Comparison of the antiemetic effects of ondansetron and dexamethasone on middle ear surgery

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ABSTRACT

Objective: To compare the antiemetic efficacy of ondansetron and dexamethasone in adults undergoing middle ear surgery.

Method: This clinical research took place in the Faculty of Medicine, Gazi University, Turkey between January to December 2004. The study included 60 cases, classified by the American Society of Anesthesiology physical status group I-II, who underwent middle ear surgery. We carried out anesthesia induction with 5 $mg.kg^{-1}$ sodium thiopental and performed muscle relaxation with 0.5 $mg.kg^{-1}$ atracurium to be followed by orotracheal intubation. Anesthesia was maintained at 5 $L.min^{-1}$ gas flows with 2–3% sevoflurane inhalation in 70/30% O_2/N_2O. We randomly distributed the cases into 2 groups, and the first group (Group O) was administered with 4 mg ondansetron intravenously (IV) at the stage of surgical skin closure and the second group (Group D) with 5 mg dexamethasone IV immediately after anesthesia induction. In the first 24 hours postoperatively, nausea vomiting score (NVS) and nausea, vomiting frequency, Metamizole-Na and non-steroidal anti-inflammatory drug use, the need for additional antiemetics and cost as well as the number of cases with nausea, vomiting and the need for extra antiemetics during 0–4, 4–12 and 12–24 hours were recorded, and their distribution to groups was evaluated.

Results: The NVS was 0 (0-0) in group O compared with 1 (0-3) in group D (p=0.003). The use of additional antiemetics was found to be significantly lower in group O (1 ± 0.6) compared with group D (3.70 ± 1.02) (p=0.028). In comparing the cost, group O (9.8 dollars) was found to have a significantly higher cost compared with group D (1.1 dollars) (p<0.0001).

Conclusion: Ondansetron had a more significant effect on nausea and vomiting in the early period, however, no difference was found after 4 hours of administration. Furthermore, dexamethasone was found to cost less compared with ondansetron.

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Postoperative nausea and vomiting (PONV) are complication frequently occurring after anesthesia. When antiemetic treatment is not administered, the rate of PONV is approximately 25–30% in general surgery population and between 62–80% after middle ear surgery. Many factors such as the site and characteristics of the surgical procedure, the kind of anesthesia and its agent as well as the age, gender, weight of the patients and vertigo history may influence PONV.[1–8] The timing and the dose of the antiemetic agent to be used in the treatment are also important.[5,9] The cost of the prophylactic treatment

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of nausea and vomiting, which may lead to serious morbidity and sometimes mortality is lower than the cost of treatment.[10,11]

Of the agents used for the treatment of nausea and vomiting, ondansetron, an antagonist of 5-OH tryptamine 3 receptor, exerts its effect by blocking the vomiting center of the brain stem and vagal afferent fibers in the gastrointestinal tract at the level of receptor. Its high cost is the most important factor limiting its clinical use.[2,3,5,12] Although antiemetic effect mechanism of dexamethasone is not completely understood, prostaglandin antagonism, serotonin inhibition in the intestine and endorphin release seems to be effective. As its action lasts up to 48–72 hours, it is effective on late period nausea and vomiting in patients undergoing chemotherapy.[4,6,9,13,14] It has been reported that in the prevention of postoperative nausea and vomiting, ondansetron is more effective when administered near the end of the operation whereas dexamethasone is given with anesthesia induction.[4,9,15]

The aim of this study is to evaluate 4 mg ondansetron, and 5 mg dexamethasone administered intravenously (IV) for prophylaxis in middle ear surgery by comparing their antiemetic efficacy and side effects.

Method. This prospective, randomized, double blind and phase IV clinical study was carried out in the theater of the Ears, Nose and Throat Department of the Faculty of Medicine, Gazi University, Ankara, Turkey. Between January to December 2004, 60 cases between the age 25-55 years, undergoing mastoidectomy under general anesthesia and who were group I-II according to the classification of American Society of Anesthesiologists (ASA) were included in the study. Ethics Committee approval and written informed consent from the patients was obtained.

Patients who used any antiemetic drugs in the last 24 hours, as well as those with history of vertigo in motor vehicles, and smokers were not included in the study. Patients did not take any food or liquids orally for 8 hours before the operation and were taken into operating theater without any premedication. After peripheric vessel access was obtained, systolic, diastolic and mean arterial blood pressure (MABP) was monitored non-invasively, heart rate (HR) with ECG and peripheric oxygen saturation (SpO_2) with a pulse oximeter was recorded every 5 minutes. The following 3 minutes of pre-oxygenation with mask, anesthesia induction commenced with 5 $mg.kg^{-1}$ sodium thiopental IV and subsequently 0.5 $mg.kg^{-1}$ atracurium for muscular relaxation. Ventilation with excessive positive pressure was avoided. Anesthesia was maintained with 2–3% sevoflurane in 70/30 O_2/N_2O following orotracheal intubation, in order to maintain hemodynamic stability and to obtain analgesia. In this study, we did not prefer to use opioids as it has side effects such as nausea and vomiting. During operation, 3–5 $mg.kg^{-1}.hour^{-1}$ IV of isotonic NaCl or Ringer lactate solution was given for hydration. Patients were randomized into 2 groups, the first group (Group O) was administered with 4 mg ondansetron IV after surgical skin closure and the second group (Group D) with 5 mg dexamethasone IV, inducted immediately after anesthesia. As the rate of nausea and vomiting is high after middle ear surgery, placebo control group was not formed. The administration of the drugs previously labeled was carried out by an investigator other than the one who collected the data and the patients were not informed of the group they belonged to in order to meet the criteria of a double blind study. Stomach aspiration was performed before extubation. Indwelling nasogastric tube was not placed. After the surgical procedure, inhalation agent was interrupted and ventilation was made with 100% O_2 at first then with 50/50% O_2/air and residual muscle relaxant effect was removed with 0.03 $mg.kg^{-1}$ neostigmine and 0.01 $mg.kg^{-1}$ atropine and then the patient was extubated. The age, body weight, length, gender, ASA group, anesthesia and operation duration of the cases were recorded. In perioperative hemodynamic monitorization, MABP and HR parameters were used. Nausea vomiting score (NMS) and nausea vomiting data at 24 hours postoperative, the employment of metamizole, Nonsteroidal anti-inflammatory drugs (NSAID) and additional antiemetics were evaluated.

During 24 hours postoperative, cough, laryngospasm, urinary retention, respiratory depression and other side effects were inquired and recorded. The patients who complained of pain and demanded analgesics were administered with 500 mg pyrazolonederivativeIV(Metamizole-Na,Novalgin®) and additional 500 mg NSAID (Naproksen Sodium, Naprosyn®) taken orally if complaint is repeated. Postoperative nausea and vomiting were scored using NVS (**Table 1**) at 0–4, 4–12, 12–24 hours. Additional antiemetics were administered when NVS ≥ 3. The money spent per person was calculated in dollars and recorded as cost. The patients were recommended not to move in the early postoperative period.

Statistical evaluation was made using the tests mentioned below and $p<0.05$ was considered statistically significant. Age, body weight, length, duration of anesthesia and operation, Metamizole-NA (mg), NSAID (mg), additional antiemetic (mg) data

were compared using the Student's t test. Heart rates, MABP were evaluated with repeated measurement variance analysis. Non-parametric data, NVS, cost were compared using the Mann-Whitney-U tests. In comparing the gender, ASA, the number of patients with nausea and vomiting and of those administered with additional antiemetics and side effects between groups was performed using the chi-square and Fisher's exact chi-square tests.

Results. In the statistical comparison between groups in terms of age, body weight, length, ASA group, gender, duration of operation and anesthesia (**Table 2**) and the MABP and HR values (**Figure 1**) during operation, no statistically significant difference was found ($p>0.05$). In the evaluation of PONV, with NVS, while the median was (25–75%) 0 (0-0) in Group O, it was found to be 1 (0-3) in Group D, which was significantly lower ($p=0.003$) (**Table 3**).

There was no difference between groups with regard to postoperative use of metamizole and NSAID ($p>0.05$), significant difference was found between Group O and Group D in terms of additional antiemetic use [Group O, 1 ± 0.6; Group D, 3.7 ± 1.02 ($p=0.028$)]. In comparing the cost in dollar, significant difference was found Group O, $9.8 (9.8-9.8) and Group D, $1.1 (1.1-1.3) ($p<0.0001$).

The number of cases with nausea ($p=0.000$)), vomiting ($p=0.021$) and the need for extra antiemetics ($p=0.015$), shows that there was a significant difference at 0–4 hours, while there was no significant difference between the values at 4–12 and 12–24 hours. There was a significant difference between groups in the need for additional antiemetics. In Group O, 3 cases (10%) and in Group D, 11 cases (36.7%) felt the need for additional antiemetics ($p=0.015$) (**Table 4**). No significant difference was found between groups in terms of side effects such as cough, laryngospasm, urinary retention, respiratory depression, and hiccough **Table 5**.

Discussion. Prevention of nausea and vomiting, which occur as a complication after anesthesia induction, influences postoperative recovery and hospitalization, cost and the general quality of life of the patient are important issue. Although symptoms are usually transient, they may lead to serious problems such as aspiration, opening of wounds, hemorrhagia, dehydration and electrolyte imbalance. [3–8,10]

Postoperative nausea and vomiting are influenced by many factors such as the type, site and the duration of the surgery, age, gender, weight, the presence of the history of dizziness in vehicles.[3–8,16,17] In the general population, the prevalence of PONV in the first 24 hours was reported to be between 30–70% and it increases in the presence of risk factors, reaching 54–92% after laparoscopic and gynecological interventions and 62–80% after middle ear operations.[2–8] Direct and indirect stimulation of the afferent fibers in vestibular apparatus leads to a

Table 1 - Nausea vomiting scores.

Nausea vomiting scores	Nausea vomiting degrees
0	No complaint
1	Mild degree of nausea
2	Moderate degree of nausea
3	Frequent vomiting (4 times)
4	Severe vomiting (continuously)

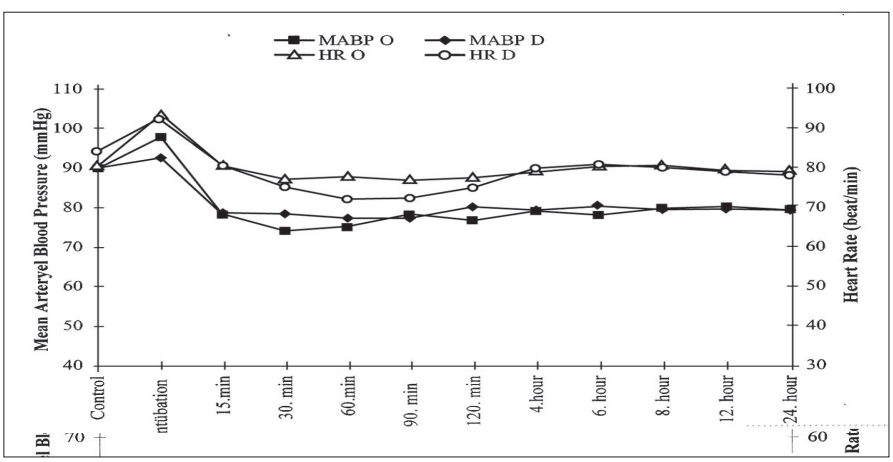

Figure 1 - Comparison of mean arterial blood pressure (MABP) and heart rate (HR) data between the 2 groups.

Table 2 - Demographics variables, duration of anesthesia and surgery [(mean ± SD), N].

Characteristics	Group O (N=30)	Group D (N=30)	t/χ^2	*P*-value
Age (year)	41.03 ± 12.6	36.2 ± 11.2	1.579	0.12
Weight (kg)	70.7 ± 11.95	67 ± 17.2	0.97	0.336
Height (cm)	164.7 ± 8.3	164.93 ± 7.55	-0.114	0.91
ASA(I:II)	26:4	24:6	0.48	0.488
Gender (female: male)	14:16	15:15	0.067	0.796
Duration of anesthesia (minutes)	224.25 ± 64.15	213.33 ± 69.59	0.631	0.531
Duration of surgery (minutes)	199 ± 63.2	189.03 ± 70.25	0.578	0.566

ASA - American Society of Anesthesiologist

Table 3 - Nausea vomiting score, additional antiemetic and additional analgesic, cost [(mean ± SD), N] median (25-75%), (min-max)].

Parameters	Group O (N=30)	Group D (N=30)	t	*P*-value
Nausea	0 (0-0)	1 (0-3)	281.5†	0.003
vomiting score	(0-3)	(0-3)*	4.32	0.889
Metamizol (mg)	633.3 ± 112.3	670.5 ± 120.7	1.176	0.147
NSAİ (mg)	260.3 ± 36.7	310.4 ± 28.7	2.069	0.028
Additional antiemetic (mg)	1 ± 0.6	3.7 ± 1*	239.49†	0.000
Cost ($)	9.8 (9.8-9.8) (9.8-10)	1.1* (1.1-1.3) (1.1-1.7)		

*p<0.005, †Mann-Whitney U test,
NSAI - Nonsteroidal anti-inflammatory drugs

Table 4 - Number of patients experiencing nausea vomiting and additional antiemetic.

Parameters	Group O		Group D		χ^2	*P*-value
	N=30	(%)	N=30	(%)		
Nausea					13.87	0.000
0-4 hour	2	(6.7)	15*	(50)		
4-12 hour	3	(10)	3	(10)		
12-24 hour	0	(0)	0	(0)		
Vomiting						
0-4 hour	2	(6.7)	10	(33.3)*	6.667	0.021
4-12 hour	1	(3.3)	2	(6.7)	0.357	0.554
12-24 hour	0	(0)	0	(0)		
Additional antiemetic	3	(10)	11	(36.7)*	5.963	0.015

*p<0.05

Table 5 - Incidence of adverse reactions.

Adverse reaction	Group O		Group D		χ^2	*P*-value
	N=30	(%)	N=30	(%)		
Cough	0	(0)	1	(3.3)	1.017	0.313
Laryngospasm	1	(3.3)	1	(3.3)	0.000	1
Urinary retention	0	(0)	1	(3.3)	1.017	0.313
Respiratory depression	1	(3.3)	2	(6.7)	2.069	0.256
Hiccough	0	(0)	1	(3.3)	1.017	0.313

more frequent nausea and vomiting in middle ear surgery.[3,4,6,16,17]

It is known that positive pressure ventilation, full stomach, and opioids, and anticholinergic used in premedication are among the factors increasing PONV in anesthesia induction.[6,17] In the present study, no premedication was carried out in our cases. We tried to avoid strong positive pressure ventilation. Before extubation, we performed gastric aspiration, decreasing the effect of such factors that increase nausea and vomiting in the preoperative period.

It has been shown that N_2O used together with O_2 in order to benefit from analgesic effects during anesthesia induction, stimulates nausea and vomiting by causing barometric changes in the middle ear.[16] It has also been reported that oxygen at high concentrations decrease nausea and vomiting.[18,19] As we used O_2/N_2O at the same ratio in both groups, we believe that it would not influence our results.

In the treatment of PONV, many different agents have been used at differing doses and time periods.[1–9] In order to evaluate their efficacy, various criteria such as NVS, their frequency and severity, the frequency of the need for antiemetics, the amount of antiemetics used, the duration of hospitalization and problems caused by nausea and vomiting in the first 4 or 24 hours postoperatively are used. In the present study, we compared the frequency of nausea and vomiting and their severity in the first 24 hours and the number of cases with nausea and vomiting and who used additional antiemetics between 0–4, 4–12 and 12–24 hours. The timing of the administration of the antiemetic drug is also important in the management of PONV.[4,9,15] At present, consensus is that treatment should be initiated during anesthesia induction before nausea and vomiting occur.[3] The administration of ondansetron after surgical procedure[4,15] and of dexamethasone immediately after anesthesia induction prophylactically increases their efficacy in PONV.[9] It has been reported that after prophylactic administration of 4 mg ondansetron in radical mastoidectomy, nausea and vomiting occurred

at the rate of 33.3% while they occurred at the rate of 81.5% after placebo.[20] Similarly, prophylactic per oral 8 mg ondansetron in orthopedic interventions, PONV occurred at 29% while they occurred at the rate of 67% after placebo.[21] Panda et al[22] concluded that the total incidence of vomiting was reduced from 28% in ondansetron group (4 mg ondansetron) to 6% in ondansetron and dexamethasone group (ondansetron 4 mg with dexamethasone 8 mg) after middle ear surgery. In patients receiving ondansetron and dexamethasone, the nausea score was significantly less at 6, 12, and 24 hours after surgery. Unlike these reports, Davies et al[23] reported that prophylactic ondansetron had no effect on PONV in hysterectomy cases.

In the present study, ondansetron was administered after closure of the skin surgically and dexamethasone after anesthesia induction before the emergence of complaints and at the time periods when they are reported to be more effective. In the ondansetron group, nausea occurred at the a rate of 6.7% at 0-4 hours postoperative, 10% at 4-12 hours postoperative and 0% at 12-24 hours postoperative and vomiting occurred at the rate of 6.7%, 3.3% and 0% at the same time periods. In the dexamethasone group, nausea occurred at the rate of 50% at 0-4 hours operative, 10% at 4-12 hours postoperative and 0% at 12-24 hours postoperative and vomiting occurred at the rate of 33.3%, 6.7% and 0% at the same time periods. The low rates of nausea and vomiting in our study compared to the other studies[24,25] may emanate from our removal of factors that can cause PONV and using high concentration oxygen. Subramaniam et al[13] in the surgery for pediatric strabismus, administered 1 $mg.kg^{-1}$ (max 25 mg) dexamethasone, 100 $\mu g.kg^{-1}$ (max 4 mg) ondansetron and placebo, found PONV in the first 0–6 hours, to be significantly low in ondansetron group (17.8%), and 24.4% in dexamethasone group and at 6–34 hours, the rate was 6.67% in dexamethasone group, 24.4% in ondansetron group and 31.1% in the placebo group. Regarding late PONV, it was 0% in dexamethasone group, 13.3% in ondansetron group and 30.3% in the placebo group. The fact that the effect of dexamethasone lasts for 48–72 hours despite its elimination period of 3 hours renders it superior to ondansetron in late period nausea especially in patients undergoing chemotherapy.[14,24] Liu et al[25] found that dexamethasone at a dosage of 10 mg administered intravenously reduced the total incidence of nausea and vomiting by 45%. In that research, dexamethasone reduced the incidence of vomiting episodes >4 times and the incidence of patients requiring rescue antiemetics in patients undergoing tympanomastoid surgery.

There are studies reporting that postoperative antiemetic efficacy of ondansetron and dexamethasone is similar.[26] However, their time of administration are different from our study. In the present study, the rate of PONV was 6.75% in the early period in Group O while the rate of nausea was 50% and vomiting 33.3% in Group D. As ondansetron is more effective in the early period, our findings are consistent with those by Subramaniam et al.[13]

Dua et al[27] reported that the side effects of ondansetron were equal to those of the placebo. We observed laryngospasm at the rate of 3.3% and respiratory depression at the rate of 3.3% in the ondansetron group while laryngospasm at the rate of 3.3% and respiratory depression at the rate of 6.7% in the dexamethasone group. There were no differences between groups.

It has been reported that additional antiemetics were required in 17% of the cases undergoing middle ear surgery and administered 4 mg ondansetron.[2] In the present study, additional need for antiemetic was 10% in the Group O while it was 36.7% in the Group D. Baxendale et al[28] reported that dexamethasone decreased postoperative pain and swellings after molar teeth were extracted. In the present study, it was established that there was no difference in the post analgesic consumption compared to ondansetron. However, due to the lack of a placebo group, it would be wrong to reach a conclusion on whether it reduces the need for analgesics.

In comparing the cost of antiemetics, there are studies which compares only the financial cost of the product as well as those taking the necessary cost of treatment when nausea and vomiting cannot be prevented. The duration of stay in the postoperative recovery room, other medical equipment used and work power should also be taken into account in calculating the cost benefit analysis.

To summarize, the effect of prophylactically 4 mg ondansetron was superior to that of 5 mg dexamethasone in the first 4 hours, there was no difference between their effects in 4–24 hours and in their side effects.

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