# THE EFFECT OF ORAL CLONIDINE PREMEDICATION ON NAUSEA AND VOMITING AFTER EAR SURGERY

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## Abstract

**Objective:** postoperative nausea and vomiting (PONV) is a most distressing adverse event for surgical patients with a considerable economic impact .The aim of the present study was to evaluate the effect of clonidine given orally for PONV in patients undergoing anesthesia for outpatient ear surgery.

**Methods:** Sixty patients 30.2±9.9 years, scheduled for ear surgery, were randomly assigned to one of two groups (clonidine or placebo) in a double-blinded manner. Anesthesia was standardized laryngeal mask airway, fentanyl, propofol, halothane, nitrous oxide.

**Results:** A complete response, defined as no PONV and no need for rescue antiemetic medication, during the first 24h after anesthesia was 33% with placebo and 67% with clonidine, respectively (P . 0.01). No clinically adverse event was observed in any of the groups.

**Conclusion:** Oral premedication with clonidine reduced the rate of PONV in patients undergoing outpatient ear surgery.

**Key words:** clonidine; premedication, postoperative nausea and vomiting; ear surgery.

## Introduction

Postoperative nausea and vomiting (PONV) is a common, distressing side effect of anesthesia and surgery, especially after minor and ambulatory surgery, delaying hospital discharge. Despite extensive research and the introduction of newer classes of antiemetic drugs with better efficacy and safety profiles, there seems to be little progress in reducing the incidence of PONV[1,2].

Clonidine, an $\alpha_2$-adrenoceptor agonist, has been reported to be a useful preanesthetic medication and has been shown to prevent the sympatho-adrenergic response to anesthesia, reduce anesthetic and analgesic requirements, and provide preoperative sedation, postoperative analgesia, and perioperative hemodynamic stability[3, 4]. In addition, recent investigations have demonstrated that premedication with oral clonidine reduces PONV after pediatric strabismus surgery and also breast cancer surgery[5-7].

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We performed a prospective, randomized, double-blinded trial in a university referral center; to evaluate the efficacy of clonidine given orally preoperatively for preventing PONV following outpatient ear surgery, interventions frequently accompanied by a high incidence of PONV.

## Methods and Materials

After obtaining approval of Hospital's Ethics Committee and patients' written informed consent, 60 patients (30 females and 30 males, aged 30.2±9.9 years), with American Society of Anesthesiologists physical status I, scheduled for outpatient ear surgery (tympanomasstoidectomy, tympanoplasty, stapedectomy and stage two surgery). Patients with nausea and vomiting prior to anesthesia or with gastrointestinal disease were excluded. The primary endpoint parameters of the study were the number of PONV-free patients. A complete response was defined as no nausea, no vomiting, and no need for rescue antiemetic medication. A number of other PONV-related factors, i.e., PONV events and need for antiemetics, were also included as secondary endpoints.

All patients were fasted overnight with an opportunity to drink clear fluids until 4 h preoperatively. Patients were randomly divided into two groups (n = 30 each) using computer-generated random numbers concealed in envelopes, to receive orally clonidine (4 µg/kg mixed with normal saline to a final volume of 15ml) or, placebo (10 ml of normal saline) one hour before induction of anesthesia.

Both patients and investigators were blinded with respect to the randomized treatment and the study code was broken in connection to data analysis.

Anesthesia was induced with a single dose of fentanyl (2 µg/kg), propofol (1.5 mg/kg) and midazolam (0.02 mg/kg). A laryngeal mask airway was inserted without ventilation assistance. Anesthesia was subsequently maintained with halothane (1-3 MAC) in $N_2O/O_2$ (2:1).

Postoperatively, all patients were admitted to the hospital for 24 hours. Clear liquids were offered only at the patient's request, and no other oral intake was allowed for 4 h after recovery from anesthesia. PONV was assessed by specially trained nursing staff without knowledge of which treatment each patient had received. Metoclopramide (0.2 mg/kg administered intravenously) was used as rescue antiemetics and were administered when patients vomited twice or more within 30 min, or when nausea was intense, with a duration of more than 30 min, and if patients explicitly asked for antiemetics.

### *Statistical analysis*

Statistical analyses were conducted using SPSS software (SPSS, Chicago, IL, USA; Version 15 for Windows Evaluation). Values were expressed as number (%) or mean ± SD and/or standard error (SE). We employed Chi-square test or Fisher's exact test for proportions and Mann–Whitney U test for continuous variables. Outcome of the two groups were compared with the Fisher exact test. Statistical significance was accepted at $p < 0.05$.

## Results

The demographic data of both groups were comparable with respect to patient characteristics and duration of anesthesia (Table 1).

*Table 1*
*Demographic characteristics of study population*

| | | **Clonidine (n = 30)** | **Placebo (n = 30)** |
|---|---|---|---|
| Sex (female/male) | | 15/15 | 15/15 |
| Age (years) | | 29.1 ± 10.3 | 31.3 ± 9.6 |
| History of motion sickness | | 4 (13.3) | 2 (6.7) |
| Type of surgery | Tympanomas-toidectomy | 14 (46.7) | 21 (70) |
| | Tympanoplasty | 10 (33.3) | 9 (30) |
| | Stapedectomy | 4 (13.3) | 0 |
| | Stage two surgery | 2 (6.7) | 0 |
| Duration of anesthesia (hours) | | 3.9 ± 0.3 | 3.8 ± 0.3 |
| Time spent in the recovery room (min) | | 33.3 ± 11.9 | 33.2 ± 10.7 |

Data are given as number (%) of patients and mean ± SD.

Administration of clonidine was associated with a significantly higher overall number of PONV-free individuals compared with placebo during 0-24 h after anesthesia (66.7% vs. 33.3%, $P < 0.05$) (Table 2). Furthermore, in patients suffering from PONV,

no statistically significant difference was observed regarding the different genders and types of surgery. No patients revealed bradycardia (<80 beats/min), or other side effects postoperatively.

*Table 2*
*Incidences of nausea and vomiting in the recovery room, the surgical unit, and the total during 24 h*

| | Clonidine (n = 30) | Placebo (n = 30) | P value |
|---|---|---|---|
| Recovery room | | | |
| PONV-free | 28 | 20 | 0.01 |
| Nausea | 2 | 10 | 0.01 |
| Vomiting | 0 | 7 | 0.005 |
| Surgical unit | | | |
| PONV-free | 21 | 14 | 0.058 |
| Nausea | 9 | 16 | 0.058 |
| Vomiting | 7 | 13 | 0.085 |
| Entire 24-h period | | | |
| PONV-free | 20 | 10 | 0.01 |
| Nausea | 10 | 20 | 0.01 |
| Vomiting | 7 | 17 | 0.008 |

PONV: postoperative nausea and vomiting.
One single patient may have nausea alone or both nausea and vomiting together.

## Discussion

The main finding of the current study was that premedication with clonidine in patients undergoing ear surgery increased the number of PONV-free patients almost twice compared with placebo (67% *vs.* 33%). This improvement was achieved without any increase in postoperative sedation or other clinically important side effects of clonidine.

Postoperative nausea and vomiting (PONV) is one of the commonest complaints following anesthesia, and can result in morbidity like wound dehiscence, bleeding, pulmonary aspiration of gastric contents, fluid and electrolyte disturbances, delayed hospital discharge, unexpected hospital admission, and decreased patient satisfaction[8].

Postoperative vomiting is multifactorial in origin, and a number of factors, including age, sex, obesity, diet, a history of motion sickness and/or previous PONV, operative procedure, anesthetic technique and postoperative pain and restlessness are considered to affect its incidence[1].

Despite the vast amount of research done in this field and the variety of antiemetic drugs available, PONV still has a high incidence. Clonidine is an effective preanesthetic medication, which has been found to offer a number of beneficial effects in the context of both general and regional anesthesia in both adults and pediatric patients such as perioperative hemodynamic stability, attenuated reflex cardiovascular response to tracheal intubation, sedative and postoperative analgesic effects and reduced anesthetic and analgesic requirements[9-11].

One of the less investigated effects of clonidine is its action regarding PONV. Mikawa et al[5] and Handa et al[6] have reported a reduced incidence of PONV after premedication with clonidine in children undergoing strabismus surgery. An antiemetic effect of clonidine has recently also been shown after breast surgery in adults[7]. However, some authors have declared no significant effect of clonidine premedication on PONV[12,13].

To the best of our knowledge, the current study is the first to explore the potential usefulness of clonidine in adult patients undergoing ear surgery using PONV as the primary endpoint of the study. In the current study, premedication with clonidine caused a clinically as well as statistically significant increase in the number of PONV-free patients when patients were moved to surgical unit and in the 24-hr period, while nausea and vomiting has increased in this transfer. But in control group the number of PONV-free patients was significantly lower compared with clonidine user group, while at the end of 24 hours follow up the control group had about 2 times more nausea and vomiting. PONV is a complication that may occur very soon during surgery or at recovery room or within later follow-up. In the open, controlled, randomized study of Woodcock et al[14], single dose oral premedication with clonidine 0.6 mg in patients undergoing middle ear or nasal surgery, significantly reduced the vapor requirement for isoflurane-induced hypotension. In the prospective study of Welfringer et al[15] and Marchal et al.[16] on patients scheduled for ear surgery, the comparative assessment of surgical field quality was in favor of the clonidine group and lower intraoperative bleeding was observed in respect to controls.

The mechanism resulting in antiemetic effects

of clonidine is unknown and probably multifactorial. It has been attributed to clonidine's ability to reduce anxiety, provide sedation and decrease anesthetic and analgesic requirements. A general reduction in sympathetic outflow caused by clonidine[9], could also have attributed to the reduction of PONV, since a high sympathetic tone and catecholamine release may trigger nausea and vomiting[1,17]. Moreover, the well-known analgesic effect of clonidine, by a reduced need for opioid as known emetogens[1,18], might influence the incidence of PONV. Further studies are necessary to gain better understanding regarding which of the aforementioned mechanisms that is most important with regard to the antiemetic effects of clonidine.

With regard to the prevention and treatment of PONV, the issues of side effects are also of great importance. It is of special interest that no increase in postoperative sedation was observed in patients given clonidine compared with placebo. This is in accordance with findings of previous publications[19].

In conclusion, the present prospective, randomized, double-blind, placebo-controlled study shows that premedication with clonidine results in an increased number of patients free of PONV after ear surgery with a low to moderate cost compared with newer antiemetics. This was accomplished without any increase in postoperative sedation or other side effects. However, our relatively small sample size may limit the interpretation of our results.

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