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ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF ORAL MIDAZOLAM, BUTORPHANOL AND CLONIDINE AS PREMEDICANTS IN CHILDREN UNDERGOING ELECTIVE SURGERY

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ABSTRACT: BACKGROUND: We compared the effects of oral midazolam, butorphanol and clonidine on preoperative sedation and anxiolysis and postoperative recovery profile of the children undergoing elective surgery. **MATERIAL AND METHODS**: 105 children of either sex, aged between 2-6 years, of ASA grade I scheduled for elective surgery were randomized into three groups. Group I: 35 children received midazolam 0.5mg/kg body weight orally, Group II: 35 children received butorphanol 0.2mg/kg orally, Group III: 35 children received clonidine 4µ/kg orally. Premedication was given 30 minutes before induction of anaesthesia. Children were assessed for attitude to venepuncture and face mask acceptance during induction of anaesthesia. **RESULTS:** The groups were statistically comparable ($p>0.05$), regarding the patients' demographic profile, hemodynamic variables, duration of surgery and awakening. Less time was required for the onset and time of maximum sedation in midazolam group. Sedation scores were highest in the clonidine group at the time of induction ($p<0.05$). Steal induction was produced in 4 out of 35 patients in clonidine group. Mask acceptance was comparable in midazolam and clonidine group ($p>0.05$) and minimal with butorphanol. Reaction to i.v cannulation was minimal with clonidine while it was comparable in midazolam and butorphanol group. **CONCLUSION:** clonidine causes the best sedation among the three drugs and it causes minimum response to i.v cannulation and comparable mask acceptance with midazolam followed by butorphanol.

KEYWORDS: Oral premedicants, children, midazolam, butorphanol, clonidine, elective surgery

INTRODUCTION: Premedication forms an integral part of anaesthetic management. An ideal premedicant drug should be anxiolytic, analgesic, sedative and amnestic. It should be safe, easy to administer, and should not produce undue depression of cardiovascular, respiratory and central nervous systems. Preoperative anxiety can affect the smoothness of induction, emergence from anaesthesia and the psychological state of the child.[1] Children from age group of 1 to 6 years have been reported to experience the greatest negative postoperative behaviour changes and therefore they must receive premedication.[2] The induction of anaesthesia appears to be the most stressful procedure the child experiences during the perioperative period.[3]

There are pharmacological and non-pharmacological methods to prepare the child for surgery. Non pharmacological measures to counter anxiety include establishing rapport with child, briefing about the procedure in an optimistic way. Pharmacological intervention includes administration of various drugs before the induction of anaesthesia through different routes such as intramuscular, intravenous, intranasal, oral, sub-lingual and rectal. The intramuscular and intravenous routes lead to better absorption of drugs but are associated with a lot of stress.[4] Oral route is advantageous in many regards. It is a painless technique.

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It avoids exposure of children to needles. It does not require sterile technique, intravenous catheters or other invasive devices. It is easy to administer. Midazolam is the most commonly used premedicant in children. It has rapid onset and relatively short duration of action. It has proven to be a useful premedicant to decrease preoperative anxiety and facilitate separation from parents and improving compliance at induction of anaesthesia with fewer side effects.[3] It has been used for preoperative sedation by intramuscular,[5] rectal,[6] oral[7] and sub-lingual routes[8] each having its own advantages and disadvantages. Oral midazolam is safer and acceptable form of sedation in adolescent patients.[9] Midazolam is effective in children with minimal effect on recovery time.[10] Clonidine is a mixed α_1 and α_2 agonist with predominant α_2 action.

Its use as premedicant has been increasing over the years because of its good anxiolytic and mild sedative properties which lead to good mask acceptance and smooth induction. Clonidine reduces requirements for both inhaled anaesthetics and opioids during and after surgery.[11] Clonidine in dose of 4µg/kg orally, 2-4µg/kg intranasal and 5µg/kg intrarectal provide adequate sedation. Butorphanol is a synthetic opioid analgesic. Oral butorphanol is a better premedicant in children in view of its excellent sedation and analgesia.[12] Also there is less incidence of PONV with oral butorphanol as premedicant.[13] The present study is being undertaken to compare the safety and efficacy of midazolam, clonidine and butorphanol when used as oral premedicants in pediatric patients.

MATERIAL AND METHODS: After attaining the approval of the Ethical Committee of the institute, written informed consent was obtained from the parents. The present study included 105 children of either sex aged between 2 to 6 years belonging to ASA grade I, undergoing elective surgery under general anaesthesia. Children having central nervous system disorders, gastro intestinal disorders affecting drug absorption, on sedatives medications, obesity and having known adverse reactions to the drugs included in the study were excluded from the study. Children were kept fasting for a period of 6 hours preoperatively. All children were given intramuscular injection of glycopyrrolate 5µg/kg body weight in preoperative room. Demographic variables (Age, sex, weight), base line values (Heart rate, blood pressure), degree of sedation and anxiety were assessed before administering the study drugs. To avoid observer bias, all parameters were recorded by a single investigator. The study drugs were administered by a second investigator.

The study drugs were reconstituted from their intravenous formulations according to per kilogram body weight by mixing them with apple juice to make them palatable. All the study drugs were mixed with apple juice to make a total volume of 5ml.This was given by tea spoon to the patients in sitting position. Each patient was randomly assigned to one of the three study groups. Group 1 included 35 patients who received midazolam 0.5mg/kg orally 30 minutes before induction of anaesthesia.

Group 2 included 35 patients who received butorphanol 0.2mg/kg orally 30 minutes before induction of anaesthesia. Group 3 included 35 patients who received clonidine 4µg/kg orally 30 minutes before induction of anaesthesia. Heart rate, blood pressure, SpO2 and degree of sedation were measured at 10, 20 and 30 minutes after administration of study drugs. The degree of sedation and reaction to parental separation was assessed according to a 5- point sedation scale. At 20 minutes after giving premedication the child was taken inside the operating room and intravenous line with 5% dextrose was started. The attitude to venipucture was noted according to a 4-point scale. Scores 3 and 4 were considered satisfactory.

Monitors were then attached to the child which included electrocardiogram, non- invasive blood pressure and pulse oximeter. Heart rate, BP, SpO2 and degree of sedation was noted at 30 minutes when induction was started. Acceptability for the face mask was recorded according to a 5-point scale at the induction of anaesthesia (30 minutes after premedication). Scores of 3 or more was considered satisfactory. Preoxygenation with 100% oxygen was done for 3 minutes followed by the induction of anaesthesia with injection sodium thiopentone 5mg/kg body weight. Tracheal intubation was facilitated with succinylcholine 1.5mg/kg body weight. Anaesthesia was maintained with nitrous oxide, oxygen, halothane and injection atracurium 0.5mg/kg body weight (Loading dose) and thereafter 1/4th of the loading dose as and when required. Analgesia was provided by injection diclofenac sodium 1.5mg/kg intramuscular, body weight after intubating the patient. Ventilation was controlled with IPPV. Any complications during intraoperative period were noted and treated accordingly. At the end of the surgery, anaesthesia was stopped and residual neuromuscular blockade was reversed by injection glycopyrrolate 0.01mg/kg body weight and injection neostigmine 0.05mg/kg body weight.

Tracheal extubation was done and patient was then assessed for the level of agitation. The child was shifted to recovery room and assessed at 10 minute intervals for 1 hour. Any adverse effects of the study drugs were noted and treated accordingly. Data was analyzed with the help of computer software SPSS version of 17.0 for windows. Sedation scores were reported as mean and standard deviation and the difference in mean values across the groups were assessed by One Way Analysis of Variance (ANOVA). Statistical significance of the qualitative variables were assessed with the use of Chi-Square Test. Intergroup comparisons were made post-hoc by Bornferroni's t-test, p-value < 0.05 was considered as statically significant unless specified otherwise. All p-values were reported to be two-tailed.

Score	Sedation	Venepuncture	Mask Acceptance
1	Agitated	Fight without success.	Combative, Crying.
2	Alert	Fight with success.	Moderate fear of mask, not easily calmed.
3	Calm	Minor resistance.	Cooperative with reassurance.
4	Drowsy	No reaction	Calm, Cooperative.
5	Asleep		Asleep, steal induction.

Table 1: Scoring of sedation, emotional status and behavior during venepuncture and mask acceptance

RESULTS: The demographic parameters of age, sex, weight of patients and duration of surgery in all the three groups were statistically comparable (P-value >0.05). The mean values for sedation score were comparable in the three groups before giving premedication to the children (P- value>0.05). In group1, sedation score was 2.31±0.83 at 10 minutes and 3.05±0.80 at 20 minutes after giving the study drug which were more than the sedation score before administration of the drug (1.94±0.68). The percentage change at 10minutes was 16.01%, and from 10 minutes to 20 minutes, the change was 24.26%. The sedation score increased to 3.71±0.85 at 30 minutes showing a change of 17.78% from the reading at 20 minutes. In group 2, the sedation score increased from base line value of 1.91±0.74 to 2.20±0.67 at 10 minutes which further increased to 3.02±0.70. Satisfactory sedation at parental separation was seen in more than the half of the patients.

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Steal induction, however, could not be produced in any of the patients. In group 3, the sedation score increased from base line value of 2.06±0.64 to 3.82±0.61 at 30 minutes. Satisfactory sedation was achieved in more than 80% patients and steal induction was produced in 4 patients. Mean heart rate decreased from 97.02±9.93 to 88.20±9.30 (Change of 9.36%) in group 1. In group 2, the decline in heart rate was 6.23% whereas in group 3, the change was 5.63%. However no patient encountered bradycardia in any of the groups. On intergroup comparison, it was found that heart rate was lowest on an average in group 3, but the maximum decline in heart rate was in group 1. Likewise, SBP decreased in all three groups and the mean values were comparable and the difference in the mean values was insignificant in all the three groups. The score of reaction to i.v cannulation was 2.97±0.70 in group 1 and group 2, but it was higher in group 3(3.17±0.56). Hence reaction to i.v cannulation was minimal in group 3. Mask acceptance in group 1 was 3.45±0.70 and group 2 was 3.34±0.59 but it was slightly lower in group 2(3.00 ± 0.76). On intergroup comparison, post-operative sedation scores were lowest in group 2 as compared to group 1 and group 3. The difference in sedation scores was significant at 10, 20, 50 and 60 minutes (P < 0.05).

	Group 1	Group 2	Group 3	P- value
Age (in Years):	4.10±1.49	4.16±1.41	4.13±1.47	0.986
Sex (M:F Ratio):	26:9	26:9	25: 10	0.981
Weight (in Kgs):	14.88±3.23	14.77±3.45	15.20 ±3.01	0.848
Sedation Scores:	1.94±0.68	1.91±0.74	2.06±0.64	0.657
Heart Rate:	97.02±9.93	100.14±11.51	93.11±8.33	0.15
SBP:	111.22±6.88	109.08±7.51	115.45±6.97	0.06
DBP:	62.85±7.35	63.71±6.37	65.25±4.74	0.270
SpO2	99.02±0.51	99.51±0.56	99.14±0.49	0.05
Duration of Surgery (in Minutes)	49.71±17.06	1.91±0.74	2.06±0.64	0.970

Table 2: Patients' characteristics and time variables

Time (in Minutes)	Group 1	Group 2	Group 3	P-value
10	2.31±0.83	2.20±0.67	2.34±0.63	0.681
20	3.05±0.81	2.62±0.68	3.00±0.76	0.021
30	3.71±0.85	3.02±0.70	3.82±0.61	<0.001

Table 3: Comparison of sedation score after giving premedication

Time (in Minutes)	Group 1	Group 2	Group 3	P- value
10	92.91±9.80	95.45±11.28	89.77±8.04	0.057
20	90.40±9.73	94.51±10.65	88.88±7.93	0.042
30	88.20±9.30	93.97±10.22	87.85±7.90	0.009

Table 4: Comparison of heart rate changes after giving premedication

Time (in Minutes)	Group 1	Group 2	Group 3	P-value
10	109.17±6.28	106.28±6.59	113.62±7.58	0.0008
20	108.42±6.17	105.88±6.74	112.62±6.56	0.0001
30	107.51±5.77	104.80±6.12	112.05±6.67	0.00001

Table 5: Comparison of SBP after giving premedication

Time (in Minutes)	Group 1	Group 2	Group 3	P-value
10	61.57±6.04	60.51±4.03	62.28±4.41	0.700
20	60.22±4.82	58.94±6.40	59.45±4.60	0.414
30	60.05±5.35	59.24±6.92	56.68±4.07	0.037

Table 6: Comparison of DBP after giving premedication

	Group 1	Group 2	Group 3	P-value
I/V Cannulation	2.94±0.70	2.77±0.70	3.42±0.56	0.000
Mask Acceptance	3.45±0.70	3.00±0.76	3.62±0.59	0.001

Table 7: Reaction to Intravenous cannulation and Mask acceptance

Time (in Minutes)	Group 1	Group 2	Group 3	P-value
Emergence	2.31±0.58	2.14±0.73	2.68±0.47	0.001
10	2.25±0.56	2.14±0.77	2.68±0.47	0.001
30	2.40±0.47	2.40±0.55	2.65±0.48	0.057
60	2.51±0.50	2.25±0.61	2.57±0.50	0.040

Table 8: Sedation score after surgery

DISCUSSION: Children suffer from severe anxiety and apprehension when they are separated from their parents or family members for the induction of anaesthesia. Preoperative anxiety can largely affect the smoothness of induction, emergence from anaesthesia and the psychological and emotional state of the child. Present study was done to compare and evaluate the efficacy of midazolam, clonidine and butorphanol as premedicants administered via oral route to the children undergoing elective surgery. The demographic parameters of age, sex and weight of patients in all the three groups were statistically comparable (P-value>0.05). The mean values for sedation score were comparable in the three groups before giving premedication to the children (P-value>0.05).

The sedation score after midazolam premedication started increasing at 10 minutes (2.31±0.83) and this increase persisted till 30 minutes. Our result is comparable to the results obtained by Yuen et al (2008) who observed that 21.9% of the patients were satisfactorily sedated at parental separation after oral midazolam premedication 0.5 mg/kg.[14] Our study is also in accordance with study done by Anjan Das et al (2013) which concluded that oral midazolam is better than oral clonidine in producing preoperative sedation.[15] Our study is in accordance with Trevor et al (2012).

In that study, at the time of separation from the parents, 80% of the children in the clonidine group were adequately sedated as compared to midazolam group, where only 30% were adequately sedated.[16] V Singh et al (2005) concluded that oral butorphanol offered comparable preoperative sedation with oral midazolam, but analgesia was an additional advantage.[13] Our study is consistent with Almenrader et al (2007) according to which oral clonidine appeared to be superior to midazolam as oral clonidine was better accepted by the child and produced more effective preoperative sedation.[17] Satisfactory sedation at parental separation in the present study was seen in more than 80% patients with clonidine and more than half of the patients with butorphanol. Steal induction however could not be produced in any of the patients with butorphanol while steal induction was possible in 4 patients in clonidine. Sedative effects of clonidine are due to inhibition of pontine locus coeruleus which is an important source of sympathetic nervous system innervations of forebrain and a vital modulator of vigilance.

The result is a calm patient who can be aroused to full consciousness. The quality of sedation produced by this is therefore different from drugs that act on GABA receptors like benzodiazepines or drugs acting on opioid receptors like butorphanol. There was no statistically significant difference in heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) amongst the three groups before administration of the study drug. On intergroup comparison, it was found that heart rate was lowest on an average in group 3 as compared to group 1 and 2. Likewise, SBP decreased in all three groups and the mean values were comparable and the difference in the mean values was insignificant in all three groups. The lowest values for DBP were recorded with group 3.Our findings are in accordance with the study of Bhakta et al (2007), who found better mask acceptance with midazolam than control group and they found 66.6% patients were agitated during mask induction in the control group.[18] On intergroup comparison, postoperative sedation score were lowest in group 2 as compared to group 2 and 3.

CONCLUSION: Oral midazolam, butorphanol and clonidine in the dose of 0.5mg/kg, 0.2mg/kg and 4µ/kg respectively provide good preoperative sedation and easier child-parent separation. However, clonidine causes the best sedation among the three drugs and it causes minimum response to i.v cannulation and comparable mask acceptance with midazolam followed by butorphanol.

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