

## Original Article

# Comparative evaluation of midazolam and butorphanol as oral premedication in pediatric patients

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## Abstract

**Background:** To compare oral midazolam (0.5 mg/kg) with oral butorphanol (0.2 mg/kg) as a premedication in 60 pediatric patients with regards to sedation, anxiolysis, rescue analgesic requirement, and recovery profile.

**Materials and Methods:** In a double blinded study design, 60 pediatric patients belonging to ASA class I and II between the age group of 2–12 years scheduled for elective surgery were randomized to receive either oral midazolam (group I) or oral butorphanol (group II) 30 min before induction of anesthesia. The children were evaluated for levels of sedation and anxiety at the time of separation from the parents, venepuncture, and at the time of facemask application for induction of anesthesia. Rescue analgesic requirement, postoperative recovery, and complications were also recorded.

**Results:** Butorphanol had better sedation potential than oral midazolam with comparable anxiolysis at the time of separation of children from their parents. Midazolam proved to be a better anxiolytic during venepuncture and facemask application. Butorphanol reduced need for supplemental analgesics perioperatively without an increase in side effects such as nausea, vomiting, or unpleasant postoperative recovery.

**Conclusion:** Oral butorphanol is a better premedication than midazolam in children in view of its excellent sedative and analgesic properties. It does not increase side effects significantly.

**Key words:** Anxiolysis, oral midazolam, oral butorphanol, premedication, pediatric anesthesia, sedation

## Introduction

Planning and carrying out a smooth transition from an awake state to surgical anesthesia in a child's is a challenge for all the anesthesiologists. Preoperative anxiety can have negative physiological and psychological effects on a child.<sup>[1]</sup> Various interventions used to allay the anxiety of a child during the perioperative period are sedative premedications, parental presence during induction, and preoperative preparation programs.<sup>[2,3]</sup> Sedation remains one of the widely

used methods for decreasing anxiety in young children. The oral route remains the most accepted method of drug administration though various combinations of drugs and routes of administration are available.<sup>[4]</sup>

In this study, an attempt was made to compare midazolam premedication, a gold standard in pediatric patients, with butorphanol, an opioid agonist–antagonist as a premedication in children. Butorphanol has desirable sedative and analgesic properties, which are not yet fully explored in pediatric patients.

## Materials and Methods

After obtaining approval from the hospital ethics committee and written informed consent from parents, 60 pediatric patients, aged 2–12 years, of ASA grade I and II were included in the study. All these children were scheduled for elective surgery with anticipated duration of surgery between 30 min and 2 h. Patients with central nervous system disorders, obesity (weight > 95<sup>th</sup> percentile for age), gastrointestinal disorders that affect drug absorption, known adverse reaction to benzodiazepines/opioids were excluded from the study. If

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the premedication was incompletely ingested, the child was excluded from the study. The patients were randomly allocated into two groups using a computer based randomization list. Children in group I received midazolam 0.5 mg/kg orally, while group II received butorphanol 0.2 mg/kg orally. Due to unavailability of oral midazolam, parental preparation of midazolam was used to prepare the syrup. Both the drugs were diluted to a fixed volume with honey by a pharmacist to make it palatable. All the observers were unaware of the contents of the premedication. Demographic data (age, sex, and weight), baseline vital parameters (heart rate and blood pressure), anxiety scores, and sedation scores were recorded by the same investigator to minimize interobserver variability. Children were administered midazolam (group I) or butorphanol (group II), 30 min before induction of anesthesia. Hemodynamic parameters—pulse rate, noninvasive systolic and diastolic blood pressure, sedation score, and anxiety score were recorded at the time of separation from parents (20 min), venepuncture (25 min), and mask application (30 min).

General anesthesia was administered in a standardized manner. Rescue analgesia in the form of intravenous fentanyl (1 mcg/kg) was administered, if heart rate/blood pressure increased >25%. Postanesthesia recovery was assessed for a period of 24 h with respect to nausea, vomiting, recollection of venepuncture/facemask application, analgesic requirement, and unpleasant recovery (irritability and excessive crying).

The grading of sedation was based on four-point scoring system: 1—awake, 2—alert, 3—drowsy, and 4—asleep. Anxiolysis was graded based on four-point grading system: 1—panicky, 2—moaning, 3—composed, and 4—friendly.<sup>[4]</sup> Patients whose anxiolysis score was greater or equal to 3 were considered to have adequate anxiolysis, while patients with sedation score greater or equal to 3 were considered to have adequate sedation. Postoperative analgesia was assessed using modified pain score and rescue analgesia was administered using paracetamol syrup 10 mg/kg.<sup>[5]</sup>

Data analysis for demographic variables was done with unpaired students-*t* test. Anxiolysis and sedation scores were compared using chi square analysis. Analgesia between both the groups was compared using Fischer's exact test. A *P* value < 0.05 was considered statistically significant.

## Results

There was no statistically significant difference between the demographics (age, sex, ASA grade, and duration of surgery) and baseline vital signs (heart rate, BP, and SpO<sub>2</sub>) of the two groups. [Table 1]

At the time of separation from parents, 30% of patients belonging to group I (midazolam) were adequately sedated, compared to 80% of patients in group II (butorphanol). The overall difference in sedation between the two groups was found to be statistically significant, as shown in Table 2. However, the difference in sedation scores at the time of interventions like facemask application and venepuncture was not statistically significant [Table 2].

Patients in group I had a lower level of anxiety than group II after administration of premedication. At the time of separation from parents, 80% of children of group I had adequate anxiolysis when compared to 60% of the butorphanol group. The difference in anxiety between the two groups was not found to be statistically significant. At the time of venepuncture, 70% of the children of group I had adequate anxiolysis when compared to 37% of children of group II, which was statistically significant. 70% of the children in group I (midazolam) had adequate anxiolysis during facemask application, when compared to 30% of the children in group II (butorphanol). The difference in anxiety between the two groups was statistically significant [Figure 1].

36.7% of children in group I (midazolam) needed rescue analgesia, when compared to 6.7% in group II, which was highly significant statistically [Table 3]. The differences in other parameters studied (recovery, nausea, and recollection) were statistically insignificant [Table 3].

## Discussion

The quest for an ideal pediatric premedication drug is still on. Oral midazolam has been considered the gold standard for premedication in children. In a study conducted in US, more than 80% of anesthesiologists preferred midazolam as a premedication.<sup>[6]</sup> It has many desirable properties such as early onset and better level of sedation with no delay in recovery.<sup>[7]</sup> Although it has a number of beneficial effects, midazolam is far from an ideal premedication, especially

**Table 1: Distribution of subjects according to demographic profile and vital signs**

	Group I (n = 30)	Group II (n = 30)
Age (years) mean ± SD*	6.90 ± 2.99	6.23 ± 2.59
Weight (kg) mean ± SD*	19.77 ± 6.15	20.00 ± 7.25
Sex (M/F) *	21/9	20/10
ASA I/II*	12/18	14/16
Duration of surgery*	97.34 ± 40.03	92.28 ± 37.51
Heart rate before surgery*	93.06 ± 7.69	94.10 ± 9.12
Systolic blood pressure*	103.86 ± 7.46	103.40 ± 8.05

\**P*-value: NS Group I—midazolam group; group II—butorphanol group

**Table 2: Comparison of sedation score at the time of separation from parents, at venepuncture, and at facemask application**

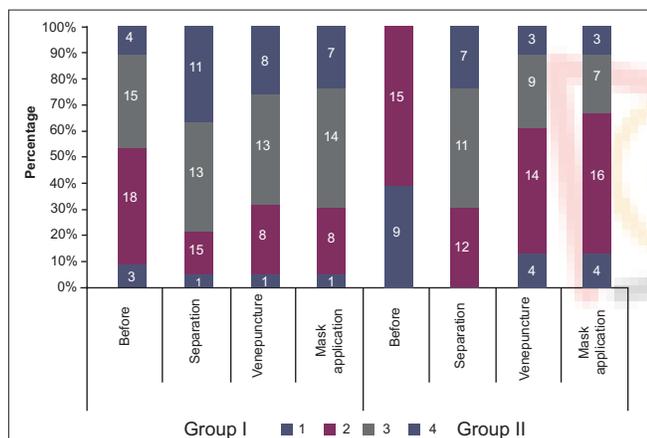
Sedation score	At separation from parents		At venepuncture		At facemask application	
	Group I no. (%)	Group II no. (%)	Group I no. (%)	Group II no. (%)	Group I no. (%)	Group II no. (%)
1	2 (6.7)	0 (0)	4 (13.3)	4 (13.3)	4 (13.3)	6 (20)
2	19 (63.3)	6 (20)	19 (63.3)	16 (53.3)	20 (66.7)	16 (53.3)
3	9 (30)	16 (53.3)	7 (23.3)	7 (23.3)	6 (20)	7 (23.3)
4	0 (0)	8 (26.7)	0 (0)	2 (6.6)	0 (0)	1 (3.3)
X2 and P- value	X2 = 18.78; P < 0.01 Very highly significant		X2 = 1.832; P = 0.608 Not significant		X2 = 1.921; P = 0.589 Not significant	

No.—number of subjects; group I—midazolam group; group II—butorphanol group

**Table 3: Recovery profile and complications among the groups**

	Group I (n) %	Group II (n) %	P value
Requirement of rescue analgesia -intraoperative	11 (36.7)	2 (6.7)	P = 0.01 highly significant (fishers exact test)
Requirement of rescue analgesia in the first 24 h	28 (93.3)	19 (63.3)	P = 0.01 highly significant (fishers exact test)
Nausea/vomiting	3 (10)	8 (26.7)	P = 0.182 NS
Recollection	4 (13.3)	1 (3.3)	P = 0.353 NS
Poor recovery (nightmares, excessive crying)	4 (13.3)	1 (3.3)	P = 0.353 NS

No.—number of subjects, group I—midazolam group, group II—butorphanol group



**Figure 1:** Comparison of anxiety score at the time of separation from parents, venepuncture, and separation. Group I—midazolam group; group II—butorphanol group

with regards to confusion, long-term behavioral changes, and respiratory depression.<sup>[8,9]</sup> Numerous studies have been done comparing it with other drugs such as ketamine, clonidine, and dexmedetomidine, with mixed results.<sup>[6,9-16]</sup>

Butorphanol is a mixed agonist antagonist with intrinsic activity at mu-opioid receptors and a kappa agonistic activity. It has been used orally as an analgesic for chronic/cancer pain,<sup>[17]</sup> but there is only one study in literature on its efficacy as a pediatric premedication.<sup>[18]</sup>

The population sample studied was homogenous with regards characteristics such as age, weight, sex, anxiety, and sedation scores. Since oral preparations of midazolam are not widely

available, we used the parenteral form of midazolam and mixed it in honey to make it palatable.<sup>[19]</sup>

Sedation and anxiety score were noted prior to premedication and at regular intervals—at the time of separation, venepuncture, and facemask application. The standard time of separation was taken as 30 min. Kain *et al.*<sup>[20]</sup> have shown that midazolam can be given as late as 10 min before separation with satisfactory results. Placebo group was not used for comparison, as the lack of placebo effect in this age group has been demonstrated previously.<sup>[21]</sup> The degree of sedation and anxiolysis in our study was far greater than that obtained by Feld *et al.*<sup>[22]</sup> This difference could be attributed to the fixed time of separation in our study as compared to their study, where separation occurred anytime between 30 and 80 min after administration of oral midazolam. Such a wide time-interval limits interpretation of the pharmacodynamic effects of oral midazolam. Gopalvar *et al.* premedicated 706 children, between age of 6 months and 6 years, with midazolam and found that 24 of these children developed paradoxical reactions such as violent crying and were struggling within 10 min of the intravenous drug administration.<sup>[23]</sup> We did not encounter paradoxical reactions and this may be due to the smaller study size and the age group chosen. Paradoxical reactions are more common in the younger age group.

Singh *et al.* orally premedicated 60 pediatric patients with midazolam (0.5 mg/kg) or butorphanol (0.2 mg/kg) and had results similar to that of our study.<sup>[18]</sup> They found that sedation score were comparable in both the groups at

parental separation and venepuncture and the butorphanol group had better scores at the time of facemask application. Anxiety scores of both the groups were not compared in their study. Analgesic requirement was more in midazolam group (30%) when compared to butorphanol group (10%). There was no increase in side effects such as vomiting or delayed recovery in the butorphanol group. In our study, butorphanol provided better sedation at all levels with decreased analgesic requirement postoperatively. Anxiolysis in our study was better in the midazolam group at all intervals except at the time of separation from parents, when it was comparable in both the groups. The analgesic requirement in the patients of butorphanol group was less (6%) compared to the midazolam group (37%).

One of the most common side effects with the use of an opioid is nausea or vomiting.<sup>[24]</sup> We did not find a significant increase in the incidence of these side effects in the butorphanol group (27%) when compared to the midazolam group (10%). The limitations of our study are that postoperative recollection of perioperative events was unreliable in children < 5 years of age and that the sample size was small.

## Conclusion

Butorphanol has better sedation potential than oral midazolam with comparable anxiolysis at the time of separation of children from their parents. However, midazolam is a better anxiolytic during venepuncture and facemask application. Butorphanol has additional analgesic property reducing need for supplemental analgesics and does not increase side effects such as nausea and vomiting.

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