I, II and III of group A was 53 ± 2.82,56.90±9.66 and 61.10±4.99 respectively.It was non significant in subgroup I and III and highly significant in subgroup II.

MAP in subgroup I, II and III of group B was 62.50 ± 4.83, 60.10±5.72 and 62.20±4.83. respectively. It was non significant in all the subgroup I , II and III.

Group A						Group B					
Sub Group	Mean ± S.D.	Mean difference	S.E	T	P value	Sub Group	Mean ± S.D.	Mean difference	S.E	t	P Value
I placebo	0.33 ± 0.70	--	--	--	--	I placebo	0.20 ± 0.42	--	--	--	--
II Lo dose	1.30 ± 0.48	0.97	I & II 0.26	3.73	<0.001 H.S.	II Lo dose	1.30 ± 0.48	1.10	I & II 0.20	5.50	<0.001 H.S.
III Hi dose	1.80 ±0.42	1.37	I & III 0.26	5.26	<0.0001 H.S.	III Hi dose	1.50 ± 0.52		I & III 0.18	7.22	<0.001 H.S.
		0.50	II & III 0.19	2.63	<0.002 H.S.			0.10	II & III 0.22	0.90	>0.05 N.S.

RESULTS

The data collected in both Group A (4-9) & Group B (10-15) were subjected to statistical analysis & following results were obtained.

Onset of action of oral atropine: (Table no. 1) It was seen that the low & high dose of oral atropine has same time of onset of action irrespective of age & weight of the patient as the difference in the readings of low & high dose groups was statistically insignificant (p > 0.05).

Heart rate (H.R.): (Table no. 2) The lower H.R. at the time of induction in placebo group was much more as compared to low & high dose groups of both Group A & Group B. H.R. depression was much more in non atropinised children than the ones who had received low & high doses of atropine in both Group A & Group B. Low & high dose groups comparison did not show any significant result in both age groups. Lowest H.R. values were attained early in placebo groups of Group A and B as compared to their Lo & Hi dose groups.

Mean Arterial Pressure(MAP): (Table no. 3) In Group A, the comparison between the A- placebo & low dose group shows non significant results , comparasion between high & placebo groups shows highly significant results but when low & high dose groups were compared, insignificant results were obtained, suggesting that both doses of oral atropine prevented the fall in MAP. The depression of MAP was found to be greater in non atropinised children. In Group B, the results in all 3 subgroups were statistically insignificant ($p > 0.05$) showing that the fall in MAP in atropinised children was same as non atropinised ones and oral atropine did not prevent fall of MAP in this age group of children (10-15 months).

Arrythmia and atropine: Authors like Eikard and Jens Rikardt Anderson[5] believed that atropine did not protect the heart against signs of vagal activity, whereas Middleton et al [1] and Ryder et al [13] and Kessel [8] did not find any arrhythmic or anti arrhythmic effect of the drug wheras Thurlow et al [15] have found an increased incidence of arrhythmias after atropine administration. However, in the present study no such arrhythmias were observed after oral administration of atropine.

Antisialogogue effect: (Table no. 4) Highly significant decrease of secretions was observed in group A (4-9months) low & high dose groups with p value < 0.001 and 0.0001 respectively. When compared with placebo group, high dose showed better results than low dose ($p < 0.002$). In Group B, the reduction in secretions was highly significant with both low and high dose. Though it was observed that high dose group had better results than low dose groups, but when subjected to statistical analysis, the results were insignificant ($p > 0.05$).

DISCUSSION

In the above conducted study, the findings revealed are being discussed as under:-

(A) **Onset of action:** (Table no. 1) It was observed that the onset of action when compared between A-Lo, B- Lo & A- Hi, B- Hi was statistically insignificant. Since the age & the weight of both groups were different but the onset of action was similar in both Hi dose & Lo dose subgroups thereby suggesting that onset of action of oral atropine was not influenced by these factors. Findings of this study was however not comparable with those of Blain, R. Miller and Robert H Freisen[3] who revealed the onset of action time to be more in Hi group and less in Lo dose group. Since this study included neonates the difference in time of onset of action of oral atropine could be due to the fact that emptying time of stomach is less and the drug reaches the duodenum earlier for absorption.

(B) **Effect on heart rate:** (Table no. 2) The study revealed a statistically significant decrease in heart rates in Group A as well as Group B patients at the time of induction with Halothane. The depression of heart rate was more in A-P group as compared to A-Lo & A-Hi. Similar results were seen in Group B. It was also observed that in Group A the time taken to reach the lowest heart rate at the time of induction was more in atropinised children than the A-P Group suggesting that bradycardia occurred much early in unatropinised children of Group A. In Group B also similar findings were observed suggesting that the time taken to reach the lowest heart rate was less in unatropinised children as compared to the atropinised ones. These findings support the study conducted by Meistelman C, Payen D and Lepaul M. The conducted study supports the findings of Blain, R. Miller and Robert H Freisen [3] who conducted a study in infants regarding the efficacy of oral atropine premedication in attenuating cardiovascular depression using halothane anaesthesia and observed that halothane produced bradycardia in dose related fashion and this bradycardia could be attenuated by oral administration of atropine in doses of 0.02 mg/kg (Lo dose) and 0.04 mg/kg (Hi dose). Mahaffey and his group [9],

Flacke and Alper [6] noted that atropine was capable of reversing bradycardia seen during deep halothane anaesthesia, thus supporting the observations of presently conducted study. The study conducted by Richard S Cartabuke, MD, Patricia J Davidson MD and Louise O Warner MD also demonstrated that premedication with oral atropine in the doses of 0.02mg/kg attenuated the bradycardia associated with halothane anaesthesia in infants and young children. This incidence of bradycardia was more in unatropinised patients.

(C). **Effect on Mean arterial pressure:**(Table no. 3) The difference in the fall of blood pressure was statistically highly significant ($p<0.01$) which suggested more severe hypotension in younger age group children. Fall in the systolic blood pressure to reach the lowest reading was more in A-P Group as compared to A-Lo & A- Hi. In Group B the fall in blood pressure in B-P was similar to fall in systolic blood pressure in B-Lo & B-Hi subgroups that suggesting that younger children are more sensitive to halothane which could be due to several age related predisposing factors like :Greater anaesthetic requirement,[4,11] Diminished baroreceptor response,[16] and Greater alveolar uptake of inhalational anaesthetics, in smaller children.[14]

Present study revealed that cardiovascular depressant effects of halothane was age related. At the same inspired concentration of halothane, infants of 4-9 months of age experienced greater decrease in MAP than did infants of 10-15 months of age. This study also suggested that less hypotension is produced in the infants who had received oral atropine either in Lo or Hi dose & more severe hypotension occurs in the non atropinised children. Atropine in both the doses was effective in preventing the in blood pressure in group A and also the time taken to reach the lowest values of systolic blood pressure was less in non atropinised patients as compred to the atropinised ones. Oral atropine premedication did not significantly attenuate the hypotension caused by halothane in group B (10-15months) patients as the percentage decrease in MAP in all the 3 groups i.e. B-P, B-Lo & B-Hi was similar. This was expected because most vascular beds lack cholinergic innervations & cholinergic sympathetic vasodilating fibers to the vessels supplying skeletal muscles. Hence blood pressure was not affected [1]. It could also be attributable to the barorecepter response to hypotension which was depressed in young infants as compared to older children. These observations of present study was similar to the one conducted by Miller and Freison. [3]

(D) **Antisialagogue effects of oral atropine:** (Table no. 4) The reduction of secretions in oral cavity were observed at the time of laryngoscopy which was done 60 mins after the oral atropine administration. The results were highly significant statistically when compared with placebo but insignificant when Lo and Hi were compared among themselves. These observations suggested that both doses of oral atropine was effective in drying the secretions of upper respiratory tract, in both Group A & Group B children. The results of this study are supported by the findings of Blain R Miller [3] who observed that high dose of oral atropine was more effective antisialagogue than low dose, but low dose was definitely better than placebo.

(E) **Effects on body temperature**: Atropine produces an increase in body temperature by inhibiting the activity of sweat glands. It may also exert a central effect on temperature regulation. As the study was conducted in air conditioned operation theatre, no clinical and statistically significant increase in body temperature was observed in any of the cases.

CONCLUSION

Oral atropine given one hour before the induction of anaesthesia in the doses of 0.02mg/kg and 0.04mg/kg was effective in attenuating cardiovascular depression caused by halothane which is the most commonly used inhalational anaesthetic agent in paediatric patients.

It preserved the heart rate in both younger and older children & prevented bradycardia which was invariably associated with halothane induction.

Atropine prevented the fall of blood pressure in younger children. In older children, the fall in blood pressure was not completely prevented in either dose of oral atropine.

Increasing the dose of oral atropine did not provide any additional protection against cardiovascular depressants effects.

Significant antisialagogue effect was observed and no major complication occurred.

Syrup is palatable, easily accepted by a child patient and is the only humane way to premedicate them. It is easily prepared and without any side effects.

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