# A Comparison of Oral Clonidine and Oral Midazolam as Preanesthetic Medications in the Pediatric Tonsillectomy Patient

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We compared the effects of oral clonidine (4 μg/kg) and midazolam (0.5 mg/kg) on the preanesthetic sedation and postoperative recovery profile in children during tonsillectomy with or without adenoidectomy. In a double-blinded, double-dummy study design, 134 ASA physical status I-II children aged 4–12 yr were randomized to receive a combination of either clonidine and placebo (Group A), or placebo and midazolam (Group B) at 60–90 min and 30 min, respectively, before the induction of anesthesia. Children in the clonidine group exhibited more intense anxiety on separation and during induction of anesthesia via a mask as measured by the modified Yale Preoperative Anxiety Scores. They also had significantly lower mean intraoperative arterial blood pressures, shorter surgery, anesthesia, and emergence times, and a decreased need for supplemental oxygen during recovery compared with the midazolam group. However, the clonidine group had larger postoperative opioid requirements, maximum excitement and pain scores based on the Children's Hospital of Eastern Ontario scale in the Phase 1 postanesthetic care unit. There were no differences between the two groups in the times to discharge readiness, postoperative emesis, unanticipated hospital admission rates, postdischarge maximum pain scores, and 24 h analgesic requirements. The percentage of parents who were completely satisfied with the child's preoperative experience was significantly higher in the midazolam group. There were no differences in parental satisfaction with the recovery period. We conclude that under the conditions of this study, oral midazolam is superior to oral clonidine as a preanesthetic medication in this patient population.

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The preoperative period can be a stressful time for children and their parents (1). An ideal preanesthetic medication should ease separation from parents and facilitate patient acceptance of the face mask during induction of anesthesia without prolonging emergence, increasing cardiorespiratory instability, or postoperative delirium, nausea, and vomiting. Midazolam, a γ-amino-butyric acid (GABA) receptor inhibitor, is the most frequently used premedicant in the United States (2). It provided effective sedation, anxiolysis, and varying degrees of anterograde amnesia, but was associated with a paradoxical hyperactive reaction in some patients (3–6). Clonidine, an α 2–adrenergic agonist, was an effective preanesthetic medication in the adult and pediatric population, and also reduced the requirements for both inhaled anesthetics during surgery as well as opioids in the postoperative period (7–13).

Tonsillectomy with or without adenoidectomy is one of the most common outpatient surgical procedures in the pediatric population (14,15). Major postoperative issues include pain, emergence delirium, airway obstruction, and hypoventilation. Opioid therapy for pain management can exacerbate airway obstruction and hypoventilation and increase postoperative emesis (16,17). Nonsteroidal antiinflammatory drugs such as ketorolac are not associated with the respiratory depressant and emetic side effects of opioid administration, but are associated with increased bleeding (18). The present study was designed to test the hypothesis that oral clonidine would provide satisfactory preanesthetic sedation, reduce perioperative anesthetic and opioid analgesic requirements, and consequently be associated with quicker recovery and earlier discharge compared with oral midazolam in

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children during tonsillectomy with or without adenoidectomy.

## Methods

One hundred thirty-four ASA physical status I-II children, aged 4–12 yr, scheduled for tonsillectomy with or without adenoidectomy were enrolled in this double-blinded, double-dummy study after obtaining approval from our IRB and obtaining written, informed consent from the parents. We excluded patients with hypertension, central nervous system disorders, obesity (weight >95th percentile for age), gastrointestinal disorders that affect drug absorption, and those with previous reactions to clonidine or benzodiazepines. Children were assigned to one of two groups based on a computer-generated random numbers table. Group A subjects received oral clonidine 4 μg/kg (maximum 300 μg) 60–90 min and equal volume placebo 30 min before induction and Group B received placebo 60–90 min and oral midazolam 0.5 mg/kg (maximum 15 mg) 30 min before induction. The medications were diluted to a fixed volume by the pharmacist to maintain the double-blinded nature of the study. These doses and times of administration were based on published data from dose-ranging studies (3,5,6,8,13,19).

An observer blinded to the group assignment recorded baseline heart rate, oxygen saturation, and blood pressure before the administration of preanesthetic medication (baseline) and at 30 and 60 min after administration of the first study drug. In addition, the observer used the modified Yale Preoperative Anxiety Scale to evaluate the child's anxiety just before administration of the preanesthetic medication, 10 min before separation from parents, immediately after separation from parents, and on the initiation of induction of anesthesia via a mask (20).

General anesthesia was induced with nitrous oxide, oxygen, and sevoflurane via a face mask. After establishment of IV access, tracheal intubation was facilitated with vecuronium 0.08 mg/kg IV, gastric contents were suctioned, and ventilation was controlled to maintain an end-tidal carbon dioxide partial pressure ($P_{CO_2}$) of 35–45 mm Hg. The inspired concentration of desflurane was adjusted to keep mean arterial blood pressure and heart rate within 30% of baseline values. In addition, patients received ondansetron 0.05 mg/kg IV, ampicillin 25 mg/kg IV, dexamethasone 0.5 mg/kg IV (maximum 10 mg), morphine 75 μg/kg IV, and rectal acetaminophen 30–35 mg/kg (maximum 975 mg). At the end of the surgical procedure, residual neuromuscular blockade was antagonized with glycopyrrolate 0.01 mg/kg IV (maximum 1.0 mg) and neostigmine 0.07 mg/kg IV (maximum 5 mg). The trachea was extubated when the patient made purposeful movements and had a regular respiratory pattern. The time from the end of surgery to tracheal extubation was recorded.

Patients were transferred to Phase 1 postanesthetic care unit (PACU) where a blinded observer recorded their heart rate, respiratory rate, and arterial blood pressure every 5 min for the first 15 min and at 15 min intervals for 60 min. Supplemental oxygen was administered to maintain oxygen saturation values more than 95%, and the duration of oxygen therapy was recorded. The observer also graded patient excitement on a scale of 0–4 (0 = no excitement and 4 = severe excitement) and the child's pain using the Children's Hospital of Eastern Ontario Pain scale (CHEOPS) (21,22). These assessments were made on admission to Phase 1 PACU and at 15 min intervals for 60 min. Children with CHEOPS scores ≥8 received postoperative morphine 25 μg/kg IV, repeated as needed. Patients were discharged from Phase 1 PACU when they had achieved a Steward score of 6, could maintain oxygen saturation values >95% in room air, and were free from bleeding, airway obstruction, and severe pain (CHEOPS score <8) (23). Patients were discharged from Phase 2 PACU after IV repletion of intravascular fluid deficits, provided they remained free from bleeding, airway obstruction, severe pain, and postoperative nausea and vomiting (PONV) for a minimum of 2 h after surgery. The time for qualification for discharge (discharge readiness time) and the actual discharge time from Phases 1 and 2 were recorded along with postoperative medications and complications such as emergence delirium and PONV.

Twenty-four hours after discharge, the parents of each subject were contacted by telephone to determine analgesic and antiemetic use, the number of emetic episodes, and the time to first intake of solid food. We also asked parents to rate the child's worst pain on a 0–10 scale (0 = no pain up to 10 = severe pain), and the quality of sleep pattern disturbances on a similar 11-point verbal rating scale (0 = normal sleep and 10 = severely disturbed sleep). Two to three weeks after surgery, the parents were again contacted to determine the time taken for the child and parent's activities of daily living to return to their preoperative status and to rate their satisfaction with the child's postoperative course. In addition, parents completed a Pre and Postoperative Behavior Questionnaire, a tool for evaluating behavioral responses and developmental regression in children after hospitalization and surgery. (24,25) Parents completed the Prehospitalization Questionnaire during the child's surgery, and the Posthospitalization Questionnaire was completed approximately 2 wk postsurgery and returned by mail.

*A priori* power analysis indicated that 61 patients would be required in each group for a 90% chance of detecting a 3-min difference in emergence times at the 0.01 level of significance. This sample size would have

a 90% power of detecting a 15-min difference in times to discharge readiness at the 0.01 level. Assuming that the incidence of emesis in the midazolam group was in keeping with other published data in this patient population (26), this sample size would have an 80% power of detecting a 25% difference in emesis (from 42% to 17%) between the two groups at the 0.05 level of significance. Allowing for a 10% drop-off rate, 134 patients were enrolled.

The Student's *t*-tests was used to compare normally distributed continuous variables between the two groups, and the nonparametric Mann-Whitney *U*-test was used for skewed data. Categorical data were analyzed by $\chi^2$ test with Yates' continuity correction or Fisher's exact test. A $P$ value of $<0.05$ was considered statistically significant.

## Results

The clonidine and midazolam groups were similar with respect to age, gender, and weight (Table 1). The times from the administration of oral clonidine and midazolam to separation from parents were 75 ± 25 min and 35 ± 13 min, respectively. The times from the administration of oral clonidine and midazolam to application of the face mask were 79 ± 24 min and 38 ± 13 min, respectively. No patient developed hypotension, bradycardia (values < 2 SD for age) or hypoxemia (oxygen saturation <95%) during the time from the administration of preoperative medication to the start of induction of anesthesia. The modified Yale Preoperative Anxiety Scale Scores at baseline and ten minutes before patient separation from parent(s) were similar between the two groups (Table 1). However, modified Yale Preoperative Anxiety Scale scores at the time of separation from parent(s) and at mask induction were higher in the clonidine group. The number of parents who were completely satisfied with the preoperative experience of their child was significantly increased in the midazolam group.

There were no clinically significant episodes of bradycardia or hypotension (values < 2 SD for age) in the two groups. However, the intraoperative averages of the mean blood pressure were significantly decreased in the clonidine group (69 ± 10 vs 63 ± 7 mm Hg, for midazolam and clonidine groups, respectively, $P < 0.05$). The duration of surgery and anesthesia were significantly shorter in the clonidine group (Table 2). Although the end-tidal desflurane concentrations at the completion of surgery were similar in the two groups, there was a significantly shorter time for emergence (surgery end to tracheal extubation) in the clonidine group (Table 2). There were no differences between the two groups in the times from end of surgery to discharge readiness and actual discharge from Phase 1, Phase 2, or entire postoperative hospital stay. Supplemental oxygen was required more frequently in the midazolam group. (Table 2).

In Phase 1 recovery, the admission and maximum CHEOPS scores and excitement scores were higher in the clonidine group than in the midazolam group (Table 3). The time to first analgesic dose was shorter (13 ± 19 vs 28 ± 45 min, respectively, $P < 0.05$) and the postoperative requirements of morphine increased in the clonidine group. There were no differences in the postdischarge use of analgesics.

There were no statistically significant differences between the midazolam and clonidine groups in the incidence of unanticipated hospitalization. A total of 13 patients were admitted–seven for social reasons (parent's request), three for respiratory complications such as airway obstruction and the continued need for supplemental oxygen, and three for IV fluid therapy for managing persistent vomiting. There were no differences between the two groups in the incidence of emesis while in hospital, after discharge or in the 24-h postoperative period.

Postdischarge emesis rates, maximum pain scores at home, and 24-h analgesic requirements were similar in both groups. The time for patients and parents to return to activities of daily living did not differ between the two study groups. The parental satisfaction scores and the number of parents who were completely satisfied with child's entire perioperative period did not differ between the groups. (Table 3). The incidence of postbehavioral changes also did not differ between the two groups.

## Discussion

This study failed to demonstrate clinically important benefits, in either the preoperative behavior or the recovery profile, of oral clonidine compared with oral midazolam as a preanesthetic medication in children undergoing tonsillectomy with or without adenoidectomy. In this study, oral midazolam was superior to clonidine in relieving preoperative anxiety and was preferred by the child's parents. The doses of midazolam and clonidine used in this study have been established as optimum for preanesthetic sedation (3,8). Satisfactory separation from parents can be achieved 10–45 minutes after ingestion of oral midazolam (5,6). In our study, patients who received midazolam were separated from their parents in this time frame after the drug was administered. There are no data available regarding the optimum time for separation after oral clonidine. In a study of 10 subjects who were observed for 3 hours, the peak sedative effect was noted from 105–120 minutes after oral administration (8). This small study forms the basis for the recommendation that children be separated 105 minutes after oral clonidine (8,9,12). However, in another

**Table 1.** Demographic and Preoperative Data

| | Clonidine | Midazolam |
|---|---|---|
| No. | 64 | 70 |
| Age (yr) | 6.7 ± 1.9 | 6.6 ± 2.0 |
| Gender (Male/Female) | 28/36 | 32/38 |
| Weight (kg) | 22.8 ± 6.6 | 24.1 ± 7.5 |
| Modified Yale Preoperative Anxiety (mYPAS) scores | | |
| Baseline | 24.6 ± 7.6 | 24.8 ± 7.9 |
| 10 min before separation from parents | 28.8 ± 10.9 | 25.4 ± 9.6 |
| After separation from parents | 38.9 ± 25.0* | 27.8 ± 15.2 |
| At induction of anesthesia | 42.9 ± 27.5* | 28.2 ± 16.2 |

Values are mean ± SD unless otherwise stated.
* $P < 0.05$ vs midazolam.

**Table 2.** Intraoperative and Immediate Postoperative Recovery Data

| | Clonidine | Midazolam |
|---|---|---|
| Duration of surgery (min) | 19 ± 6* | 22 ± 8 |
| Duration of anesthesia (min) | 47 ± 11* | 52 ± 11 |
| End-tidal desflurane on completion of surgery (%) | 2.1 ± 1.3 | 1.7 ± 1.2 |
| Emergence time (min) (End surgery to Tracheal Extubation) | 7.2 ± 4.9* | 8.7 ± 3.9 |
| Discharge readiness time (min) | | |
| Phase 1 PACU | 39 ± 28 | 44 ± 42 |
| [a]Hospital | | |
| Mean ± SD | 139 ± 309 | 199 ± 469 |
| Median (Interquartile range) | 76 (21–141) | 86 (31–153) |
| Actual Discharge times (min) | | |
| Phase 1 PACU | 65 ± 30 | 74 ± 34 |
| [a]Hospital | | |
| Mean ± SD | 247 ± 267 | 294 ± 409 |
| Median (Interquartile range) | 195 (154–236) | 201 (152–240) |
| Supplemental oxygen in PACU, *n* (%) | 13 (20)* | 26 (37) |

Values are mean ± SD unless otherwise stated.
PACU = postanesthetic care unit.
[a] Includes patients admitted to hospital.
* $P < 0.05$ vs midazolam.

**Table 3.** Delayed Recovery Data and Postoperative Complications

| | Clonidine | Midazolam |
|---|---|---|
| Excitement score in Phase 1 postanesthetic care unit | | |
| Median (Interquartile Range) | 2.5 (0–4)* | 2 (1–4) |
| Maximum Pain Score on the Children's Hospital of Eastern Ontario Pain Scale | | |
| Median (Interquartile Range) | 10 (8–12)* | 8 (4–12) |
| Rescue morphine (μg/kg) (mean ± SD) | 132 ± 48* | 115 ± 53 |
| Emesis, *n* (%) | | |
| In hospital | 12 (19) | 12 (17) |
| Post discharge | 15 (23) | 18 (26) |
| 0–24 h | 19 (30) | 20 (29) |
| Severe postoperative vomiting (>2 episodes) | 9 (19) | 8 (18) |
| Unanticipated Hospital Admission (Total) | 8 | 5 |
| For social reasons | 4 | 3 |
| For respiratory complications | 2 | 1 |
| For IV fluid therapy | 2 | 1 |
| Return to baseline preoperative activity (days) (mean ± SD) | 16 ± 8 | 13 ± 5 |
| Number of parents not completely satisfied, *n* (%) | | |
| With preoperative experience of child | 28 (44)* | 17 (24) |
| With entire perioperative experience | 23 (36) | 21 (30) |

* $P < 0.05$ vs. midazolam.

study, 63% of patients who received oral clonidine 4 μg/kg were asleep or drowsy 60–90 minutes later and could be easily separated from their parents (27). In our study, separation in the clonidine group of patients occurred within this time frame after drug administration. Clonidine 4 μg/kg is more effective for preinduction sedation than oral diazepam 0.4 mg/kg if it is administered at least 90 minutes before induction (8). However, midazolam was a superior medication for preanesthetic anxiolysis in our study. It is possible that we could have noted greater sedative effects in the clonidine group if we had waited longer. However, there are obvious disadvantages to using a preanesthetic sedative drug with a long onset time in a busy outpatient surgical center.

Practitioners may be willing to accept the disadvantages of clonidine during the preoperative period if it provided an improved recovery profile and permitted earlier discharge from the hospital. Clonidine decreases the requirements for both intraoperative anesthetic agents and postoperative analgesics, and is also effective in reducing postoperative emesis after strabismus surgery (7,13). Our hypothesis that these improved recovery characteristics would result in earlier discharge was not proved. In this study, the time from the end of surgery to tracheal extubation was shorter in the clonidine group, but the overall time to discharge and the duration of stay in Phases 1 and 2 of the PACU were not significantly different between the two groups. The clonidine group had shorter surgical procedures and decreased total anesthetic times, but the end-tidal concentration of desflurane at the end of surgery did not differ between the two groups. It is possible that the decreased mean blood pressures in the clonidine group permitted surgeons to establish hemostasis of the tonsillar bed earlier in these subjects.

Oxygen supplementation to prevent hypoxemia was required more frequently in patients who received midazolam. However, this did not result in longer times to achieving discharge criteria. In this study agitation and pain scores were higher in the clonidine group in Phase 1 of the PACU. The increased use of opioid analgesics in this group may have contributed to our inability to demonstrate earlier discharge despite the shorter duration of anesthesia and surgery, decreased time to tracheal extubation, and postoperative oxygen requirements in the clonidine group. Oral clonidine has an analgesic-sparing effect in children undergoing strabismus surgery and minor urological procedures associated with mild to moderate pain (8,9,13). However, IV clonidine was not effective in reducing postoperative morphine use in children undergoing tonsillectomy procedures, a procedure associated with moderate to severe postoperative pain and discomfort (27).

We used the CHEOPS score, a validated instrument, to gauge the degree of pain experienced by our subjects and the need for analgesia (21,22). Behavioral pain scores do not always correlate with self-reported pain assessments made with a visual analog scale. Nonverbal patients with emergence delirium will be rated to have higher pain scores on the CHEOPS scale than more stoic patients, even though the latter may have worse pain (21). Inadequate preoperative sedation and stormy inductions may be associated with increased emergence delirium (28). The higher agitation scores and increased use of opioids in the PACU in the clonidine group may reflect the lack of satisfactory preinduction sedation rather than increased pain in the postoperative period, as opioids are used to treat both pain and emergence delirium in the nonverbal child.

Clonidine decreases the incidence of emesis compared with placebo or benzodiazepine in children who have received no prophylactic antiemetics during anesthesia for strabismus surgery (29). In our study there were no significant differences in the incidence of postoperative emesis between the clonidine and midazolam study groups. This could reflect the routine use of prophylactic ondansetron and dexamethasone in our study protocol. There was also no difference in the incidence of behavioral changes in the postoperative period or in the time taken for patients and parents to return to normal activities of daily living. Of interest is the long time taken for patients to return to normal after this so-called routine minor surgery (14,17). The need for better management of postdischarge pain after outpatient tonsillectomy surgery is evident.

In conclusion, clonidine did not offer a better recovery profile or an equivalent preoperative profile in comparison with oral midazolam under the conditions of this study. We would recommend the preferential use of oral midazolam as a preanesthetic medication in children undergoing tonsillectomy.

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