# Comparison of the efficacy of propofol and metoclopramide in preventing postoperative nausea and vomiting after middle ear surgery

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## ABSTRACT

**الأهداف:** مقارنة جرعة من عقار بروبوفول مع عقار ميتوكلوبراميد في منع حدوث الغثيان والتقيؤ (PONV) بعد إجراء جراحة للأذن الوسطى.

**الطريقة:** أجري هذا البحث السريري في كلية الطب بجامعة غازي – أنقرة – تركيا، خلال الفترة الفترة ما بين ديسمبر 2004م وحتى أكتوبر 2005م. عقب الحصول على موافقة لجنة الأخلاق الطبية بالمستشفى، تم وضع 60 مريضاً بالغاً لإجراء عملية الأذن الوسطى وتم تقسيمهم عشوائياً إلى ثلاثة مجموعات. تلقى المرضى $0.5mg.kg^{-1}$ من عقار بروبوفول في المجموعة (P)، وفي المجموعة (M) تلقى المرضى مقدار $0.2mg.kg^{-1}$ من عقار ميتوكلوبراميد، وفي المجموعة (C) تلقى المرضى المحلول الملحي بمقدار 0.9%. أصيب عدد من المرضى من الغثيان والتقيؤ عند 0–4، 4–12 و12–24 ساعة بعد العملية الجراحية كما تم تسجيل الاستعمال الإضافي من مضادات القيء.

**النتائج:** أظهرت نتائج البيانات أنه عند 0–4 ساعة، بلغت نسبة حدوث التقيؤ 25% في المجموعة (P)، و 40% في مجموعة (M)، و75% في مجموعة (C). كان معدل الإصابة لدى المجموعة (P) أقل بشكل ملحوظ من المجموعة (C) ($p$=0.002)، كانت نسبة استخدام مضادات القيء في المجموعة (C) أعلى من المجموعة (P) ($p$=0.028). كما كانت نقاط التقيؤ والغثيان للمجموعة (C) أعلى بشكل ملحوظ من المجموعة (P) ($p$=0.005). لم يكن هناك فروقات إحصائية بين القيم عند الساعة من 4-12 والساعة من 12-24.

**خاتمة:** تبين أن جرعة عقار بروبوفول في نهاية العملية الجراحية على الأقل فعالة كعقار ميتوكلوبراميد في منع حدوث التقيؤ والغثيان (PONV) في الفترة المبكرة بعد العملية الجراحية لدى البالغين الخاضعين لعملية جراحية في الأذن الوسطى.

**Objectives:** To compare the administration of sub hypnotic dose of propofol with metoclopramide and placebo in prevention of postoperative nausea and vomiting (PONV) after middle ear surgery.

**Methods:** This clinical research was performed in the Faculty of Medicine, Gazi University, Besevler, Ankara, Turkey, between December 2004 and October 2005. Following approval by the hospital ethics committee, 60 adult patients scheduled for a middle ear operation were randomly assigned into 3 groups. The patients in group P received 0.5 $mg.kg^{-1}$ propofol; in group M, 0.2 $mg.kg^{-1}$ metoclopramide, and in group C, 0.9% saline solution. The number of patients suffering from nausea and vomiting at 0-4, 4-12, and 12-24 hours postoperatively, and additional use of antiemetics was recorded.

**Results:** Comparisons of the data showed that at 0-4th hours, the incidence of vomiting was 25% in group P, 40% in group M, and 75% in group C. The incidence rate of group P was significantly lower than that of group C ($p$=0.002), and the rate of antiemetics use in group C was higher than that in group P ($p$=0.028). The Nausea Vomiting Scale scores of group C were also significantly higher than those of group P ($p$=0.005). There were no significant differences between the values at 4-12 and 12-24 hours.

**Conclusion:** The administration of a sub hypnotic dose of propofol at the end of surgery was found to be at least as effective as metoclopramide in preventing PONV in the early postoperative period in adult patients undergoing middle ear surgery.


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Despite advances in anesthetic drugs and techniques, postoperative nausea and vomiting (PONV) remain the second most common postoperative complaint after surgery. Despite the increasing attention on postoperative pain control, PONV is still been

considered as a minor complication.[1] Determination of the true incidence of PONV is difficult due to lack of a single stimulus of onset and multiple etiologies (medical, surgical, and patient and anesthesia associated). In the absence of antiemetic treatment, the incidence of PONV is estimated to be 25-30% for all surgical interventions and patient populations. Of these, 0.18% is resistant PONV.[2] However, the incidence rate of PONV after middle ear operations has been higher than in other operations due to direct or indirect stimulation of vestibular afferent fibers. A rate of 62-80% has been reported in patients not receiving any antiemetic treatment after middle ear operations.[3] Propofol anesthesia is known to cause the least severe PONV symptoms. Thus, it has been used in infusion or single bolus forms at various times of operation, and its antiemetic efficiency has been investigated. While it was found to be effective by some studies, contrary results were noted by others.[4] This prospective double-blinded placebo controlled trial was designed to compare the use of sub hypnotic propofol dose or metoclopramide for the prevention of PONV in patients undergoing middle ear surgery.

**Methods.** This randomized, double blinded, and phase IV clinical study was performed at the ENT Department of Gazi University, Faculty of Medicine, Ankara, Turkey, between December 2004 and October 2005. After the approval of the ethical committee and informed consent of the volunteers was obtained, 60 adult patients (age range: 25-55 years, 39 female/21 male patients) scheduled for middle ear operation with American Society of Anesthesiologist (ASA) risk of 1 or 2 were randomly assigned into 3 groups as follows: propofol group (group P), metoclopramide group (group M), and placebo control group (group C). All the groups received an equal volume of the drug used in the study. The patients were assigned to one of the 3 study groups using a computer-generated random number table. Those with a history of hepatic, renal, cardiovascular diseases, chronic obstructive pulmonary disease, hematological and/or gastrointestinal disorders, hypersensitivity to propofol or any other drugs, and patients with history of vertigo and motion sickness, pregnant or menstruating patients, and patients who had taken antiemetics 24 hours before the surgery were excluded from the study. The patients fasted for 8 hours before the operation and were not premedicated. In the operation room, the heart beat rates (HBR), systolic (SAP), diastolic (DAP), and mean (MAP) arterial pressures and peripheric oxygen saturations ($SpO_2$) (Drager Julian plus PM8040 vitara, Lubeck, Netherlands) of the patients were monitored. All the patients in the 3 groups were induced with thiopentone 5 $mg.kg^{-1}$ (intravenous, bolus dose) followed by remifentanil infusion at a dose of 0.2 µg. $kg^{-1}.min^{-1}$ and sevoflurane inspiration at 1-2% concentration. After all the patients were given vecuronium (0.1 mg. $kg^{-1}$), they were mechanically ventilated with $O_2$/air (50/50%), 4 L/min end-tidal $CO_2$ 35-40 mm Hg through orotracheal intubation (Drager Julian Plus, Medizinetechnik, Lubeck, Germany). The maintenance doses of remifentanil and sevoflurane were adjusted for hemodynamic stability. Throughout the operation, hydration was maintained with infusion of isotonic or ringer lactate solution at a rate of 3-5 $ml^{-1}kg^{-1}$. The values of hemodynamic parameters and peripheric oxygen saturation were recorded before and after the infusion, at every fifth minute for half an hour after the intubation, followed by 15-minute intervals, after the 90$^{th}$ minute for every 30 minutes, and this was continued for 24 hours postoperatively. At the time of skin incision closure, the patients in group P were given intravenous 0.5 mg. $kg^{-1}$ (bolus) propofol (propofol 1% Fresenius®, Kabi, Sweden); in group M, intravenous 0.2 mg. $kg^{-1}$ metoclopramide (Primperan® Amp, 10 mg/2mL, Biofarma, İstanbul, Turkey), and in group C (control) intravenous serum physiological solution (0.9%) (bolus) at the same volume. All syringes with propofol, metoclopramide, or placebo were prepared by the same investigator. Administration of anesthesia and drugs used in the study and intraoperative data collection were made by the other investigators blinded to the study drugs. At the time of the last surgical suture, all the anesthetic inductions were terminated and the time was recorded. The lungs were manually ventilated with 100% oxygen (4 L $min^{-1}$) until spontaneous respiration was achieved. Residual muscle relaxation was antagonized with 0.03 $mg.kg^{-1}$ neostigmine and 0.01 $mg.kg^{-1}$ atropine, and the patients were appropriately extubated. The time of extubation, eye-opening, and response to verbal stimulation and place, time, and people orientation times were recorded. All the patients were removed to the postoperative recovery room and re-monitored after extubation. They were kept in this room for evaluation of potential postoperative complications and recovery for a minimum of one hour. Degree of postoperative nausea and vomiting were scored using the Nausea Vomiting Scale (NVS) (**Table 1**) at 0-4, 4-12, 12-24 hours. Additional antiemetics (10 mg metoclopropamide) were administered intravenously when the NVS score was more than 3. The patients were observed for 24 hours postoperatively and nausea and vomiting times, and the time of additional antiemetics and analgesics administration were recorded.

Statistical analyses were performed by SPSS statistical package for windows. Parametric values were evaluated with one-way ANOVA with Bonferroni adjustment. Non-parametric values were studied with Kruskal-Wallis test, and the differences were evaluated

**Table 1 -** Nausea-vomiting scale (NVS).

| Nausea-vomiting scale | Nausea-vomiting severity |
|---|---|
| 0 | No complaints |
| 1 | Mild nausea |
| 2 | Moderate nausea |
| 3 | Frequent vomiting (4 times) |
| 4 | Severe vomiting (continuous vomit) |

**Table 2 -** Demographic data.

| Parameters | Group P (n=20) | Group M (n=20)2 | Group C (n=20) |
|---|---|---|---|
| Age (year) (mean±SD) | 45.8±16.5 | 43.9±12.2 | 46.1±13.1 |
| Weight (kg) (mean±SD) | 69.7±14.3 | 66.9±13.1 | 67.4±12.6 |
| Height (cm) (mean±SD) | 167.2±8.5 | 163.4±5.2 | 168.4±8.5 |
| ASA (I/II) (n) | 14/6 | 14/6 | 16/2 |
| Gender (F/M) (n) | 13/7 | 14/6 | 12/8 |
| Duration of operation (min) (mean±SD) | 152.5±50.9 | 166.9±52.1 | 164.3±47.7 |

ASA - American Society of Anesthesiologists

with Mann-Whitney U test. Side effect, gender, and ASA were compared using Chi-square and Fisher's exact tests. $P<0.05$ was considered statistically significant.

**Results.** There was no significant difference among the study groups in terms of age, body weight, length, ASA group, gender, duration of operation, and anesthesia (**Table 2**) ($p>0.05$). The comparisons of the groups for the number of patients with nausea showed a significant difference at 0-4 hours, while there were no statistically significant differences at 4-12 and 12-24 hours. The incidence of nausea at 0-4 hours is shown in (**Table 3**). The incidence rate of vomiting group P was statistically significantly lower than that of group C ($p=0.002$). The comparisons of the groups for the incidence of vomiting at 0-4 hours showed a rate of 25% in group P, 40% in group M, and 75% in group C ($p=0.005$). The incidence rate of vomiting in group P was significantly lower than that of group C at 0-4 hours ($p=0.004$) (**Table 3**). In the comparison of the groups with respect to the number of cases with nausea ($p=0.005$), vomiting ($p=0.004$), and the need for extra antiemetics ($p=0.028$), it was found that there was a significant difference at 0-4 hours, while there were no significant differences between the values at 4-12 and 12-24 hours. There were significant differences between

**Table 3 -** Number of patients experiencing nausea and vomiting.

| Nausea and vomiting | Group P (n=20) | Group M (n=20) | Group C (n=20) |
|---|---|---|---|
| | | n (%) | |
| *Nausea* | | | |
| 0-4 hour | 6 (30) | 9 (45) | 16 (80)* |
| 4-12 hour | 4 (20) | 6 (30) | 7 (35) |
| 12-24 hour | 2 (10) | 3 (15) | 3 (15) |
| *Vomiting* | | | |
| 0-4 hour | 5 (25) | 8 (40) | 15 (75)* |
| 4-12 hour | 4 (20) | 5 (25) | 6 (30) |
| 12-24 hour | 2 (10) | 3 (15) | 3 (15) |

*Compared to group P (nausea, $p=0.002$; vomiting, $p=0.004$)

**Table 4 -** The number of patients subjected to nausea-vomiting scale and additional antiemetics, median (25-75%).

| Parameters | Group P (n=20) | Group M (n=20) | Group C (n=20) |
|---|---|---|---|
| | | n (%) | |
| Additional antiemetics | 5 (25) | 7 (35) | 13 (65)* |
| Nausea-vomiting scale | 0 (0-1.75) | 1 (0-2) | 2 (1.25-3)* |

*Compared to group P (additional antiemetics, $p=0.025$; nausea-vomiting scale, $p=0.005$)

**Table 5 -** The incidence of adverse reactions.

| Adverse reactions | Group P (n=20) | Group M (n=20) | Group C (n=20) |
|---|---|---|---|
| | | n (%) | |
| Cough | 0 (0) | 1 (5) | 2 (10) |
| Laryngospasm | 0 (0) | 1 (5) | 2 (10) |
| Urinary retention | 0 (0) | 0 (0) | 0 (0) |
| Respiratory depression | 1 (5) | 1 (5) | 2 (10) |
| Hiccup | 0 (0) | 1 (5) | 2 (10) |

groups in the need for additional antiemetics as shown in **Table 4**. Fifteen (75%) patients in group P, 13 (65%) in group M and 7 (35%) in group C did not receive any metoclopramide. In the evaluation of PONV, with NVS, while the median was 25-75% 0 (0-1.75) in group P, it was found to be 2 (1.25–3) in group C, which was significantly lower ($p=0.005$) (**Table 4**). The amount of additional antiemetics used was significantly higher in group C than in group P ($p=0.025$). The NVS of group C was significantly higher than that of group P

($p$=0.005).There was no difference between groups with regard to postoperative use of metamizole and NSAIDs ($p$>0.05); however, a significant difference was found between group P and group C in terms of additional antiemetic use (group P: 5 [25%] group C: 13 [65%]) ($p$=0.025). Side effects are presented in **Table 5**. There were no differences between the groups with respect to cough, laryngospasm, urinary retention, respiratory depression, and hiccup (**Table 5**).

**Discussion.** Various agents have been used in the treatment of PONV at various doses and time intervals.[2-7] To evaluate the efficiency of these agents, various parameters such as nausea and vomiting scores for 4 hours in the early postoperative period or for postoperative 24 hour, the number, and severity of vomiting, the number of antiemetics required, the amount of antiemetics used, hospitalization time, and the problems caused by nausea and vomiting are studied. In our study, the severity of nausea and vomiting was measured with NVS for postoperative 24 hours, and the number of patients with nausea vomiting, and need for additional antiemetics was compared for postoperative 0-4, 4-12, and 12-24 hours, and the results were expressed in percentages. We have found out that an immediate postoperative bolus dose of 0.5 mg.kg$^{-1}$ propofol is at least as effective as 0.2 mg.kg$^{-1}$ metoclopramide for control of PONV during the first 4 hours of the postoperative period. However, there was no significant differences for postoperative recovery. The PONV develops as a complication after anesthesia, and if not prevented, surgical recovery and hospitalization time are prolonged; thus, it leads to unpleasant hospital experiences for patients and increasing health care costs. Prolonged vomiting may result in electrolyte imbalance (hypokalemia, hypochloremia, hyponatremic metabolic alkalosis) and dehydration, Mallory Weis tear, esophageal rupture, wound opening, and hematoma formation under skin flaps associated with abdominal, vascular, eye, or plastic surgery.[2,3,5]

A higher incidence rate of PONV has been reported after middle ear operations than in other operations due to direct or indirect stimulation of vestibular afferent fibers. Furthermore, this rate has been reported to be 62-80% in patients who did not receive any antiemetic treatment after middle ear operations.[3] In our study, this rate was 75% for the placebo group (group C), supporting the hypothesis that antiemetic treatment is necessary in this kind of surgical interventions. Propofol was used as an induction agent or continuously induced for maintenance, and was found to cause less PONV compared to other induction agents and anesthesia techniques.[8,9] Despite a much lower incidence of PONV with the use of propofol, in total intravenous anesthesia (TIVA), high cost constitutes a negative aspect on its usage for this purpose.[10-12] The antiemetic mechanism of propofol is not clearly known. This characteristic has been attributed to either its sedative effect or modulation of subcortical pathway,[4,13] and possibly due to its weak serotonin antagonist effect.[4,14]

Discovery of antiemetic effects of propofol has aroused interest into investigations for prevention of chemotherapy associated nausea and vomiting. In various studies, sub hypnotic doses (1mg. kg$^{-1}$ hr-1) of propofol were infused in patients under chemotherapy and it was determined that propofol was effective in prevention of severe nausea and vomiting due to chemotherapy, without causing any significant side effects.[15,16] Torn et al[17] found that in patients who had undergone total knee arthroplasty under spinal anesthesia, sub hypnotic doses of propofol (10 mg bolus and 30 mg/24 hour infusion) reduced the incidence of PONV. Similar results have been reported by subsequent studies.[18-21] However, the most important factor that limits infusion of propofol as an antiemetic is sedation. When it is infused at lower doses to avoid sedation, it yields no antiemetic effect.[13,22] The efficiency of propofol induced in a single bolus sub hypnotic dose in prevention of PONV has remained controversial. Some authors have claimed that sub hypnotic doses of propofol are not effective in prevention of PONV.[23-25] Contrary to these findings, some studies support the antiemetic effect of a single dose of propofol. Song et al[26] determined that low doses of (0.5 mg.kg$^{-1}$) propofol infused at the end of the operations in patients who have undergone laparoscopic cholecystectomy under general anesthesia reduce the incidence of PONV.

Numazaki et al[14] have reported that the minimum dose of propofol for effective prevention of PONV is 0.5 mg.kg$^{-1}$ given intravenously at the end of the operation, and when used at a dose of 0.25 mg.kg$^{-1}$, its effect is no different from that of placebo. The authors have also concluded that at doses of 0.5 mg.kg$^{-1}$ and 0.75 mg.kg$^{-1}$, propofol has similar effects and at doses under 1 mg.kg$^{-1}$, it yields less sedation, dysphoria, and extrapyramidal signs; thus, this dose is not recommended.[14] Based on this knowledge, we preferred to administer 0.5 mg.kg$^{-1}$ bolus propofol. Metoclopramide is one of the options for conventional antiemetic treatment. Generally, intravenous use of 10 mg or 0.2 mg.kg$^{-1}$ metoclopramide is recommended.[6,27] Numazaki and Fuji[27] compared the effects of sub hypnotic (1.0 mg.kg$^{-1}$hr$^{-1}$) propofol and droperidol (1.25 mg) and metoclopramide (10 mg) infused at the end of cesarean operation, and determined that they had similar efficiency in prevention of PONV. In another study, comparisons of propofol used at sub hypnotic doses (0.5 mg.kg$^{-1}$, bolus), droperidol (20 µg.kg$^{-1}$, bolus), and metoclopramide (0.2 mg.kg$^{-1}$, bolus) in thyroidectomies showed that propofol was

significantly more effective in preventing PONV.[7] In order to neutralize patient and anesthesia dependent factors, we tried to homogenize study groups in terms of age, body weight, length, ASA group, gender, duration of operation, and anesthesia. Such differences may be the cause of differences observed in previous studies. This study had potential limitations. First, the absence of pre-study power analysis. Second, the use of anticholinesterase and atropine were not avoidable. Third, these data may not be applicable to different surgical procedures or various anesthetic techniques.

In conclusion, sub hypnotic bolus doses of propofol used at the end of middle ear operations is at least as effective as metoclopramide in preventing PONV. Further studies are needed to compare the efficacy of sub hypnotic doses of propofol with other commonly used and well-established antiemetics.

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