

# The Prevention of Emergence Agitation With Tropisetron or Clonidine After Sevoflurane Anesthesia in Small Children Undergoing Adenoidectomy

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Postoperative agitation is a common problem after sevoflurane anesthesia in children. In the present study, we evaluated if tropisetron or clonidine could reduce the incidence of postoperative agitation after day case adenoidectomy in small children. We included 75 unpremedicated children aged 1–7 yr who were randomly assigned to receive either placebo, tropisetron (0.1 mg/kg) or clonidine (1.5 µg/kg) after anesthesia induction. Anesthesia was induced and maintained with sevoflurane. Patients also received alfentanil (20 µg/kg) and diclofenac (1 mg/kg). Postoperative pain was treated with IV oxycodone (0.05 mg/kg). Time to achieve discharge criteria was recorded. Modified pain/discomfort scale was used to assess the postoperative behavior.

The incidence of postoperative agitation was significantly less (32%, 8/25 patients) in the tropisetron group compared with placebo (62%, 16/26 patients),  $P < 0.05$ . Clonidine could not prevent agitation (incidence 54%, 13/24). No adverse effects were noted during the study. Discharge times were similar between the groups (between 80 and 99 min on average). In conclusion, tropisetron 0.1 mg/kg significantly reduced the incidence of postoperative agitation after sevoflurane anesthesia. Clonidine 1.5 µg/kg did not differ from placebo with respect to postoperative agitation.

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**S**evoflurane is currently the most popular inhaled anesthetic in pediatric anesthesia. It is a smooth induction drug, which allows a safe and pleasant mask induction. Sevoflurane provides fast recovery and disturbs less cardiovascular function.

Emergence from sevoflurane anesthesia is often associated with agitation in small children (1,2). The reason for postoperative agitation or delirium is unclear. Factors such as pain, rapid recovery, premedication drugs, gender, and age have been suggested. However, emergence agitation occurs even if sufficient analgesia is present (3). Agitation is more common in younger children, especially in preschool boys (4). Although agitation usually lasts a short time, it does not appear to have long-term implications. Agitated children need more time and care from the personnel than nonagitated children. Also, parents are

often worried and question the adequacy of treatment when seeing their child agitated.

It is not clear if preventive methods should be used or if agitation should be treated only when it occurs. There have been numerous publications about the prevention of this problem.

Kulka et al. (5) reported that clonidine could prevent agitation in small boys undergoing circumcision. Ondansetron, a 5HT<sub>3</sub> antagonist, has been used successfully as a treatment for postcardiotomy delirium in adults (6). Investigators suggest that the reason for postcardiotomy delirium is changes in serotonin metabolism. In our clinical practice, we have used another 5HT<sub>3</sub> antagonist, tropisetron successfully in the prevention of emergence agitation after sevoflurane anesthesia in small children.

The purpose of our study was to investigate whether tropisetron or clonidine administered during anesthesia induction could prevent emergence agitation after outpatient adenoidectomy.

## Methods

After approval from the local ethics committee and obtaining written, informed parental consent, we

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**Table 1.** Modified Pain/Discomfort Scale

Score	0	1	2
Crying	Not crying	Responding to comforting	Not responding to comforting
Moving	None	Restless	Thrashing
Agitation	Asleep or calm	Mild agitation	Severe agitation / hysterical

studied 75 children aged 1–7 yr (ASA physical status I–II) undergoing elective outpatient adenoidectomy. Exclusion criteria were known allergy to the study medicines, bronchial asthma, or cardiovascular disease. The children were randomly assigned into three groups using a computer-generated random number assignment. The study was double-blind and placebo-controlled. No premedication was used. Parents were allowed to accompany their children into the operating room and stay during the induction.

Heart rate, noninvasive arterial blood pressure, and oxygen saturation were recorded before anesthesia induction and every 5 min during surgery. Oxygen saturation, electrocardiogram, and end-tidal carbon dioxide values were monitored continuously. Anesthesia was induced with sevoflurane in 100% oxygen via a facemask, with a gradual increase of sevoflurane concentration with every single breath to a maximum of 8%. After anesthesia induction, an IV-cannula was established and children were randomized to receive IV placebo, tropisetron (0.1 mg/kg), or clonidine (1.5 µg/kg). A nurse who did not take part in the care of the children prepared the study drugs. All observers, as well as the children and their parents, were unaware of the contents of the study drug. For analgesia children received alfentanil (20 µg/kg). Endotracheal intubation conditions were assessed according to 4-point scoring system for laryngoscopy, position of vocal cords, and coughing.

Anesthesia was maintained with sevoflurane in N<sub>2</sub>O/O<sub>2</sub> (70% and 30% of the gas mixture, respectively). The sevoflurane concentration during surgery was adjusted to maintain the patient’s arterial blood pressure within 20% of preinduction values. At the end of surgery the anesthetics were discontinued, the oropharynx was suctioned and the patient’s trachea was extubated when spontaneous breathing was regarded as adequate. The child was then transferred to the recovery room and the parents were allowed to join their children when they were awake and hemodynamically stable.

Oxycodone (0.05 mg/kg IV) was used for postoperative pain relief. The need of oxycodone was estimated by a same experienced nurse who treated all these patients. In a recovery room a modified Aldrete score (7) was used to assess recovery from anesthesia and a modified pain/discomfort scale (8) to assess postoperative behavior (Table 1). The modified Aldrete and pain/discomfort scales were evaluated at

10, 20, 30, 45, 60, 90, and 120 min postoperatively if the patient was not discharged before the evaluation point.

The following recovery times were recorded: time to eye opening, time to making sounds, time to interaction (responding to the nurse or parent), time to first dose of oxycodone, time to ambulation, and time to discharge home. If the sum of the pain/discomfort scale exceeds three at any time, the child was considered as agitated. Discharge criteria included being fully awake, stable vital signs for 30 min, no bleeding, no pain, no nausea or vomiting, and able to ambulate according to age.

Parents were asked to record (in a postoperative questionnaire) well being (pain, vomiting, tiredness, sleep) at home for 24 h.

According to a power analysis, a sample size of 25 patients per group would have an 80% power to detect a reduction in the incidence of agitation from 45% to 20% at a significance level of 5%. Demographic data such as age and weight are presented as mean ± SD were compared by using unpaired Student’s *t*-test. Differences in tracheal extubation times, recovery times, and time to first analgesics among groups were analyzed with the Mann-Whitney *U*-test.  $\chi^2$  test was used to compare data of agitation incidence among groups. A *P* value of ≤0.05 was considered statistically significant.

## Results

There were 26 patients in the placebo group, 25 in the tropisetron group, and 24 in the clonidine group. The groups were similar with respect to age, weight, duration of anesthesia, and duration of surgery (Table 2). Endotracheal intubation and operation conditions were good in all groups. No adverse hemodynamic complications were noted during the study.

The incidence of postoperative agitation was significantly less (32%, 8/25 patients) in the tropisetron group compared with the placebo group (62%, 16/26 patients; *P* < 0.05). This gives a number needed to treat of 3 and an absolute risk reduction of 30%. Clonidine could not prevent agitation (incidence 54%, 13/24; *P* = 0.60 versus placebo).

In the placebo group 12 children vomited during the recovery period; of these 12 children 8 were also considered agitated. In the tropisetron group 9 children

**Table 2.** Demographic and Anaesthetic Data

	Placebo (n = 26)	Clonidine (n = 24)	Tropisetron (n = 25)
Age (mo)	36 ± 22	31 ± 20	38 ± 20
Weight (kg)	15 ± 5	15 ± 5	16 ± 6
Duration of surgery (min)	13 ± 5	12 ± 5	13 ± 4
Duration of anesthesia (min)	22 ± 7	19 ± 4	19 ± 4
Time to eye opening (min)	11 ± 4	13 ± 7	10 ± 4
Time to reach discharge criteria (min)	89 ± 34	99 ± 54	80 ± 33

Values are mean ± SD.

vomited, and 3 of these nine children were agitated. In the clonidine group 5 children vomited and 2 of these patients were agitated. The incidence of vomiting was significantly less frequent in the clonidine group compared with the placebo group ( $P < 0.05$ ).

All the patients, except one in the placebo group and one patient in the tropisetron group, received at least one dose of postoperative oxycodone. The patients received, on average,  $1.6 \pm 0.85$  (0–3),  $1.2 \pm 0.42$  (1–2), and  $1.3 \pm 0.48$  (0–2) doses of oxycodone in the placebo, clonidine, and tropisetron groups, respectively (placebo versus clonidine  $P < 0.05$ , placebo versus tropisetron  $P < 0.14$ ).

In recovery of anesthesia, time to eye opening and time to discharge criteria were similar in all groups (Table 2). There were no significant differences between the agitated and nonagitated children (Table 3). According to the questionnaires no adverse effects were detected during the first postoperative day at home.

## Discussion

Our study demonstrated that prophylactic administration of IV tropisetron significantly reduced postoperative agitation after sevoflurane anesthesia in children undergoing outpatient adenoidectomy. On the other hand, clonidine  $1.5 \mu\text{g}/\text{kg}$  did not reduce the agitation frequency in our study.

The incidence of agitation in our placebo group was 62%. This is similar to other studies, although there are no consistent scales to evaluate patients with emergence agitation.

Multiple factors have been shown to be associated with it. In the study of Voepel-Lewis et al. (9), otorhinolaryngologic surgery was found to be an independent risk factor for postoperative agitation as well as shorter time for awakening. Young age (1), sevoflurane anesthesia (10), waking up in a strange environment (11), and psychological immaturity (4) have also

**Table 3.** Comparison of Agitated and Nonagitated Patients

	Agitated (n = 37)	Not agitated (n = 38)
Time to eye opening (min)	11 ± 6	11 ± 5
Vomiting	13 (35%)	13 (34%)
Time to first postoperative analgesic (min)	9 ± 5	9 ± 5
Oxycodone doses postoperatively	1.4 ± 0.7	1.3 ± 0.6
Time to reach discharge criteria (min)	94 ± 31	84 ± 50

Values are mean ± SD or number (%) of patients.

been considered possible risk factors for postoperative agitation. Our study included young children, sevoflurane, and otorhinolaryngological procedures. Therefore, these patients were considered to be at high risk for this complication.

Clonidine  $1.5 \mu\text{g}/\text{kg}$  IV could not prevent agitation with our patients. The dose of clonidine was derived from our pilot study, where we noted that  $2 \mu\text{g}/\text{kg}$  clonidine caused too much sedation and delayed home discharge. In contrast to our findings, Kulka et al. (5), in their study of  $2 \mu\text{g}/\text{kg}$  clonidine, reported a decrease in agitation and no delay in patient discharge. However, they did not study whether clonidine influenced "ready to discharge times" or the degree of sedation. Bock et al. (12) have shown that clonidine reduced the incidence of agitation with a dosage of  $3 \mu\text{g}/\text{kg}$ , although a smaller dose ( $1 \mu\text{g}/\text{kg}$ ) failed to prevent agitation. These authors presumed that the mechanism of action of clonidine is dose-dependent. Also, the number of adverse events is likely to increase with larger doses. Clonidine is an  $\alpha_2$  adrenoreceptor agonist, and it has sedative and analgesic effects. With  $1.5 \mu\text{g}/\text{kg}$  dose of clonidine, we noted no decrease in heart rate or blood pressure. More studies are needed to establish the optimal dosage of clonidine for the prevention of emergence agitation after sevoflurane anesthesia. Another  $\alpha_2$  adrenoreceptor agonist, dexmedetomidine, has also been found to effectively reduce the incidence of postoperative agitation (13).

We found that a 5-HT<sub>3</sub> antagonist, tropisetron, could reduce agitation; however, its mechanism of action remains unresolved. Of interest was that the reduction in the incidence of agitation was not associated with a reduction in postoperative vomiting.

Another possible explanation for reduced agitation has been suggested by Bayindir et al. (6). They stated that the serotonergic system may have an important role in acute delirium. They were able to treat postbypass delirium with another 5-HT<sub>3</sub> antagonist, ondansetron. It remains to be solved if the mechanism of postcardiotomy delirium and postanesthesia agitation with small children is the same. Also, we cannot be

sure if all the 5-HT<sub>3</sub> antagonists have a similar effect in that receptor binding affinities and specific cytochrome P450 isoenzyme activities vary (14).

Insufficient analgesia has also been shown to be a risk factor for postoperative agitation (15). Perioperative fentanyl has reduced the incidence of postoperative agitation (15-17). In our study, all the children received alfentanil, oxycodone, and diclofenac for analgesia. The amount of opioids given in every study group was similar, and we assume that the analgesia was adequate with all patients.

In conclusion, prophylactic IV tropisetron significantly reduced the incidence of postoperative agitation after sevoflurane anesthesia. A clonidine dose of 1.5 µg/kg, on the other hand, did not reduce the incidence of postoperative agitation. Agitation was short in duration and did not lengthen discharge times. The mechanism of action and cost effectiveness of tropisetron remain to be resolved in future studies.

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