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Original Article

Oral administration of intravenous solution of midazolam mixed in syrup of paracetamol is an effective way of premedicating children undergoing surgery under general anaesthesia

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Objective: The purpose of this study was to evaluate the efficacy of injection midazolam administered by oral route mixed in paracetamol syrup as a premedication in children undergoing surgery.
Methods: 60 children undergoing elective hernia repair under general anaesthesia were randomized into two groups: the study group (group A) was given oral midazolam 0.5mg/kg (mixed in paracetamol syrup) and the control group (group B) was given just the paracetamol syrup before bringing them inside the operating theater. They were evaluated for ease of separation from their parents, ease of i.v. cannulation and induction, and for recovery time from anaesthesia.
Results: it was found that in group A-96.7% of children showed satisfactory parent child separation while in group B- only 53.3% of children showed satisfactory separation ($P < 0.05$). Similarly in group A -73.3 % of children shad satisfactory induction while in group B only 33.3% of children had satisfactory induction. The recovery time from general anaesthesia did not differ in the two groups. No significant peri operative complications directly related to oral midazolam was noted.
Conclusion: It was concluded that injection midazolam mixed in syrup paracetamol administered orally is a convenient and efficient method of premedicating children undergoing general anaesthesia. Parent-child separation and induction of anaesthesia was smooth and the recovery uneventful in children premedicated with oral midazolam.

Key words: Anxiety, midazolam, paracetamol, premedication, oral, parent-child separation, induction, recovery.

Preoperative preparation of a child undergoing surgery is a major challenge in anaesthesia. Between 40 and 50% of children undergoing anaesthesia and surgery will experience peri-operative anxiety. When we provide anaesthesia care to children we must insure the reduction of anxiety, facilitate parental separation and strive to reduce the negative behavioural changes associated with the preoperative experience.[14, 16]

Despite reassurance from the parents as well as the anaesthesiologist most of the children especially in the age group of one to six years old, are usually very anxious and stressed when they come for surgery. They are often consumed by an overriding fear of needles. Separating the child from their parents to take them to the operating theater is usually a big problem due to separation anxiety. Variables like age (1-6years), previous poor quality medical encounters, previous surgery or hospitalization, shy or inhibited temperament, poor social adaptability, increased parental anxiety, parents who employ avoidance coping methods and children of separated or divorced parents are all risk factors for the development of peri-operative anxiety in children.[11,12,14,16]

Various interventions like parental presence during surgery, preoperative preparation programme for children prior to surgery and different pharmacological pre-medication has been tried to tackle the peri-operative anxiety in children. Different pharmacological preparations has been tried and used by different routes for pre-medications in paediatric population. Oral and transmucosal routes have been the most popular since these routes are the ones most accepted by the children. The ideal premedicant for anaesthesia in children should possess the following attributes: an acceptable and atraumatic route of administration, rapid and reliable unset, minimal side effects, rapid elimination.[4, 8-15, 17, 18, 28]

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Recent reports have indicated that oral midazolam fulfil many of these characteristics. Midazolam is an imidazo benzodiazepine derivative utilized as a premedicant, sedative, and an anaesthetic induction agent. It is one of the most lipid soluble of the benzodiazepine. The high lipophilicity has a number of clinical consequences including rapid absorption of midazolam from the gastro intestinal tract and rapid entry of it into brain tissue after intravenous administration. Midazoalm has the anxiolytic, hypnotic, anticonvulsant, muscle relaxant and anti grade amnestic effects characteristics of benzodiazepines. After oral administration, midazolam is absorbed very rapidly from the gastrointestinal tract. Peak plasma concentration generally are achieved within 30 minutes of ingestion and the onset of clinical effects after oral administration is correspondingly rapid (< 10 mins). There is extensive first pass hepatic metabolism after oral administration and on average only 40 to 50% of an orally administered dose reaches the systemic circulation in its non metabolized form. The elimination half life of oral midazolam is similar to or identical to that observed after i.v administration indicating that the rate of elimination is independent of the route of administration. In clinical practice midazolam is remarkably free of side effects. [1,6,19, 23-26]

Paracetamol (Acetaminophen) is commonly used in children because of its analgesic and antipyretic properties and because of its safety. It is extensively metabolized to sulphate and glucuronide derivatives in the liver, with only 2 % to 5% being excreted unchanged. Between 85% to 95% of paracetamol or its metabolite is excreted in the urine within 24 hours of administration in healthy subjects. After oral administration time to peak plasma concentration (T_{max}) is 20-90 minutes and the half life ($T_{1/2}$) of paracetamol is 1.9 to 2.5 hours.[3,7]

Materials and methods

This was a single-blind placebo controlled randomized study of 60 patients aged 1-6 years undergoing elective inguinal hernia repair under general anaesthesia. Each child was brought to the operation theater preparation room along with their parents and was administered one of the preanaesthetic medication. The patients were randomly assigned to one of the two groups. One group (study group) received 0.5 mg per kg oral midazolam in a volume of 0.1ml/kg (5mg/ml parenteral formulation) diluted in 5-10ml of flavoured syrup of paracetamol (125mg/5ml commercial preparation). For children up to 15 kg, 5ml of syrup paracetamol was used and for bigger children (weight more than 15 kgs), 10 ml syrup paracetamol was used. Second group received syrup paracetamol (5-10 ml) only, according to body weight. (control group).

After 20 minutes the children were separated from their parents and taken to the operation theater for the induction of anaesthesia. At the time of parent-child separation, a four-point "separation score" was assigned and recorded for each child (Table 1)

Table 1: Ease of separation score

1. Excellent – patient unafraid, cooperative or asleep.
2. Good – slight fear and/or crying, quiet with reassurance.
3. Fair – moderate fear and crying, not quiet with reassurance.
4. Poor – crying, need for restraint.

In the operating theatre, after placing appropriate monitors (ECG, pulse oximeter, blood pressure cuff for NIIBP, precordial stethoscope), one of the anaesthetist took care of the airway and oxygenation by holding a face mask over the child, while another person attempted to secure an i.v. access. At the time of application of the facemask and securing an i.v. access for i.v. induction, the patients were assessed for ease of induction by again using the four-point scale (Table 2). If the child was not cooperative and it was difficult to secure an i.v. access, halothane was administered by face mask to calm the patient.

Table 2: Ease of induction scoring

1. Excellent – patient unafraid, cooperative or asleep.
2. Good – slight fear and/or crying, but quiet with reassurance.
3. Fair – moderate fear and crying, not quiet with reassurance.
4. Poor – crying, need for restraint.

Once peripheral i.v. cannula was placed, Atropine 0.015 mg/kg intravenous was given to all patients .The children were then induced with intravenous ketamine and kept on spontaneous respiration with oxygen support provided by face mask using paediatric breathing circuit (Jackson-Reese modified T-piece). Ilioinguinal-iliohypogastric nerve block was performed in all patients with injection lignocaine 1% with adrenaline. Anaesthesia was maintained with additional boluses of intravenous

ketamine according to the patient response. After the end of surgery patients were allowed to recover in left lateral position fully monitored, and transported to the post operative ward only after the patient was awake, obeying to verbal command and had adequate respiration. The time from the end of surgery and the transfer of the patient to the post-operative ward was noted as the recovery time.

Results

In the study group, out of 30 patients, 22 patients (73.3%) showed excellent parent-child separation, 7 patients (23.3%) showed good separation, while only 1 patient (3.3%) had a poor separation (Table 3). On the other hand in the placebo group, only 6 patients (20.0%) showed excellent parent-child separation, 10 patients (33.3%) showed good separation and 11 patients (36.7%) had poor separation. So, although the number of patients having good parent-child separation was similar in both groups, the number of patients having excellent separation was significantly higher whereas the number of patients having poor separation was significantly lower, in the study group (p value – 0.00010499).

Parent-child separation was considered as satisfactory if the patients had either "excellent" or "good" ease of separation score. Similarly parent-child separation was considered as unsatisfactory if the patients had either "fair" or "poor" ease of separation score. In the study group 96.7% (29 out of 30) showed satisfactory separation, whereas in the placebo group only 53.3% (16 out of 30) showed satisfactory separation. (P = 0.0003466) (Table 4)

In the study group, out of 30 patients, the ease of induction score was "excellent" in 9 patients (30%) (Table 5) "good" in 13 patients (43.3%), "fair" in 6 patients (20.0%), and "poor" in 2 patients (6.7%). On the other hand in the placebo group, out of 30 patients, the ease of induction was "excellent" only in 1 patient (3.3%), "good" in 9 patients (30.0%), "fair" in 7 patients (23.3%), and "poor" in 13 patients (43.3%). So although the number of patients with ease of induction scores of "good" and "fair" were similar in both the groups, the number of patients with the ease of induction score being excellent was significantly higher and the number of patients with ease of induction score being poor was significantly lower in the study group.

Induction was considered to be satisfactory in those patients who showed "excellent" or "good" ease of induction score. Similarly induction was considered to be unsatisfactory in those patients showing "fair" or "poor" ease of induction score. So in the study (midazolam) group, 73.3% (22 out of 30) had satisfactory induction with only 26.7% (8 out of 30) having unsatisfactory induction, while in the placebo group, only 33.3% (10 out of 30) had satisfactory induction and 66.7% (20 out of 30) had unsatisfactory induction.

There was no significant difference in the recovery time between the patients in the study group and the placebo group (p-value 0.560634).

Table 3: Ease of parent-child separation

			Ease of separation score				Total
			Excellent	Good	Fair	Poor	
Patient Group	Study Group	Number	*22*	*7*	*1*		*30*
		Percent	*73.3%*	*23.3%*	*3.3%*		*100.0%*
	Placebo Group	Number	*6*	*10*	*11*	*3*	*30*
		Percent	*20.0%*	*33.3%*	*36.7%*	*10.0%*	*100.0%*
Total		Number	*28*	*17*	*12*	*3*	*60*
		Percent	*46.7%*	*28.3%*	*20.0%*	*5.0%*	*100.0%*

Table 4: Ease of separation score according to patient

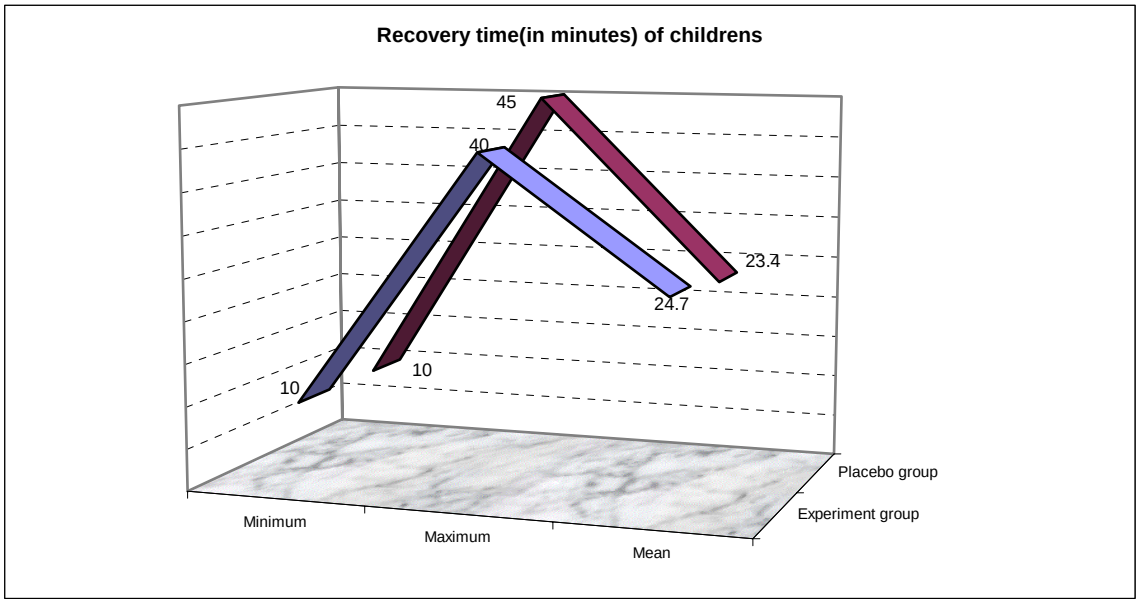
			Ease of separation score		Total
			satisfactory separation	unsatisfactory separation	
	Study Group	NO	29	1	30
		%	96.7%	3.3%	100.0%
	Placebo Group	NO	16	14	30
		%	53.3%	46.7%	100.0%
Total		NO	45	15	60
		%	75.0%	25.0%	100.0%

Table 5: Ease of induction score

			Ease of induction score				Total
			Excellent	Good	Fair	Poor	
Patient Group	Study Group	Number	*9*	*13*	*6*	*2*	*30*
		Percent	*30.0%*	*43.3%*	*20.0%*	*6.7%*	*100.0%*
	Placebo Group	Number	*1*	*9*	*7*	*13*	*30*
		Percent	*3.3%*	*30.0%*	*23.3%*	*43.3%*	*100.0%*
Total		Number	*10*	*22*	*13*	*15*	*60*
		Percent	*16.7%*	*36.7%*	*21.7%*	*25.0%*	*100.0%*

Table 6: Ease of induction score according to patient group

			Ease of induction score		Total
			Satisfactory induction	unsatisfactory induction	
	Study group	NO	22	8	30
		%	73.3%	26.7%	100.0%
	Placebo Group	NO	10	20	30
		%	33.3%	66.7%	100.0%
Total		NO	32	28	60
		%	53.3%	46.7%	100.0%



Discussion

Preoperative preparation of a child undergoing surgery is a major challenge in paediatric anaesthesia. Between 40 and 50% of children undergoing anaesthesia and surgery will experience perioperative anxiety. When we provide anaesthesia care to children, we must ensure the reduction of anxiety, facilitate parental separation and strive to reduce the negative behavioural changes associated with the preoperative experience.[14, 16]

Despite reassurance from the parents as well as the anaesthetist, most of the children, especially in the age group of one to six years old, are usually very anxious and stressed when they come for the surgery. Separating the child from their parents to take them to the operating theater is usually a big problem due to separation anxiety.

Although methods like parental presence in the operation theater, preoperative counselling of the children, use of dolls and toys for distraction, etc, have all been tried as a means making the surgery a less traumatic experience for the children, none of the methods were always successful and practical.

Many drugs have been studied and used as a premedication by different routes of administration. Out of all those midazolam given orally have gained the most popularity as a premedication in the children. It is the most commonly used premedication in children in the United States currently[29-33].

This study was done to evaluate the efficacy of intravenous solution of midazolam given orally as a premedication to children undergoing surgery. Children, aged 1 to 6 years, were chosen because this age group is most vulnerable to anxiety and stress while coming for surgery. They are the ones that are most difficult to separate from their parents. Since oral preparations of midazolam are not yet available in Nepal, we used the injection form of midazolam mixed in syrup of Paracetamol to make it palatable. Injection midazolam has been mixed with plain syrups, flavoured syrups, apple juice, etc to mask the bitter taste and make it more palatable for oral administration.[20,21] We decided to use commercially available flavoured paracetamol syrup to mix with injection midazolam, since paracetamol is commonly used in children because of its analgesic and antipyretic effects and because of its safety. Paracetamol is often administered orally (10-15mg/kg) or given rectally as a suppository to children before the start of the surgery with the aim of providing analgesia and antipyresia in the immediate post-operative period.[3,7] So besides making the bitter intravenous solution of midazolam more acceptable for children to swallow, flavoured paracetamol syrup can also play a role in providing additional analgesia intraoperatively as well as in the immediate post-operative period, but this aspect of paracetamol was not evaluated in this study.

In our study, we found that the children who were premedicated with oral midazolam were much easier

to separate from their parents and also were easier to induce in comparison to children who were given just the paracetamol syrup (placebo). Almost all the children tolerated the oral midazolam well and swallowed it without difficulty. There were not any significant perioperative complications attributable to midazolam premedication. The recovery times from general anaesthesia were noted and it was found to be similar in both the study groups. In our study the use of midazolam as a premedication did not significantly prolong the recovery period, which is one of the major concern to the anaesthesiologists when using sedatives as a premedication.

Conclusion

From these findings we can conclude that giving intravenous solution of midazolam 0.5mg/kg body weight orally (mixed with 5-10 ml of syrup paracetamol) is a safe and effective method of premedicating children undergoing surgery under general anaesthesia. But comparative studies with other oral premedication drugs like ketamine, promethazine, diazepam, lorazepam etc has to be done in order to prove midazolam's superiority over the other drugs as a premedicant.

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