

A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients

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ABSTRACT

Background: This study was designed to evaluate the efficacy and safety of oral midazolam, tramadol drops, and intranasal sufentanil for premedication of pediatric patients.

Methods: Sixty children, three to 10 years of age, who were designated as American Society of Anesthesiologists physical status I and who were undergoing adenotonsillectomy as inpatients were randomized to receive a dosage of 0.5 mg/kg (total of 4 mL) midazolam in cherry juice ($n = 20$, Group M), 3 mg/kg tramadol drops ($n = 20$, Group T), or 2 μ g/kg intranasal sufentanil ($n = 20$, Group S). Clinical responses (sedation, anxiolysis, cooperation) and adverse effects (respiratory, hemodynamic, etc.) were recorded. Safety was assessed by continuous oxygen saturation monitoring and observation. Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate) were recorded before drug administration (baseline) and then every 10 minutes until the induction of anesthesia.

Results: Mean blood pressure decreased significantly after five minutes of intranasal sufentanil administration relative to Groups M ($p < 0.01$) and T ($p < 0.05$), whereas heart rate remained unchanged. Oxygen saturation and respiratory rate decreased significantly after 20 and 30 minutes of intranasal sufentanil administration relative to Groups M and T ($p < 0.05$). Anxiety scores showed rates of 45 percent in Group M, 5 percent in Group T, and 40 percent in Group S. Anxiety scores in Groups M and S were better than those of Group T ($p < 0.01$). Cooperation scores for face-mask acceptance showed rates of 85 percent in Group M, 45 percent in Group T, and 85 percent in Group S ($p < 0.01$).

Conclusion: Intranasal sufentanil and oral midazolam are more appropriate premedication options than tramadol drops in children.

Key words: children, oral midazolam, oral tramadol, intranasal sufentanil

INTRODUCTION

Surgery and anesthesia induce considerable emotional stress in both parents and children.¹ The aftereffects of this stress, including prolonged night terrors, negativism, a variety of phobias, hysterical reactions, and anxiety reactions, may endure long after the hospital experience has ended. Preanesthetic medication may reduce the risks of adverse psychological and physiological sequelae of induction of anesthesia in distressed children. Premedication may be administered orally, intramuscularly, intravenously, rectally, nasally, or sublingually, and should provide effective anxiolysis and conscious sedation in order to improve the conditions surrounding parental separation and induction of general anesthesia.

Midazolam is the most commonly ordered premedication in pediatric anesthesia practice. More than 85 percent of anesthesiologists responding to a national survey of premedication practices conducted by Kain et al.² indicated that they prescribed midazolam when they chose to premedicate. The benefits of effective premedication include a reduction in both patient and parental separation anxiety, partial anterograde amnesia, facilitation of a smooth anesthetic induction, and a reduction in reported undesirable postoperative behavioral changes.^{3,4} There are numerous published reports documenting the safety and efficacy of oral midazolam premedication in children between one and 12 years of age.^{5,6}

Tramadol hydrochloride is a racemic mixture of two enantiomers. It has analgesic activity suitable for mild to moderate pain, with part of its analgesic activity modulated via μ receptors. It has a low affinity for opioid receptors, but it also exerts its effect through direct modulation of central monoaminergic pathways. In children older than one year, tramadol is well tolerated and is an effective postoperative analgesic, with adverse effects similar to those of other opioids.⁷

Sufentanil is the most potent opioid available today,

and is perhaps closer to the future of opioids than any of the other drugs available to clinicians. It is more than twice as lipid soluble as fentanyl; however, its properties, including its high degree of plasma protein binding (98 percent) and lower volume of distribution, are the probable explanation for sufentanil's shorter elimination half-life and duration of effect compared with fentanyl. Sufentanil also has a high affinity for the μ receptor—higher than that of any other opioid.⁸ Intranasal sufentanil has been used in pediatric populations to ease separation from parents, decrease coughing, decrease inhalation anesthetic requirements, and provide faster and smoother recoveries.⁹ Nasal midazolam in doses of 0.2 or 0.3 mg/kg has been used to provide sedation within five to 10 minutes and to ease separation.

Intranasal sufentanil, oral midazolam, and oral tramadol are all effective for preinduction of pediatric patients, but there are no data on which to base a choice between them. The purpose of this study was to evaluate the efficacy and safety of three different pediatric premedication regimens.

METHODS

After obtaining institutional review board approval and informed parental consent, we studied children aged three to 10 years with American Society of Anesthesiologists (ASA) physical status I who were undergoing minor surgery for adenotonsillectomy with general anesthesia. Exclusion criteria included 1) known adverse reaction to benzodiazepines; 2) use of sedative/hypnotic, narcotic, anticonvulsant, stimulant, or other medications reported to affect the minimum alveolar anesthetic concentration of inhaled anesthetics within the previous month; and 3) the presence of neurologic, renal, or hepatic disease. All patients were allowed food ad libitum eight hours before surgery and a maximum of 10 mL/kg clear liquid four hours before the anticipated time of general anesthesia induction. Patients were randomly assigned to one of the following groups according to computer-generated random numbers: 0.5 mg/kg midazolam in cherry juice (4 mL total) (n = 20, Group M), 3 mg/kg tramadol drops (n = 20, Group T), or 2 μ g/kg intranasal sufentanil (n = 20, Group S). Noninvasive mean blood pressure (MBP), heart rate (HR), respiratory rate (RR), and oxyhemoglobin saturation (SpO₂) were measured before drug administration and 40 minutes before separation from parents. Safety was assessed by measuring RR and SpO₂ throughout the study. An SpO₂ of < 90 percent was considered clinically significant. An RR of < 16 breaths/min (three to seven years old) or < 12 breaths/min (seven to 10 years old) was defined as hypoventilation.

Clinical responses (sedation, anxiolysis, cooperation) and adverse effects (respiratory, hemodynamic, etc.)

were assessed by an observer blinded to dose. Safety was assessed by continuous SpO₂ monitoring and observation. Vital signs (BP, pulse, RR) were recorded before drug administration (baseline) and then every 10 minutes until the induction of anesthesia. There was no attempt to control for surgical procedure or additional drugs administered during the induction of anesthesia, as the primary end points for the study were patients' pharmacodynamic responses prior to induction. The authors felt this type of study would be the most generalizable because it closely reflects standard anesthetic practices. A blinded observer evaluated preoperative emotional state, response to premedication, induction, and side effects.

Anxiolysis was assessed on a 4-point scale (poor = afraid, combative, crying, restrained; fair = fearful, moderate apprehension; good = slightly fearful, easily calmed by strangers, noncombative; excellent = no fear or apprehension displayed; not applicable = patient asleep).¹⁰ An anxiety score was also recorded at the time of attempted separation from parents. An anxiety score of 3 or 4 was considered satisfactory. The timing of attempted child-parent separation, which occurred from five to 40 minutes after premedication, was determined by operating-room availability and patient response.

Cooperation was also assessed using a 4-point scale (poor = strongly refuses intervention; fair = considerable effort required to achieve compliance with intervention; good = accepts intervention reluctantly; excellent = accepts intervention readily; not applicable = patient asleep). A cooperation score of 3 or 4 was considered satisfactory. Cooperation was assessed at the time of face-mask application (67 percent N₂O in oxygen [6 L/min fresh gas flow]) and 30 seconds later, when sevoflurane (2 percent) was added.¹¹

Anesthetic technique was standardized. After standard monitors were applied, including an automated BP cuff, electrocardiograph, and pulse oximeter, general anesthesia was induced in all patients using sevoflurane and 67 percent N₂O in oxygen. The concentration of sevoflurane was gradually increased by 0.5 percent every four to five breaths. When the patient was asleep, a forearm peripheral vein was cannulated, and intravenous administration of lactated Ringer's solution containing 2 percent dextrose was started. Ventilation was first assisted and then controlled to obtain end-tidal CO₂ tensions between 30 and 35 mmHg. End-tidal sevoflurane concentration was maintained at 2 percent in 67 percent N₂O in oxygen throughout anesthesia and surgery. When hemodynamic variables were stable, 0.1 mg/kg vecuronium was administered intravenously in all patients. The complications of mask induction and endotracheal intubation were noted, including laryngospasm, arterial oxygen saturation less than 90 percent, and vomiting. At the completion of surgery, residual muscle relaxant was antagonized with 0.02 mg/kg atropine and 0.05 mg/kg

Table 1. Patients' demographic, surgical, and anesthetic data (mean ± SD)

	Group M (n = 20)	Group T (n = 20)	Group S (n = 20)
Age (years)	6.20 ± 1.70	6.75 ± 1.60	6.25 ± 1.50
Male/female	12/8	12/8	7/13
Weight (kg)	22.95 ± 5.89	20.80 ± 7.24	21.90 ± 4.50
Duration of surgery (min)	62 ± 12	58 ± 15	60 ± 14
Duration of anesthesia (min)	78 ± 10	75 ± 12	74 ± 16

neostigmine administered intravenously, and sevoflurane and N₂O were discontinued. The patient's trachea was extubated after confirming spontaneous respiration, spontaneous eye opening, or purposeful muscular movements in the upper extremities.

Statistical analysis was performed using one-way analysis of variance to compare demographic variables and hemodynamic data among groups. When a significant difference was identified, it was followed by an unpaired Student's t-test with Bonferroni correction to adjust for multiple comparisons. Intergroup differences in categoric demographic data, the level of sedation, incidence of adverse effects, and parental satisfaction were also compared using the χ^2 test or Fisher's exact test as appropriate. Changes in hemodynamics and SpO₂ over time were analyzed by two-way analysis of variance with repeated measures, followed by the Wilcoxon signed-rank test. A p value less than 0.05 was considered statistically significant.

RESULTS

There were no significant differences among the three groups in terms of age, gender distribution, weight, duration of surgery, or anesthesia (Table 1). Significant difference was seen with respect to MBP and SpO₂ before premedication among different groups (Table 2). MBP decreased significantly five minutes after intranasal sufentanil administration relative to Groups M (p < 0.01) and T (p < 0.05), whereas HR remained unchanged. SpO₂ and RR decreased significantly 20 and 30 minutes after intranasal sufentanil administration relative to Groups M and T (p < 0.05). There were no clinically important mean changes in MBP, RR, or SpO₂ measurements between the treatment groups.

Upon separation from parent(s), significantly greater proportions of children in the midazolam and tramadol groups were classified as being "asleep" and "calm but awake" than in the sufentanil group. Although three children in the sufentanil group were restless, agitated, crying, or upset at the time of separation, none required restraint when an anesthetic mask was applied for inhalational

induction. An anxiety score was also recorded at the time of attempted separation from parents. Satisfactory anxiety scores were achieved with rates of 45 percent in Group M, 5 percent in Group T, and 40 percent in Group S. Anxiety scores in Groups M and S were better than those in Group T (p < 0.01). Cooperation scores for face-mask acceptance showed rates of 85 percent in Group M, 45 percent in Group T, and 85 percent in Group S (p < 0.01).

Five patients experienced nausea before mask induction (one patient in Group M, three patients in Group T, and one patient in Group S). No clinically important desaturation or laryngospasms were observed in any children during or after the administration of medication.

DISCUSSION

The present results show that oral midazolam and intranasal sufentanil are superior to oral tramadol. Although midazolam can be used as a preanesthetic medication via oral, nasal, rectal, intramuscular, or intravenous routes, oral administration is the most common for children. It is reported that 80 percent of children premedicated with oral midazolam at a dose of between 0.5 and 1.0 mg/kg are sedated satisfactorily for minor surgery.^{6,11} Pediatric pharmacokinetic studies show that the time to maximum plasma concentration after oral administration of 0.25 to 1.0 mg/kg midazolam is 50 minutes (15 to 60 minutes), although clinical studies show a peak sedative effect occurring at 30 minutes after oral administration of midazolam 0.5 mg/kg.¹¹⁻¹³ In the present study, children entered the operating room 40 minutes after midazolam medication, as we predicted that the peak plasma level of midazolam would occur at that time.

During the past two decades, anesthesiologists have been provided with a number of new, potent opioid analgesics and sedatives/hypnotics, as well as an increased understanding of the pharmacokinetic and pharmacodynamic principles that govern the medications' action and disposition. These developments have suggested that nasal mucous membranes may be useful as an alternate route of analgesic and anesthetic drug delivery.¹⁴ The easiest mucosal technology is the

Table 2. Preoperative changes in MBP, HR, SpO₂, and RR (mean ± SD)

	MBP			HR			SpO ₂			RR		
	Group			Group			Group			Group		
Time	M	T	S	M	T	S	M	T	S	M	T	S
Basal	77.9 ± 6.1	77.5 ± 7.9	73.8 ± 10.2	103.4 ± 9.7	99.3 ± 9.3	98.3 ± 10.1	98.6 ± 0.6	98.8 ± 0.4	98.5 ± 0.6	20.8 ± 3.1	18.2 ± 3.5	18.8 ± 1.8
5 min	80.1 ± 6.8	77.2 ± 9.6*	70.1 ± 7.5**	97.4 ± 22.2	99.6 ± 8.6	102.8 ± 8.8	98.5 ± 0.6	98.6 ± 0.7	98.3 ± 0.5	20.2 ± 3.2	18.5 ± 3.0	18.7 ± 1.8
10 min	78.7 ± 8.5	76.7 ± 10.2	71.8 ± 10.1	100.4 ± 7.3	101.4 ± 8.8	99.9 ± 12.3	98.7 ± 0.5	98.6 ± 0.7	98.3 ± 0.8	19.8 ± 3.5	18.6 ± 3.3	17.8 ± 2.1
20 min	75.9 ± 8.5	77.6 ± 9.6	72.8 ± 10.1	98.8 ± 7.3	100.1 ± 9.8	99.8 ± 12.5	98.4 ± 0.6	98.4 ± 0.5	97.7 ± 1.2***	19.7 ± 3.4	18.1 ± 2.7	17.4 ± 2.1***
30 min	75.3 ± 7.2	78.6 ± 8.5	73.1 ± 11.3	99.1 ± 7.3	101.9 ± 12.0	96.1 ± 12.5	98.1 ± 1.0	98.8 ± 0.5	97.9 ± 0.9***	19.9 ± 3.2	18.7 ± 3.3	17.3 ± 2.2***
40 min	78.7 ± 3.5	78.3 ± 7.5	77.3 ± 7.2	98.05 ± 7.8	100.9 ± 8.0	97.1 ± 10.0	98.8 ± 0.4	98.8 ± 0.6	98.8 ± 0.4	19.2 ± 3.1	18.5 ± 2.8	18.1 ± 2.1

n = 20 in each group; MBP (mmHg) = mean blood pressure; HR (beats/min) = heart rate; SpO₂ (percent) = peripheral oxygen saturation; RR(breaths/min) = respiratory rate; * p < 0.05, Group M compared to Group T; ** p < 0.001, Group M compared to Group S; *** p < 0.05, Group S compared to Groups M and T.

transnasal mucosal approach, and this route has been the subject of recent investigation. In one study, sufentanil (1.5, 3.0, or 4.5 µg/kg) was administered to 80 children ranging in age from six months to seven years. Easy separation from parents was achieved in 86 percent of the children 10 minutes after premedication administration. Unfortunately, 61 percent of the children cried after drug administration, and side effects included reduced ventilatory compliance (chest-wall rigidity) with higher doses (3.0 and 4.5 µg/kg). Nevertheless, nasal transmucosal drug delivery may have value, especially for frightened or uncooperative children.⁹ Nasal sufentanil has been used in pediatric populations to ease separation from parents, decrease coughing, decrease requirements for inhalation anesthetic, and provide faster and smoother recoveries.^{9,15} In our study, we found that intranasal sufentanil has similar premedication qualities as compared with midazolam but is a better premedication than tramadol.

Tramadol, a synthetic 4-phenyl-piperidine analog of codeine, is a centrally acting atypical opioid.¹⁶ Although tramadol's mode of action is not completely understood, at least two complementary mechanisms are believed to contribute to its effect. Tramadol's opioid activity results

from low-affinity binding of the parent compound to µ opioid receptors and higher-affinity binding of the M1 (O-desmethylated) metabolite.¹⁷ Tramadol is also a weak inhibitor of norepinephrine and serotonin reuptake.¹⁸ In one study, Payne and Roelofse¹⁹ administered tramadol drops 3 mg/kg plus oral midazolam 0.5 mg/kg 30 minutes prior to anesthesia. They found that no respiratory depression was seen, and preanesthetic behavior patterns were largely the same between the study group and the control: 85 percent of patients in the tramadol group were drowsy but awake, versus 90 percent in the placebo group, and similarly satisfactory induction behavior was seen in 95 percent of the tramadol group versus 90 percent of the placebo group. The researchers concluded that tramadol 3 mg/kg has no clinical respiratory depressant effect and that behavior and recovery times are unaffected. After oral administration, tramadol demonstrates 68 percent bioavailability, with peak serum concentrations reached within two hours.¹⁶ In our present study, children entered the operating room 40 minutes after administration of tramadol, as we thought that it was predicted that the peak plasma level of tramadol occurred at that time, and that intranasal sufentanil and midazolam are better premedications than tramadol.

This study demonstrated a wide safety profile for oral midazolam, oral tramadol, and nasal sufentanil administration; no patient developed clinically important desaturation before the induction of anesthesia. There were slightly significant BP, RR, and SpO₂ decreases in Group S, but these changes were not clinically important. In this study, five patients experienced nausea before mask induction; these events may have been related to the drug or to the patient's response to having to ingest something he or she did not want; it is difficult in many instances to separate a true pharmacodynamic effect from the psychological response of a child. There were no adverse respiratory events before induction. It must be understood, however, that this study involved a highly selected population of patients, the vast majority of whom were ASA class I. This study excluded patients with serious underlying medical conditions, and the responses of and potential for adverse respiratory events in higher-risk patients are likely to be different.

In summary, the data demonstrate that commercially prepared oral midazolam and intranasal sufentanil are rapidly taken up, with the majority of patients demonstrating a satisfactory degree of sedation and anxiolysis within five minutes of consumption relative to tramadol drops. Satisfactory sedation and anxiolysis seem to last for up to 40 to 45 minutes. The present results show that oral midazolam and intranasal sufentanil are superior premedications in pediatric patients as compared to oral tramadol.

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