ORAL PREMEDICATION IN CHILDREN: A COMPARISON OF COMBINATION OF MIDAZOLAM AND KETAMINE, CLONIDINE, MIDAZOLAM AND PLACEBO FOR DAY SURGERY

Gulshan Dhawan[1], Arvind Kumar Singh[2], RAK Sharma[3], Preeti Dhawan[4]

[1]Classified Specialist, Department of Anaesthesia, Military Hospital, Panagarh.
[2]Senior Advisor, Department of Anaesthesia, Command Hospital, Lucknow.
[3]Classified Specialist, Department of Anaesthesia, Military Hospital, Dehradun.
[4]Professor, Department of Paedodontics, Seema Dental College & Hospital, Rishikesh.

ABSTRACT

BACKGROUND

Every child administered Paediatric Anaesthesia requires anxiolysis, sedation and early recovery.

Aim of this article is to compare the efficacy of various premedicants with low dose combination of Oral Midazolam and Oral Ketamine.

MATERIALS AND METHODS

The sample population consists of 120 children between the age group of 1-8 years, randomly divided into four groups, each group comprising 30 children. Four Groups i.e. Low dose combination of Oral Midazolam (0.25 mg/kg) and Oral Ketamine (3 mg/kg), Oral Clonidine (4 mcg/kg), Oral Midazolam (0.5 mg/kg) and Placebo (Strawberry syrup) were administered 90 minutes before the anticipated time of induction of anaesthesia. Time taken to achieve the desired level of sedation and time taken for discharge from post-anaesthesia care unit using 5-point sedation score and Modified Aldrete Score respectively was noted. Statistical analysis was done using SPSS V.10 and significance was calculated using student t-test.

RESULTS

When low dose combination of Midazolam and Ketamine (Group I) was compared with other groups in relation to sedation level, a highly significant difference in time taken to reach desired level ($P<0.000001$) was found. No significant difference was found between Oral Clonidine (Group II) and Oral Midazolam (Group III). When low dose combination of Midazolam and Ketamine (Group I) was compared with other groups in relation to Modified Aldrete Score, a highly significant difference ($P<0.000001$) in time taken for discharge from post-anaesthesia care unit was found.

CONCLUSIONS

Low dose combination of Midazolam and Ketamine showed a highly significant reduction in time taken to achieve desired sedation level and recovery as compared to Oral Clonidine and Oral Midazolam.

KEYWORDS

Premedicants, Low Dose Combination of Oral Midazolam and Oral Ketamine, Sedation, Modified Aldrete Score.

HOW TO CITE THIS ARTICLE: Dhawan G, Singh AK, Sharma RAK, et al. Oral premedication in children: A comparison of combination of midazolam and ketamine, clonidine, midazolam and placebo for day surgery. J. Evolution Med. Dent. Sci. 2016;5(87):6485-6487, DOI: 10.14260/jemds/2016/1466

BACKGROUND

The different modalities adopted to achieve anxiolysis and sedation in Paediatric anaesthesia involve pharmacological and non-pharmacological approaches. Regarding the pharmacological approaches, the various premedicants used are midazolam, clonidine, ketamine, triclofos sodium and various combinations. Midazolam is most widely used for paediatric premedication. A dose of 0.25-0.5 mg/kg orally has several beneficial effects as anxiolysis, amnesia, rapid onset of action; however, adverse post-behaviour changes, hiccups and paradoxical reactions have been observed.[1] Clonidine, alpha-2 agonist produces pre-operative sedation and anxiolysis reliably in addition to analgesic effect and maintaining haemodynamic stability.[2] Ketamine is an alternative premedicant and even sub-anaesthetic concentration of it are known to cause undesirable side-effects.[3] Low dose combination of midazolam and ketamine adds anxiolytic properties of midazolam to sedative and analgesic properties of ketamine without psychedelic side effects.[4] The main objective of this study was to compare the efficacy of various premedicants with low dose combination of Midazolam and Ketamine during paediatric anaesthesia.

Financial or Other, Competing Interest: None.
Submission 23-09-2016, Peer Review 17-10-2016,
Acceptance 24-10-2016, Published 28-10-2016.
Corresponding Author:
Dr. Gulshan Dhawan,
Classified Specialist,
Department of Anaesthesia,
Military Hospital, Panagarh.
E-mail: gulshan.dhawan@gmail.com
DOI: 10.14260/jemds/2016/1466

MATERIALS AND METHODS

The sample population consists of 120 children between the age group of 1-8 yrs. who reported to Dept. of Anaesthesia for day care surgeries. Those children who were having no other illness other than for which they have reported and have no allergy to Midazolam, Ketamine or clonidine were included in the study. The children were randomly assigned into four groups, consisting of 30 children in each group. Group I includes the children premedicated with low dose combination of Midazolam (0.25 mg/kg) and Ketamine (3 mg/kg), Group II was the Clonidine group (4 mcg/kg), Group

III was Midazolam group (0.5 mg/kg), Group IV was the placebo group. Medications were prepared according to randomised sequence using strawberry flavoured glucose syrup. Oral premedication was administered 90 min. before the anticipated time of induction of anaesthesia. After administration of oral premedication, the children were made to relax in the holding area along with their parents. The effectiveness of oral premedicants were recorded by assessing sedation (Time taken to achieve desired level of sedation) and recovery (Time taken to discharge from post-anaesthesia care unit to home) using 5-point sedation score[5] and Modified Aldrete Score[6] respectively. Statistical analysis was done using SPSS V.10. The significance was calculated using student t-test.

RESULTS

The sample population consists of 120 children between the age group of 1-8 years. Table 1 shows the variance of time taken for desired sedation level with different premedicants. Low dose combination of Midazolam and Ketamine (Group I) shows a highly significant difference in sedation level (P<0.000001) as compared to other three groups. No significant difference was found between Clonidine (Group II) and Midazolam (Group III).

Group	t-value	p-value	Significance
I-II	8.224	P<0.000001	Highly Significant
I-III	6.108	P<0.000001	Highly Significant
I-IV	12.157	P<0.000001	Highly Significant
II-III	2.444	0.01759	Non-significant
II-IV	5.796	P<0.000001	Highly Significant
III-IV	7.709	P<0.000001	Highly Significant

Table 1. Analysis of Variance of Time taken for desired Sedation Level with different Premedicants with Respect to 5-point Sedation Score

The difference between various groups with respect to Sedation score was found to be highly significant between Group I and IV (P<0.000001) and non-significant between Groups II and III (p value is 0.01759). When comparison of recovery profile for different premedicants was made with respect to Modified Aldrete Score, there was highly significant recovery among children of Group I (p<0.000001) in comparison to Clonidine, Midazolam and Placebo groups. The difference between various groups with respect to Modified Aldrete Score were found to be highly significant.

Intergroups	t value	p value	Significance
I-II	15.654	P<0.000001	Highly significant
I-III	7.225	P<0.000001	Highly significant
I-IV	21.570	P<0.000001	Highly significant
II-III	7.562	P<0.000001	Highly significant
II-IV	8.381	P<0.000001	Highly significant
III-IV	14.253	P<0.000001	Highly significant

Table 2. Intergroup Comparison of Mean Values for Modified Aldrete Score

DISCUSSION

Our study provides evidence that a combination of Midazolam and Ketamine results in better sedation and recovery than clonidine, Midazolam or Placebo group. Ketamine as a single drug has well known side effects of IV administration. Similar side effects have been published for oral administration.[7] A combination with Midazolam seems to be logical to reduce psychedelic effects and broadens the pharmacodynamic profile of the mixture. The combination of Oral Ketamine and Oral Midazolam was described by Lin. Moynihan and Hackel[8] in 1993. They found faster onset time (vs. both drugs given independently), less oral secretions and nystagmus (vs. Ketamine) and faster recovery (vs. Midazolam). No post-operative complications such as dreaming or nightmares were observed. Warner, Cabaret and Velling[6] found that midazolam (0.4 mg/kg) and ketamine (4 mg/kg) combination was more effective than midazolam 0.5 mg/kg or ketamine 6 mg/kg alone with no psychological disturbances in immediate post-operative period. W. Funk, W. Jakob, T. Riedl, K. Taeger[9] observed significantly better anxiolysis and separation with a combination even in awake children than with midazolam or ketamine alone. The results of our study comparing low dose combination with Midazolam alone are consistent with above-mentioned studies.

No study has been conducted so far comparing low dose combination of Midazolam and Ketamine with oral Clonidine. However, studies comparing Midazolam and Clonidine such as Almenrader et al[10] demonstrated clinical advantages of oral Clonidine in both preoperative and recovery period compared with oral midazolam. They observed a trend towards a lower incidence of emergence agitation in children premedicated with clonidine in comparison to midazolam. Studies by Kanegaye[11] and Breschan et al[12] also failed to show a reduction in emergence agitation after midazolam premedication. It has been suggested that alpha-2 agonists prevent emergence agitation by reducing noradrenergic output from locus coeruleus, thus allowing increased firing of inhibitory systems such as gamma-aminobutyric acid system.[13] Our study demonstrated highly significant difference in the recovery profile of Oral Clonidine and Oral Midazolam and no significant difference in the level of sedation achieved between clonidine or midazolam group.

The level of sedation was graded by 5-point score[5] (1-asleep, not readily arousable; 2-asleep, responds slowly to gentle stimulation; 3- drowsy, readily responds; 4- awake, calm and quiet; 5-awake, active). Average time taken to reach the desired sedation level in Group I (12+- 6.8 min.), Group II (30 +- 13.1 min.), Group III (38.5 +- 14.6 min.) and Placebo (Children were shifted to operating room suite after 90 min.) were compared. Level of Sedation achieved by low dose combination group was highly significant in comparison to other three groups. In our study, level of sedation achieved by oral clonidine or oral Midazolam was highly significant in comparison to Placebo group. Even though the time taken to achieve desired sedation level between Group II and Group III were clinically significant, it was not statistically significant.

To compare the recovery profile, time taken to achieve Modified Aldrete Score[6] more than 9 was noted. Modified Aldrete Score more than 9 must be met for the safe discharge from Post-Anesthesia Care Unit. Consciousness, Respiration, BP, HR, SpO_2 and activity were recorded (Appendix 1).[14] For each child tracked in the study, child's admission number, age, gender, pre-anaesthetic status, diagnosis, surgery and anaesthesia technique were recorded. Immediately on reaching Post-anaesthesia care unit, the admission time was noted and Modified Aldrete Scoring was recorded and was re-evaluated at every 5 min. interval period. Duration of anaesthesia and surgery was not assessed in relation to

discharge time in this study. Average time taken to reach the desired Modified Aldrete Score in Group I (15+- 4.8 min.), Group II (86.8+- 45.8 min.), Group III (36.5 +-21.6 min.) and Placebo (150.8+-65.7 min.) were compared. Recovery profile of each group was highly significant in relation to any other group.

Parameter	Description of Patient	Score
Activity Level	Moves all extremities voluntarily/on command	2
	Moves 2 Extremities	1
	Cannot move Extremities	0
Respirations	Breathes Deeply and coughs freely	2
	Is Dyspnoeic, with shallow, limited breathing	1
	Is apnoeic	0
Circulation (Blood Pressure)	Is 20 mmHg > Preanaesthetic level	2
	Is 20 to 50 mmHg > Preanaesthetic level	1
	Is 50 mmHg > Preanaesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level >90% when breathing room air	2
	Requires supplemental oxygen to maintain level >90%	1
	Has Level <90% with oxygen supplementation	0
Appendix 1		

Maximum total score is 10; a score of ≥9 is required for discharge.

CONCLUSION

In conclusion, it can be stated that low dose combination of Oral midazolam and Oral ketamine showed a highly significant pre-anaesthetic sedation levels in comparison to Oral Clonidine and Oral Midazolam alone. Low dose combination of midazolam and ketamine helps in eliminating the psychedelic side effects of ketamine and its other advantages such as anxiolysis, sedation, analgesic properties and better recovery profile makes it the most useful premedicant in paediatric anaesthesia.

REFERENCES

1. McGraw T, Kendrick A. Oral midazolam premedication and postoperative behavior in children. Paediatr Anaesth 1998;8(2):117-21.
2. Mikawa K, Maekawa N, Nishna K, et al. Efficacy of oral clonidine premedication in children. Anaesthesiology 1993;79(5):926-31.
3. Bowdle TA, Radiant AD, Cowley DS, et al. Psychedelic effects of ketamine in healthy volunteers: relationship to steady state plasma concentrations. Anaesthesiology 1998;88(1):82-8.
4. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric oral premedicant. Paediatr Anaesth 1995;5(5):293-5.
5. Pandit UA, Collier PJ, Malviya S, et al. Oral transmucosal midazolam premedication for preschool children. Can J Anaesth 2001;48(2):191-5.
6. Aldrete JA. The post-anaesthesia recovery score revisited. J Clin Anesth 1995;7(1):89-91.
7. Donahue PJ, Dineen PS. Emergence delirium following oral ketamine. Anaesthesiology 1992;77(3):604-5.
8. Lin YC, Moynihan RJ, Hackel A. A comparison of oral midazolam, oral ketamine and oral midazolam combined with ketamine as preanaesthetic medication for pediatric outpatients. Anaesthesiology 1993;77:A1177.
9. Funk W, Jakob W, Riedl T, et al. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. Br J Anaesth 2000;84(3):335-40.
10. Almenrader N, Passariello M, Coccetti B, et al. Premedication in children: a comparison of oral midazolam and oral clonidine. Paediatr Anaesth 2007;17(12):1143-9.
11. Kanegaye JT, Favela JL, Acosta M, et al. High-dose rectal midazolam for paediatric procedures: a randomized controlled trial of sedative efficacy and agitation. Peditr Emer Care 2003;19(5):329-36.
12. Breschan C, Platzer M, Jost R, et al. Midazolam does not reduce emergence delirium after sevoflurane anaesthesia in children. Pediatr Anesth 2007;17(4):347-52.
13. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anaesthesiology. Pediatric Crit Care Med 2007;8(2):115-31.
14. Barone CP, Pablo CS, Barone GW. Post-anesthetic Care in the Critical Care Unit. Crit Care Nurse February 2004;24(1):38-45.