Original article:

Comparison of Drug Clonidine and Midazolam as Premedication's in Children: An Institutional Based Study

Dr. Gurdeep Singh Jheetay

Associate Professor, Department of Anaesthesia, Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun, Uttarakhand, India.

Corresponding Author: Dr. Gurdeep Singh Jheetay, Associate Professor, Department of Anaesthesia, Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun, Uttarakhand, India.

Abstract:

Introduction: Premedication plays an essential role in general anesthesia. The most stressful procedure that children experience during the peri-operative period is an induction of anesthesia.Many negativebehaviours have been associated with anesthesia induction during and after the surgical experience, like post-operative pain, sleep disturbances, parent-child conflict and separation anxiety.The primary aim of the study was to compare the efficacy of oral clonidine with oral midazolam as a premedication in children. The secondary aim was to assess the effects of premedication with regards to the drug acceptance, pre-operative sedation, and anxiolysis, to compare the ease of separation from the parents, acceptance of face mask at induction, an effect on the hemodynamics and postoperative recovery profile.

Material and Methods: 100 children who were aged between 2-8 years, and were listed for surgery under general anaesthesia, were randomly assigned to receive either oral clonidine 4 mcg/kg (Group I, n = 50) or oral midazolam 0.5 mg/kg (Group II, n = 50), 60 minutes earlier to the anaesthesia induction. The minimum time interval which was necessary for the child to become drowsy or asleep is called as the onset of the sedation. Anxiety was evaluated by a 4-point scale: 1 = crying, very anxious, 2 = anxious, not crying, 3 = calm, but not cooperative and 4 = calm, cooperative or asleep.

Results: Onset of sedation was faster in group II 31.6 ± 13.26 (15-60) minutes compare to group I 39.8 ± 11.44 (15-60) minutes. The p value was <0.05, which was statistically significant. Nevertheless, group I ($p<0.05$) showed significantly better level of sedation compare to group II children. A sedation score of ≥ 2 was achieved in all children of both groups. There was no statistically significant ($p>0.05$) difference in sedation score of both group.

Conclusions: Findings of the current study suggest that oral use of drug clonidine can be a more effective alternative for children in comparison of oral use of drug midazolam. Although satisfactory level of sedation is achieved with both drugs; nonetheless, use of oral clonidine leads to a better sedation, anxiolytic and improved quality of induction compare to use of oral midazolam. Moreover, post-operative shivering is not found with the use of drug clonidine. However, studies on larger populations are warranted to prove clonidine as better drug compare to midazolam.

Key words: Paediatric Anaesthesia, Clonidine, Midazolam, Premedication.

Introduction

Premedication plays an essential role in general anesthesia. The most stressful procedure that children experience during the peri-operative period is an induction of anesthesia.Many negativebehaviour's have been associated with anesthesia induction during and after the surgical experience, like post-operative pain, sleep disturbances, parent-child conflict and separation anxiety.[1] It also stimulates the human stress response which led to elevated level of serum cortisol and epinephrine and natural killer cell activity.[2] Due to the inadequate energy of the reserves, large brain masses and the obligatory glucose requirements Children are particularly susceptible to the global surgical stress response.[3]

Numerous approaches whether pharmacological (e.g., sedatives) or non-pharmacological (e.g. parental presence, behavioral preparation programs, music, acupuncture, etc) have been proved to be useful for reducing the incidence of pre-operative anxiety in children. Children accept oral medication better than another route of administration. They are given to soothe anxiety, to produce amnesia, sedation, analgesia, to facilitate smooth induction and to decrease secretion. Amnestic, hypnotic and skeletal muscle relaxant effects are produced by Midazolam which is a benzodiazepine and can be given through the intranasal, sublingual, rectal and the oral routes. The rapid onset and short half-life of midazolam is the pharmacological agent of choice for pre-operative anxiety in day care surgery. Even though midazolam is an effective agent in alleviating anxiety in children, it is not without its own disadvantages. In some examinations, its use has been related to a delay in either the discharge of the patients from the hospital or in the recovery time. Maladaptive behavioral changes were seen in several children, after the premedication with midazolam.[1] In the context of pediatric premedication A number of drugs, are preferable other than midazolam.[4]

Clonidine is a centrally acting α-2 agonist commonly known as an antihypertensive drug having significant sedative and analgesic, hypnotic properties for which it is used in anesthesia. In 1993 it was first introduced as a pediatric premedicant and although it is less popular than midazolam, its use has been continually increasing Its main site of action is on the upper brainstem in the floor of the fourth ventricle (locus ceruleus).[2] It has been shown that oral clonidine acts as an analgesic, it decreases the volatile anesthetic agent requirement and effectively produces pre-operative sedation and anxiolysis in children, it and also improves the peri-operative hemodynamic stability. Clonidine can be given by mouth (4 mcg/kg) and intranasally (2 mcg/kg).[5]

The primary aim of the study was to compare the efficacy of oral clonidine with oral midazolam as a premedication in children. The secondary aim was to assess the effects of premedication with regards to the drug acceptance, pre-operative sedation, and anxiolysis, to compare the ease of separation from the parents, acceptance of face mask at induction, an effect on the hemodynamics and postoperative recovery profile. The side effects if any were noted.

MATERIALS AND METHODS

After obtaining local ethical committee approval and patient's parent written informed consent, a pre-anaesthetic check up was done which included taking a detailed history and a thorough general physical examination of the patients. All these examinations were carried out a day prior to surgery.

100 children who were aged between 2-8 years, and were listed for surgery under general anaesthesia, were randomly assigned to receive either oral clonidine 4 mcg/kg[6] (Group I, n = 50) or oral midazolam 0.5 mg/kg[7] (Group II, n = 50), 60 minutes earlier to the anaesthesia induction. In the honey and a water solution, by dissolving the respective tablets both the drugs were given. In a solution of 2ml of honey and 3ml of water the tablet was dissolved and then this mixture was filled in a 5 ml syringe and the drug solution was then given to the child according to the calculated dose. The drug acceptance by the children was noted. With respect to their tastes on a three-point scale: 1 = good, 2 = indifferent and 3 = bitter and unpleasant. At the time of administration of the premedication the heart rate, blood pressure, respiratory rate, oxygen saturation and the sedation and anxiety levels were noted and then they were monitored continuously. After every 15 minutes for up to 60 minutes, the readings were recorded. The minimum time interval which was necessary for the child to become drowsy or asleep is called as the onset of the sedation. Assesment of the level of sedation was done by using a 3-point scale: 1 = awake, 2 = drowsy, and3 = asleep. A sedation score of more than2 was considered as

www.ijbamr.com P ISSN: 2250-284X E ISSN: 2250-2858

satisfactory. Anxiety was evaluated by a 4-point scale: 1 = crying, very anxious, 2 = anxious, not crying, 3 = calm, but not cooperative and 4 = calm, cooperative or asleep. The anxiolysis score of more than3 was considered as satisfactory. The minimum time interval necessary to achieve a satisfactory anxiolysis was called as the onset of anxiolysis. Any inconvenient side effect like apnoea, hypoxaemia, bradycardia, hypotension and any other if present, was looked for.

The children were transferred to the induction room when a sedation score of 2 or 3 was reached. The children were excluded from further studies if no satisfactory sedation level was achieved.

The parting of the children from their parents was assessed on a three-point scale: 1 = Poor: Anxious or aggressive, 2 = Good: Anxious but easily assured and 3 = Excellent: Calm/Sleeping. A steal induction was attempted in case If the children came to the induction room while they were already asleep. To facilitate venous cannulation all the children received halothane, nitrous oxide and oxygen via a mask. Immediately the mask acceptance and the quality of the induction was assessed on a 5-point scale: 1 = combative, crying, 2 = moderate fear of the mask, not easily calmed, 3 = cooperative with reassurance, 4 = calm, cooperative and 5 = asleep, steal induction. A successful response to the premedication was said to be achieved when a mask induction score of 3–5 was recorded. An intravenous line was secured and with Isolyte P an intravenous infusion was started.

All the children were given intravenous atropine 0.02 mg/kg body weight. Anaesthesia was induced by giving propofol 2 mg/kg body weight intravenously, plus 60% nitrous oxide and 40% oxygen with incremental halothane administration from the start of 0.5% induction up to 3%, depending on the necessity. Vecuronium 0.1 mg/kg body weight which is a muscle relaxant was used to facilitate endotracheal intubation. later than the effect of vecuronium wore off, the neuromuscular blockade was the add-on with vecuronium 0.08 mg/kg body weight intravenously and the IPPV was sustained with 0.5% halothane and 60% nitrous oxide in 40% oxygen. Intra-operatively no opioids or any other tranquillizer were administered. An entire lot of patients received rectal acetaminophen for postoperative analgesia. Halothane was discontinued and nitrous oxide was switched off at the end. The neuromuscular blockade was reversed with glycopyrrolate 0.01mg/kg and neostigmine 0.04 mg/kg body weight intravenously. The tube was removed from children after satisfactory neuromuscular recovery and when they made purposeful movements and had normal respiratory patterns. During the peri-operative period, a record was maintained of all the adverse effects including hypotension, bradycardia, respiratory depression, nausea/vomiting and shivering.

RESULTS

Table 1 show that there was no significant difference between basic parameters of both groups. Fig 1 shows that tolerance for the medicine in group I.

It is evident from figure 1 that tolerance for test of clonidine ($p<0.05$) was significantly high in children compare to midazolam.

Table 2 shows that onset of sedation was faster in group II 31.6 ± 13.26 (15-60) minutes compare to group I 39.8 ± 11.44 (15-60) minutes. The p value was <0.05, which was statistically significant. Nevertheless, group I ($p<0.05$) showed significantly better level of sedation compare to group II children.

A sedation score of ≥ 2 was achieved in all children of both groups. There was no statistically significant ($p>0.05$) difference in sedation score of both group. There was an insignificant difference in onset of anxiety for

www.ijbamr.com P ISSN: 2250-284X E ISSN: 2250-2858

both groups. Nonetheless, pre-operative anxiolysis was qualitatively better in group I ($p<0.05$) compare to group II. (Table 3)

Clonidine group ($p<0.05$) shows significantly better acceptance of mask and quality of the induction compare to midazolam group. Steal induction was performed in 52% of Clonidine group ($p<0.05$) compare to no child of midazolam group. However, quality of induction was satisfactory for both groups and there was a statistically insignificant difference in both groups ($p>0.05$). (Fig 2)

No adverse effects like bradycardia, hypotension, hypoxaemia or apnoea were observed during any of the pre-operative, intra-operative or the post-operative periods in both the clonidine and the midazolam groups.Shivering was not seen in any of the patients in the clonidine group, but it was seen in 13.3% of the patients in the midazolam group. These results were found to be statistically significant.

Table 1: Basic parameters of both groups.

Parameters	Group I (Clonidine)	Group II (Midazolam)
Age (Yrs)	4.8±1.46	4.92±1.28
Gender (M/F)	25/25	26/24
Weight (Kg)	19.8±4.24	20.4±3.89
ASA I/II (%)	78.6/24.6	81/21.2
Duration of surgery	41.6±5.44	43.8±5.86

Fig 1: Comparison of tolerance of medicine in both groups.

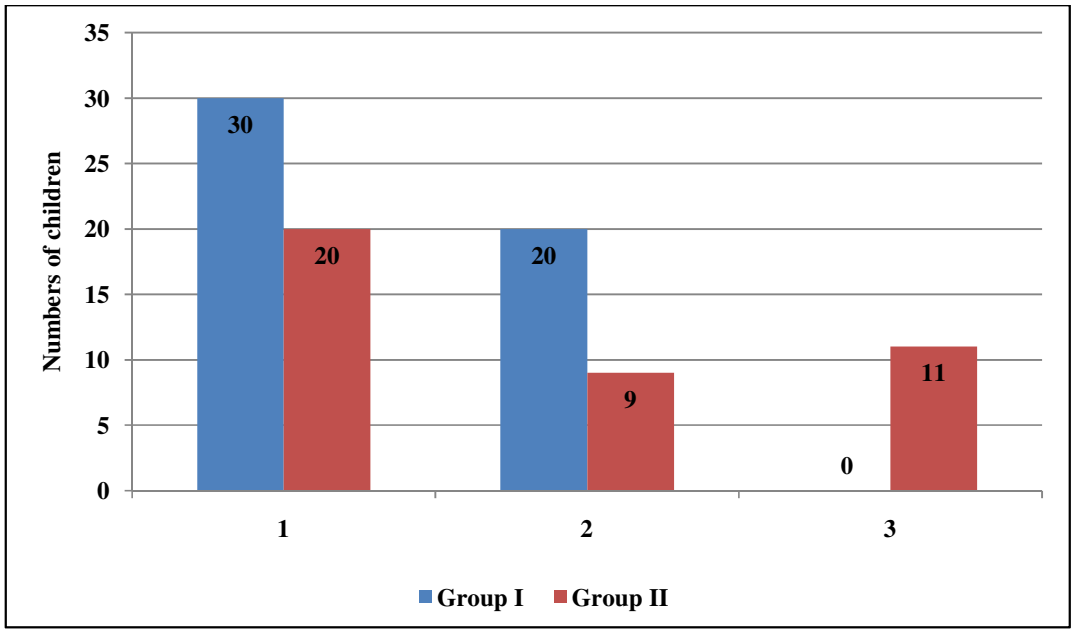


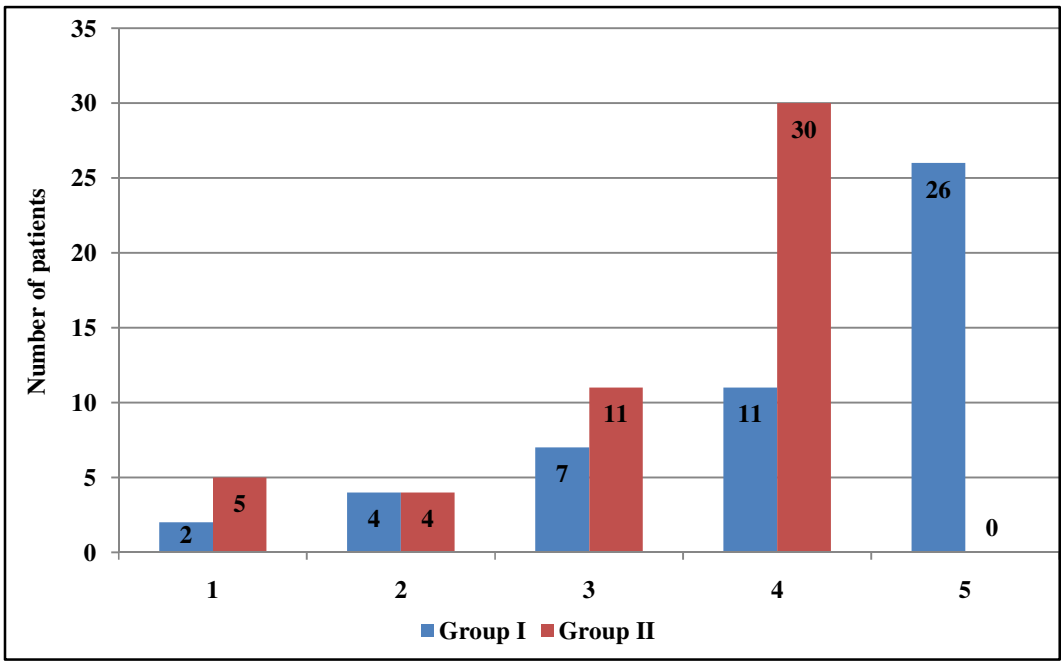
Table 2:Comparison of onset time of sedation in both groups.

Times	Group I (Clonidine)				Group II (Midazolam)				Df	X^2	p value
(Min)	1	2	3	N	1	2	3	N	-	-	-
0	50	0	0	50	50	0	0	50	-	-	-
15	44	6	0	50	40		0	50	1	2.12	0.136^{NS}
30	20	16	8	44	14	20	0	34	2	9.65	0.01^{*}
45	6	4	14	26	4	7	0	11	2	9.82	0.001^{**}
60	0	2	4	6	0	2	3	5	1	1.76	0.182^{NS}

Table 3: Comparison of sedation score of both groups.

Times	Group I (Clonidine)					Group II (Midazolam)					Df	X^2	p value
(Min)	1	2	3	4	N	1	2	3	4	N	-	-	-
0	36	14	-	-	50	40	10	-	-	50	1	0.384	0.654^{NS}
15	2	6	36	6	50	0	2	36	12	50	3	2.86	0.29^{NS}
30	0	4	23	23	50	0	0	28	4	32	2	13.2	0.001^{**}
45	0	0	10	14	24	0	0	12	0	12	1	6.75	0.01^{*}
60	0	0	2	6	8	0	0	2	0	2	1	1.87	1.54^{NS}

Fig 2: Comparison of quality of induction in both groups.



DISCUSSION

Findings of the present study shows that children liked more the taste of oral clonidine compare to oral midazolam. Though, both drugs were given same solution of water and honey. Similarly, Peterson M reported test of oral midazolam was bitter even after mixing with grape juice. Moreover, its test was unpleasant for the children.

Results of the current study revealed that oral clonidine hadsignificantly better level of sedation compare to oral midazolamin children.However, level of sedation was satisfactory for both groups. Further, results suggest that onset of sedation was slower in clonidine group comparison of midazolam group. These findings are consistent with the findings of earlier study of Almenrader N et al[9] as they recorded statistically significant difference between sedation levels of oral clonidine compare to oral oral midazolam. Moreover, they suggested it is necessary to administer oral clonidine and oral midazolam, 45 minutes prior and 30 minutes prior respectively to attain the optimum sedation level. However, thesy did not onserve any significant difference between anxiolysis of both drugs.

Alike, Cao J et al[10]observed that anxiety was significantly decreased in children of clonidine group compare to midazolam group. They suggested that clonidine acts as in both was as sedative and analgesic due to its central alpha-2 adrenergic agonism.

In contrast to the presnt study Fazi L et al[11]showed that the sedation level with drug midazolam was better than drug clonidine. This difference may be due to population of their study group was between 4 to 12 years age group. Whereas, present study included children of 4 to 8 years age group. Moreover, they induced sedative drugs for tonsillectomy which is a leads to a post-operative painful stage.

Furhter, findings of the current study have shown that there were significantly better acceptance of mask and quality of the induction in clonidine group compare to midazolam group. Steal induction was performed in 52% of clonidine group while none of the child of midazolam group could perform steal induction.

This may be due to sedation caused be clonidine is similar to that of natural sleep in which the subject can easily arouse to perform normally. The child with clonidine drug goes from natural sleep to anaesthetic sleep which is essential to perform steal induction. [12]Nonetheless, both drugs achieved a satisfactory quality of induction in our study. The premedication with midazolam was characterized by significant anxiolytic and amnestic effects which could allow a calm mask induction even if the child was awake.[9]

No clinical side effects on haemodynamics like hypoxaemia, hypotension, bradycardia and apnoea were observed after administration of either drug. The shivering in children was significantly more with oral drug midazolam than withoral drug clonidine. This could be explained by the mechanism of clonidine in preventing shivering is correlated with the inhibition of vasoconstriction and a decrease in the shivering threshold.[13]

CONCLUSION

Findings of the current study suggest that oral use of drug clonidine can be a more effective alternative for children in comparison of oral use of drug midazolam.Although satisfactory level of sedation is achieved with both drugs; nonetheless, use of oral clonidine leads to a better sedation, anxiolytic and improved quality of induction compare to use of oral midazolam. Moreover, post-operative shivering is not found with the use of drug clonidine. However, studies on larger populations are warranted to prove clonidine as better drug compare to midazolam.

REFERENCES

1. Wright KD, Stewart SH, Finley GA, Susan E, Buffett-Jerrott. Prevention and intervention strategies to alleviate pre-operative anxiety in children. A critical review. Behaviour Modification 2007;31(1):32-79.
2. McCann ME, Kain ZN. The management of pre-operative anxiety in children: An update. Anesth Analg 2001;93(1):98-105.
3. Deshpande S, Platt MP, Aynsley-Green A. Patterns of the metabolic and endocrine stress response to surgery and medical illness in infancy and childhood. Crit Care Med 1993; 21 (9 Suppl): S359-61.
4. Committee on Drugs. Reappraisal of the lytic cocktail/ demerol, phenargan and thorazine for sedation in children. Paediatrics 1995;95:598-602.
5. Rosebaum A, Kain ZN, Larsson P, Lönnqvist P, Wolf AR. The place of the premedication in the paediatric practice. Paediatric Anesthesia 2009;19:817-28.
6. Mikawa K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H. Efficacy of the oral clonidine premedication in children. Anesthesiology 1993;79(5):926-31.
7. McMillan CO, Spahr-schopfer LA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. Can J Anaesth 1992;39(6):545-50.
8. Peterson M. Making oral midazolam palatable for children. Anesthesiology 1990; 73: 1053.
9. Almenrader N, Passariello M, Coccetti B, Haiberger R, Pietropaoli P. Premedication in children: a comparison of oral midazolam and oral clonidine. Paediatr Anaesth 2007;17(12):1143-49.
10. Cao J, Shi X, Miao X, Xu J. Effects of the premedication of midazolam or clonidine on the peri-operative anxiety and pain in children. BioScience Trends 2009;3(3):115-18.
11. Fazi L, Jantzen EC, Rose JB, Kurth CD, Watcha MF. A comparison of oral clonidine and oral midazolam as pre-anesthetic medications in pediatric tonsillectomy patients. Anesth Analg 2001;92(1):56-61.
12. Hall JE, Uhrich TD, Ebert TJ. The sedative, analgesic and cognitive effects of clonidine infusions in humans. Br J Anaesth 2001; 86:5-11.
13. Horn EP, Standl T, Sessler DI, von Knobelsdorff G, Büchs C, am Esch J S. Physostigmine prevents post-anesthetic shivering as does meperidine or clonedine. Anesthesiology. 1998; 88:108-13.