Original Article

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Anaesthesia Section

Comparison of Oral Clonidine and Midazolam as Premedications in Children

RUBINA KHULLAR MAHAJAN, IQBAL SINGH, AMAR PARKASH KATARIA

ABSTRACT

Background: Oral premedication is widely being used in paediatric anaesthesia to reduce the pre-operative anxiety and to ensure a smooth induction. Midazolam is currently the most commonly used premedicant in children. Clonidine, an alpha-2 agonist due to its sedative properties, is also being used.

Aim: The aim of the present study was to compare the clinical effects of oral midazolam and oral clonidine.

Settings and Design: This study was conducted as a single blind trial on 60 children who were in the age group of 2-8 years.

Methods and Material: The children were randomly divided into two groups and they were given either clonidine 4 mcg/kg (Group I, n=30) or midazolam 0.5 mg/kg (Group II, n=30) orally, which were dissolved in honey and water solution, 60 minutes prior to the mask induction. The drug acceptance, pre-operative sedation and anxiolysis, parental separation, quality of induction and mask acceptance, the effect on the haemodynamics and the adverse effects were evaluated.

Statistical Analysis Used: All the values were reported as range and mean±SD. The data analysis for the numerical data was performed by the unpaired Student's t-test and for the categorical data, the analysis was performed by the Fisher's exact test or the Chi-Square test. Other data were reported as mean ± SD or frequency (%). A p value of≤ 0.05 was considered as statistically significant.

Results and Conclusions: Oral clonidine tasted significantly better than oral midazolam. The onset of the sedation was significantly faster after the premedication with midazolam (30.5 ± 10.8 minutes) than with clonidine (38.5 ± 12.26 minutes). A satisfactory sedation could be achieved with both the drugs, but the quality of the sedation was significantly better after the premedication with clonidine. The difference in the onset of the anxiolysis was found to be statistically insignificant. A satisfactory anxiolysis was achieved with both, but the quality of the anxiolysis was better with clonidine. The quality of the mask induction was equally satisfactory in both the groups. A steal-induction was performed on 56.7% of the patients of the clonidine group, but on none in the midazolam group. No adverse effects like bradycardia, hypotension, hypoxaemia or apnoea were observed during the peri-operative period in both the clonidine and the midazolam groups. We concluded that oral clonidine is a good alternative to oral midazolam as a premedication in children.

Key Words: Premedication, Clonidine, Midazolam, Paediatric anaesthesia

INTRODUCTION

Anaesthesia induction appears to be the most stressful procedure that children experience during the peri-operative period. It has been associated with many negative behaviours during and after the surgical experience, like post-operative pain, sleeping disturbances, parent child conflict and separation anxiety [1]. It also activates the human stress response, leading to increased levels of serum cortisol and epinephrine and natural killer cell activity [2]. Children are particularly vulnerable to the global surgical stress response because of the limited energy of the reserves, large brain masses and the obligatory glucose requirements [3].

For reducing the incidence of pre-operative anxiety in children, a number of pharmacological (e.g., sedatives) and non-pharmacological (e.g. parental presence, behavioural preparation programs, music, acupuncture, etc) approaches have proven to be useful.

Midazolam is a benzodiazepine which produces anxiolytic, amnestic, hypnotic and skeletal muscle relaxant effects. It can be administered via the intranasal, sublingual, rectal and the oral routes. It has been the pharmacological agent of choice for pre-operative anxiety in day care surgery because of its rapid onset and short half life. Although midazolam is an effective agent in alleviating anxiety in children, it is not without its own disadvantages. In some investigations, its use has been associated with a delay in either the discharge of the patients from the hospital or in the recovery time. Furthermore, some children, after the premedication with midazolam, experience maladaptive behavioural changes [1].

A number of drugs, other than midazolam, are preferable in the context of paediatric premedication [4].

Clonidine has significant sedative and analgesic properties because of its alpha-2 adrenergic agonism. It was first introduced as a paediatric premedicant in 1993 and although it is less popular than midazolam, its use has been constantly increasing. It has been shown that oral clonidine effectively produces pre-operative sedation and anxiolysis in children, it acts as an analgesic, it decreases the volatile anaesthetic agent requirement and also improves the peri-operative haemodynamic stability. Clonidine can be administered orally (4 mcg/kg) and intranasally (2mcg/kg) [5].

The present study was conducted to compare the efficacy of oral clonidine with oral midazolam as a premedication in children. The effects of the premedication were assessed with regards to the drug acceptance, pre-operative sedation and anxiolysis, parental

separation, the mask acceptance for inhalational induction, effect on the haemodynamics and the side effects if any were noted.

MATERIAL AND METHODS

This study was approved by the local ethics committee and an informed parental consent was obtained from the parents of the patients. A pre-anaesthetic check up which included taking a detailed history and a thorough general physical examination of the patients was carried out a day prior to surgery.

60 children, American Society of Anaesthesiology (ASA) Grade I–II, who were aged 2-8 years, who were scheduled for surgery under general anaesthesia, were randomly assigned to receive either oral clonidine 4 mcg/kg [6] (Group I, n = 30) or oral midazolam 0.5 mg/kg [7] (Group II, n = 30), 60 minutes prior to the anaesthesia induction.

Both the drugs were given by dissolving the respective tablets in honey and a water solution. 2 ml of honey and 3 ml of water were mixed and the tablet was dissolved in the solution. 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. The heart rate, blood pressure, respiratory rate, oxygen saturation and the sedation and anxiety levels were noted at the time of administration of the premedication and then they were monitored continuously. The readings were recorded every 15 minutes for upto 60 minutes. The onset of the sedation was defined as the minimum time interval which was necessary for the child to become drowsy or asleep. The level of sedation was assessed by using a 3-point scale: 1 = awake, 2 = drowsy, and 3 = asleep. A sedation score of ≥2 was considered as 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 ≥3 was considered as satisfactory. The onset of anxiolysis was defined as the minimum time interval necessary to achieve a satisfactory anxiolysis. Any untoward side effect like apnoea, hypoxaemia, bradycardia, hypotension and any other if present, was looked for.

When a sedation score of 2 or 3 was reached, the children were transferred to the induction room. If no satisfactory sedation level was achieved, the children were excluded from further studies. The separation of the children from their parents was evaluated on a three point scale: 1 = Poor: Anxious or combative, 2 = Good: Anxious but easily assured and 3 = Excellent : Calm/Sleeping. If the children came to the induction room while they were already asleep, a steal induction was attempted. All the children received halothane, nitrous oxide and oxygen via a mask to facilitate venous cannulation. The quality of the induction and the mask acceptance was immediately evaluated on a 5-point scale: 1 = combative, crying, 2 = moderate fear of the mask, not easily calmed, 3 = co-operative with reassurance, 4 = calm, cooperative and 5 = asleep, steal induction. A mask induction score of 3–5 was regarded as a successful response to the premedication. An intravenous line was secured and an intravenous infusion was started with Isolyte P. All the children received 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 upto 3%, depending on the requirement. The muscle relaxant, vecuronium 0.1 mg/kg body weight was used to facilitate endotracheal intubation. After the effect of vecuronium wore off, the neuromuscular blockade was supplemented with vecuronium 0.08 mg/kg body weight intravenously and the IPPV was maintained with 0.5% halothane and 60% nitrous oxide in 40% oxygen. No opioids or any other sedatives were administered intra-operatively. All the patients received rectal acetaminophen for post-operative analgesia. At the end, halothane was discontinued and nitrous oxide was switched off. The neuromuscular blockade was reversed with glycopyrrolate 0.01mg/kg and neostigmine 0.04 mg/kg body weight intravenously. The children were extubated after adequate neuromuscular recovery and when they made purposeful movements and had regular respiratory patterns. All the adverse effects including hypotension, bradycardia, respiratory depression, nausea/vomiting and shivering were recorded in the peri-operative period.

STATISTICAL ANALYSIS

All the values were reported as mean plus SD and range. The data analysis for the numerical data was performed by the unpaired Student's t-test to detect the differences between the groups for age, weight, onset of the anxiolysis and sedation. The data analysis for the categorical data was performed by Fisher's exact test or by the Chi-Square test to detect the differences for the scores. Other data were reported as mean ± SD or frequency (%). A p value of≤ 0.05 was considered as statistically significant.

RESULTS

The two groups were similar with respect to age, weight, gender, the ASA physical status and duration of the surgery [Table/Fig-1]. The children judged the taste of clonidine as significantly better than the taste of midazolam (P<0.05) [Table/Fig-2]. The onset of the sedation was 38.5 ± 12.26 (15-60) min in group I and it was 30.5 ± 10.78 (15-45) min in group II. This difference was statistically significant (P<0.05). However, the level of sedation was significantly better in group I than in group II (P<0.05) [Table/Fig-3]. A satisfactory sedation with a sedation score of ≥ 2 was achieved in 100% of the children in both the clonidine and the midazolam groups. These results were found to be statistically insignificant (P>0.05).

There was no significant difference in the onset of anxiolysis and in the satisfactory anxiolysis in both the groups (P>0.05). However, the quality of the pre-operative anxiolysis was significantly better with oral clonidine (P<0.05) [Table/Fig-4].

The quality of the parental separation was significantly better in the clonidine group (P<0.05) [Table/Fig-5]. The mask acceptance and the quality of the induction were significantly better in the clonidine group as compared to those in the midazolam group (P<0.05). A steal induction could be performed in 56.7% patients of group I, but in no patient of group II. However, a satisfactory quality of induction could be achieved in both the groups (P>0.05) [Table/Fig-6].

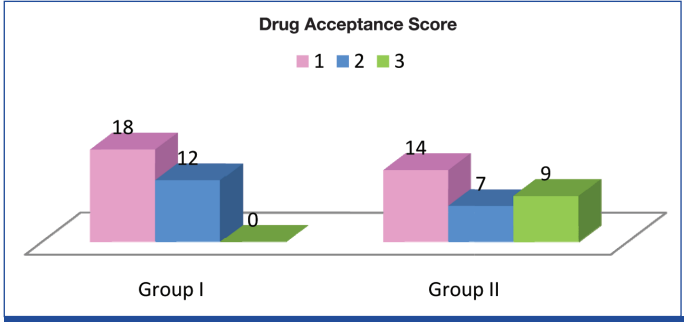
No adverse effects like bradycardia, hypotension, hypoxaemia or apnoea were observed during any of the pre-operative, intra-operative or the post-operative periods in both the clonidine and the midazolam groups.

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.

Post-operative nausea and vomiting (PONV) were seen in 6.67%

	Group I (Clonidine)	Group II (Midazolam)
Age (yrs)	5.03±1.86	4.8±1.87
Weight (kg)	19.0±4.15	18.4±4.21
Gender(M/F)	15/15	14/16
ASA I/II (%)	76.7/23.3	80/20
Duration of surgery (mins)	42.8±5.89	43.9±6.21

[Table/Fig-1]: Patient Data



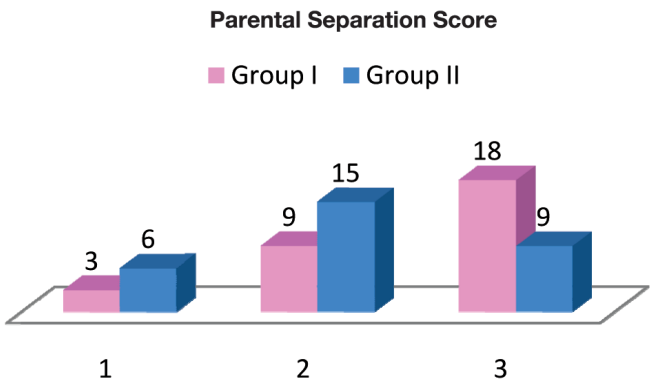
[Table/Fig-2]: Drug Acceptance

Time (mins)	Group I n = 30				Group II n = 30				df	χ^2	p value and significance
	1	2	3	n	1	2	3	N	-	-	-
0	30	0	0	30	30	0	0	30	-	-	-
15	28	2	0	30	24	6	0	30	1	2.308	0.129 NS
30	14	10	4	28	6	18	0	24	2	9.233	0.010 *
45	4	2	8	14	1	5	0	6	2	9.388	0.009 **
60	0	1	3	4	0	1	0	1	1	1.875	0.171 NS

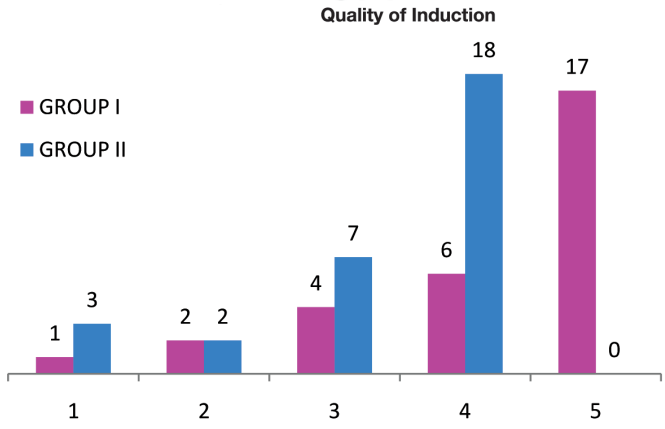
[Table/Fig-3]: Sedation Scores
χ^2: Chi Square test, n: number of patients, df: degrees of freedom, NS: Not significant, *: p < 0.05: Significant at 5% significance level, **: Significant at 1% significance level.

Time (mins)	Group I n = 30					Group II n = 30					df	χ^2	p value and significance
	1	2	3	4	n	1	2	3	4	n			
0	22	8	0	0	30	24	6	0	0	30	1	0.373	0.542 NS
15	1	3	23	3	30	0	1	23	6	30	3	3.000	0.392 NS
30	0	2	13	13	28	0	0	22	2	24	2	12.125	0.002**
45	0	0	6	8	14	0	0	6	0	6	1	5.714	0.017*
60	0	0	1	3	4	0	0	1	0	1	1	1.875	1.171 NS

[Table/Fig-4]: Anxiolysis Scores
χ^2: Chi Square test, n: number of patients, df: degrees of freedom, NS: Not significant, *: p < 0.05: Significant at 5% significance level, **: Significant at 1% significance level.



[Table/Fig-5]: Parental Separation



[Table/Fig-6]: Quality of Induction

of the patients in the clonidine group and in 10% of the patients in the midazolam group. These results were found to be statistically insignificant.

DISCUSSION

This study demonstrated that clonidine was a suitable alternative to midazolam as a premedication in children. The children judged the taste of oral clonidine as significantly better than that of oral midazolam, although both the drugs were given with the same sweet tasting honey and water solution. Midazolam has a bitter taste that is difficult to disguise even when it is given in a mixture with grape juice [8]. The quality of sedation and anxiolysis was significantly better in the clonidine group, whereas a satisfactory sedation and anxiolysis could be achieved by both. The onset of sedation was significantly slower with oral clonidine, whereas the difference in the onset of anxiolysis was statistically insignificant in both the groups. The quality of the parental separation was significantly better with oral clonidine.

Almenrader et al., conducted a study and they achieved a significantly better level of sedation with oral clonidine than with oral midazolam, but clonidine needed to be administered at least 45 minutes prior to the induction for an optimum sedation, which could be achieved in 30 minutes with oral midazolam. No significant difference in the onset of anxiolysis was found [9].

Another study by Cao et al., demonstrated that the clonidine premedication provided better levels of anti-anxiety in children than midazolam. Clonidine acts as a sedative and analgesic because of its central alpha-2 adrenergic agonism. A significantly higher parental separation score was noted in the clonidine group [10].

Fazi et al., found that the premedication with midazolam was superior than the clonidine premedication. Some differences may explain the different outcomes of their study and our study: firstly, the age of the study population (4–12 years) was different as compared to that of the patients in the present study (2–8 years). Secondly, unlike this study, the patients in Fazi's study were scheduled only for tonsillectomy. Tonsillectomy can affect the post-operative period more adversely, as the patients may suffer more pain and PONV. Furthermore, in this study, the one major outcome was pre-operative sedation, which was not assessed in the study of Fazi et al., [11].

The qualities of the induction and the mask acceptance in this study were significantly better with oral clonidine and steal induction with the child asleep could be performed in 56.7% patients in the clonidine group. It could be performed in none of the patients in

the midazolam group. Clonidine causes a sedation which is similar to that of natural sleep, where the patient can be easily aroused to perform the cognitive tests. The asleep state is essential to perform a steal induction in which the child passes from natural to anaesthetic sleep [12]. A satisfactory quality of induction could be achieved in both the groups 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 adverse effects like bradycardia, hypotension, hypoxaemia, apnoea or PONV were observed on haemodynamics during the peri-operative period in both the groups. Oral clonidine 4 mcg/kg [6] and oral midazolam 0.5 mg/kg [7] are effective premedications in paediatric surgery, with no clinically significant side effects on the haemodynamics. The incidence of shivering was significantly more in the midazolam group than in the clonidine group. The mechanism of clonidine in preventing shivering was correlated with the inhibition of vasoconstriction and a decrease in the shivering threshold [13].

CONCLUSION

The premedication with oral clonidine is a suitable alternative to oral midazolam. Although satisfactory levels could be achieved by both, the oral clonidine premedication provided a better sedation, anxiolytic, parental separation and quality of induction and it prevented the post-operative shivering, with few adverse effects.

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AUTHOR(S):
1. Dr. Rubina Khullar Mahajan.
2. Dr. Iqbal Singh
2. Dr. Amar Parkash Kataria

PARTICULARS OF CONTRIBUTORS:
1. Anaesthesiology, Government Medical College Amritsar, Punjab, India.
2. Anaesthesiology, Punjab Institute of Medical Sciences, Jalandhar, Punjab, India.
3. Anaesthesiology, Government Medical College, Amritsar, Punjab, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Rubina Khullar Mahajan
100-Dayanand Nagar, Lawrence Road, Amritsar, India.
Phone No. 09585887884
E-mail: khullar.rubina@gmail.com

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