A comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after tympanoplasty

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Purpose: To evaluate the effects on PONV and headache after tympanoplasty of prochlorperazine 0.2 mg·kg^{-1} im, ondansetron 0.06 mg·kg^{-1} iv or placebo (isotonic saline) 0.02 ml·kg^{-1} iv given immediately after induction of anaesthesia prior to tracheal intubation.

Methods: The study was randomised, double blind and prospective. One hundred and forty-eight patients, aged 9–61 yr, received a standardised balanced inhalational anaesthetic with controlled ventilation and induced hypotension. Postoperatively, the frequencies of retching and vomiting in the PACU and of nausea, retching, vomiting, headache, analgesic and antiemetic requirements in the surgical ward for 24 hr were recorded.

Results: The four test groups (n = 37 each) were comparable. The incidences of vomiting in the PACU were similar. During the first 24 hr after surgery the antiemetics produced no reductions in the incidence of nausea alone or of vomiting alone. However, the combination of nausea and vomiting was reduced from 53% (placebo) to 16% (P < 0.0005), 19% (P < 0.0005) and 30% (P < 0.05) by im. prochlorperazine, iv ondansetron and iv prochlorperazine, respectively. The frequency of those experiencing no PONV was increased from 27% (placebo) by prochlorperazine im to 57% (P < 0.01), by ondansetron iv to 62% (P < 0.005) and by prochlorperazine iv

Key words

ANTIEMETICS: ondansetron, prochlorperazine;
COMPLICATIONS: postoperative nausea, vomiting, headache;
SURGERY: tympanoplasty.

to 43% (P = NS). The onset of PONV was delayed in those given prochlorperazine im, and vomiting was less severe in those given ondansetron iv. Headache occurred with similar frequency in each group.

Conclusion: Prophylactic prochlorperazine 0.2 mg·kg^{-1} im and ondansetron 0.06 mg·kg^{-1} iv are similarly efficacious in reducing nausea with vomiting after tympanoplasty, while prochlorperazine 0.1 mg·kg^{-1} iv is less efficacious. Neither drug given as described appeared to reduce the frequency of postoperative nausea alone or vomiting alone.

Objectif: Évaluer après la tympanoplastie l'effet sur les nausées et vomissements postopératoires (NVPO) de la prochlorpérazine 0,2 mg·kg^{-1} im, de l'ondansetron 0,06 mg·kg^{-1} iv ou d'un placebo (soluté isotonique) 0,02 mg·kg^{-1} iv administrés immédiatement après l'induction de l'anesthésie et avant l'intubation de la trachée.

Méthodes: L'étude était aléatoire, prospective et en double aveugle. Cent quarante-huit patients, âgés de neuf à 61 ans ont reçu une anesthésie équilibrée standardisée avec ventilation contrôlée et hypotension délibérée. En postopératoire, ont été enregistrés, à l'unité des soins postanesthésiques (USPA), la fréquence des efforts pour vomir et les vomissements; pendant 24 h, la fréquence des nausées, des efforts pour vomir, des vomissements, de la céphalée, les analgésiques et antiémétiques requis.

Résultats: Les quatre groupes (n = 37) étaient comparables. L'incidence des vomissements à l'USPA était identique. Pendant les premieres 24 h après la chirurgie, les antiémétiques n'ont modifié ni l'incidence des nausées considérées indépendamment ni celle des vomissements seuls. Cependant, l'association des nausées et de vomissements était réduite de 53% (placebo) à 16% (P < 0,0005), 19% (P < 0,005) et 30% (P < 0,05), respectivement par la prochlorpérazine im, l'ondensetron iv et la prochlorpérazine iv. L'incidence d'absence de NVPO augmentait de 27% (placebo) avec la prochlorpérazine im à 57% (P < 0,01), avec l'ondensetron iv à 62% (P < 0,005) et avec la prochlopérazine iv à 43% (P = NS).

L'apparition des NVPO était retardée par la prochlorpérazine im, et les vomissements étaient moins importants avec l'ondensetron iv. Les céphalées survenaient à une fréquence identique dans tous les groupes.

Conclusion: L'administration prophylactique de prochlorpérazine 0,2 mg·kg⁻¹ im et d'ondensetron 0,06 mg·kg⁻¹ iv est également efficace pour réduire les nauseés et les vomissements après la tympanoplastie, alors que celle de la prochlorpérazine 0,1 mg·kg⁻¹ iv l'est moins. Aucun des médicaments administrés de la façon décrite réduit les nausées et les vomissements lorsqu'ils sont considérés indépendamment.

Postoperative nausea and vomiting (PONV) is a frequent and debilitating consequence of middle ear surgery. In this institution about 60% of patients experience emesis and about 50% experience headache after tympanoplasty.[1,2] In anaesthetic practice PONV is commonly prevented or treated using the antidopaminergic drugs droperidol, metoclopramide or prochlorperazine.[3] Of these prochlorperazine 0.2 mg·kg⁻¹ *im* or 0.1 mg·kg⁻¹ *iv* are considered to be the most efficacious,[3] and have proved to be so in this hospital.[4] Its use, however, as with all antidopaminergic drugs, may induce extrapyramidal (iatrogenic) reactions. Ondansetron is a newer antiemetic derived from cocaine and metoclopramide, which exerts its effect via antagonism of five hydroxy-tryptamine subtype 3 (5-HT₃) receptors, while exhibiting no cholinergic, adrenergic, dopaminergic or histaminergic effects.[5] Though not likely to induce extrapyramidal reactions, its mode of action may increase the incidence of postoperative headache.[6,7]

Ondansetron has been shown to be superior as a prophylactic antiemetic than metoclopramide[8] and droperidol[9] in gynaecological patients. The relative antiemetic efficacies of ondansetron and prochlorperazine have not been studied, especially in middle ear surgery where PONV constitutes a major postoperative morbidity. This study was undertaken to compare the antiemetic efficacies and effects on postoperative headache of ondansetron 0.06 mg·kg⁻¹ *iv*,[10] prochlorperazine 0.2 mg·kg⁻¹ *im* (as per licensing regulations in Europe) and prochlorperazine 0.1 mg·kg⁻¹ *iv* (as per licensing regulations in North America),[11] each given with induction of general anaesthesia for tympanoplasty.

Methods

With Hospital Ethics Committee approval and written, informed consent of patient or guardian, 148 consecutive Saudi nationals presenting for elective tympanoplasty were studied between January 1994 and July 1995. Inclusion criteria consisted of ASA physical class 1 or 2 men and non-pregnant women. Patients were excluded from the study if they had received any antiemetic medication within 24 hr of surgery. Patients were visited on the afternoon before surgery, the nature of the investigation explained, consent obtained and a history of motion sickness or PONV enquired into. On arrival in the operating theatre each patient was block randomised to receive saline (as placebo) or one of the three antiemetic formulations immediately following induction of anaesthesia.

Premedication comprised temazepam (0.5 mg·kg⁻¹ to the nearest 10 mg) *po* and EMLA cream applied topically to the dorsum of the left hand approximately 1.5 hr before surgery. In theatre, routine monitoring devices (ECG, Hewlett Packard 80300A: blood pressure, Dinamap Critikon 1846: oxygen saturation, Ohmeda Biox 3700) were applied, a pre-induction value of heart rate and blood pressure recorded, an intra-venous cannula inserted and pre-oxygenation commenced.

Anaesthesia was induced and deliberate (controlled) hypotension commenced, with thiopentone (4.0 mg·kg⁻¹), atracurium (0.6 mg·kg⁻¹), nalbuphine (0.2 mg·kg⁻¹) and labetalol (1 mg·kg⁻¹) *iv*, after which the appropriate test drug was administered (ondansetron *iv* 0.06 mg·kg⁻¹, prochlorperazine 0.2 mg·kg⁻¹ *im*, prochlorperazine 0.1 mg·kg⁻¹ *iv* or saline 1–2 ml *iv*). The larynx was then sprayed with aerosolized lidocaine (10%)[12] and an endotracheal tube inserted. Anaesthesia was maintained with nitrous oxide (67%) and isoflurane (0.8%) in oxygen administered via controlled ventilation using an Ohmeda AV7700 Ventilator with a respiratory rate of 8 to 12 breaths per minute, an inspiratory:expiratory ratio of 1:3, a tidal volume of 10 ml·kg⁻¹ and a fresh gas flow of 70 ml·kg⁻¹·min⁻¹ using a Bain Circuit to maintain an end-tidal carbon dioxide concentration of 4.5–5.0 kPa (Hewlett Packard 47210A Capnometer). Ringer-lactate was infused intraoperatively at a rate of 8 ml·kg⁻¹·hr⁻¹ and dextrose-saline infused postoperatively at a rate of 2.0 ml·kg⁻¹·hr⁻¹ until oral fluids were tolerated.

At the commencement of surgery the operating table was inclined to a 10° anti-Trendelenburg (head-up) position and glyceryl trinitrate (50 mg glyceryl.trinitrate in 500 ml dextrose 5% saline 0.225% solution) titrated by *iv* infusion to maintain a mean arterial pressure between 55 mmHg and 65 mmHg. Following microscopic examination of the tympanic membrane, the surgeon injected lidocaine 1% containing 1:200,000 adrenaline (1 ml·10 kg⁻¹) subcutaneously behind the auricle. At the end of surgery, the glyceryl trinitrate infusion was discontinued and residual neuromuscular blockade reversed with 0.035 mg·kg⁻¹ neostigmine and 0.017 mg·kg⁻¹ atropine. Nalbuphine (0.1 mg·kg⁻¹ *iv* or 0.2 mg·kg⁻¹ *im*) paracetamol (10 mg·kg⁻¹ *po*) and prochlorperazine (0.2 mg·kg⁻¹ *im*) were prescribed for

TABLE I   Patient characteristics and Perioperative anaesthetic data

	Saline	im Prochlorperazine	iv Prochlorperazine	iv Ondansetron
Patient numbers	37	37	37	37
Sex (M:F)	21:16	19:18	20:17	19:18
Age (yr) mean (SD)	28.1 (11.5)	29.4 (13.5)	31.5 (14.6)	29.8 (13.5)
Age (yr) range	9–51	9–53	8–61	7–58
Weight (kg)	64.1 (18.4)	61.9 (20.2)	66.8 (19.7)	58.4 (21.7)
History of MS	1	2	1	2
History of PONV	5	4	4	5
Duration of surgery (min)	98.1 (45.3)	100.5 (53.3)	115.0 (59.2)	90.2 (30.6)
Recovery ward				
– time (min)	33.3 (16.7)	37.1 (14.6)	33 (11)	28 (8)
– nalbuphine	0	1 (3%)	1 (3%)	0 (0%)
– prochlorperazine	1 (3%)	0 (0%)	0 (0%)	0 (0%)
– vomiting	6 (16%)	2 (5%)	3 (8%)	3 (8%)
Surgical ward				
– nalbuphine	5 (22%)	7 (26%)	4 (17%)	4 (17%)
– paracetamol	19 (78%)	20 (74%)	19 (83%)	20 (83%)
– prochlorperazine	9 (24%)	3 (8%)	6 (16%)	6 (16%)

Data given as mean (SD) or number (percentage). MS = motion sickness; PONV = postoperative nausea and vomiting. No between group statistical differences.

administration by nurses, at their discretion, in the recovery and postoperative surgical wards to treat postoperative pain and emesis.

The test drugs were coded and, to ensure blindness, the anaesthetic chart was appropriately endorsed. All data were recorded on customised forms in the operating theatre, recovery and surgical wards. Before induction of anaesthesia a note was made of patient details, test drug group and baseline heart rate (HR), systolic, diastolic and mean (SAP, DAP, MAP) arterial pressures. At the termination of surgery and anaesthesia the duration of surgery was noted, as well as any vomiting or retching immediately after extubation. Nurses in the recovery ward, blind to the test drug given, recorded details of vomiting, retching, extrapyramidal movements, antiemetic and analgesic requirements. Nausea was not enquired into because of the difficulty of eliciting this complaint from drowsy Arabic speaking patients by our English speaking British and Philipino nurses.

During the first 24 hr after surgery note was made by nurses, also unaware of the test drug given, of nausea, retching or vomiting reported to them. The time of onset of the complaint was recorded, and whether retching and vomiting was a single or repeated episode.[13] They also recorded details of antiemetic and analgesic drugs given (nature, time of administration and whether given to treat nausea, retching, vomiting or headache, surgical pain or pyrexia, respectively) and the occurrence of extrapyramidal signs (tremors, involuntary movements, muscle spasms or rigidity). On the day after surgery the author, conversant in Arabic but also blinded to the drug

given intraoperatively, visited the ward to review drug, fluid balance and nursing records, and to interview each patient and/or their relative or guardian with respect to nausea, retching, vomiting and headache (other than earache related to surgery).

Data were analysed using unpaired Students t and Chi-squared tests with Yates' correction where appropriate. Chi-squared tests were used to test for differences in nausea, vomiting and postoperative drug requirement incidences. The effects of the antiemetics in modifying the severity of vomiting were assessed using Chi-squared tests after grouping the vomiters in each test group into single and multiple vomiters. Student t tests were used to compare the mean times of occurrence of any symptom of PONV. Retching and vomiting were considered as similar morbidities and analysed collectively. $P < 0.05$ was considered significant.

Results

Comparability of test groups

One hundred and forty eight consecutive patients aged between 7 and 61 yr presenting for tympanoplasty were studied between the period January 1994 and August 1995. The study population comprised four groups of 37 patients, that were comparable for sex, age, weight, duration of anaesthesia, time spent in the recovery ward, need for analgesia and antiemesis in the recovery ward, and need for analgesia and antiemesis during the first 24 hr after surgery (Table I). Vomiting or retching immediately after extubation or during recovery from anaesthe-

TABLE II   Surgical ward. Distribution of patients experiencing postoperative nausea, vomiting, nausea with vomiting and no nausea or vomiting

| | Test drug group | | | | | | | | | | | |
| | Saline (placebo) | | | im Prochlorperazine | | | iv Prochlorperazine | | | iv Ondansetron | | |
Morbidity	N	n	%	N	n	%	N	n	%	N	n	%
Nausea	36	2	5	37	3	8	37	3	3	37	3	8
P (versus placebo)					ns			ns			ns	
Vomiting	37	6	16	37	7	19	37	9	24	37	4	11
P value (versus placebo)					ns			ns			ns	
Nausea with vomiting	36	19	53	37	6	16	37	11	30	37	7	19
P value (versus placebo)					<0.0005			<0.05			<0.0005	
No PONV	37	10	27	37	21	57	37	14	43	37	23	62
P value (versus placebo)					<0.01			ns			<0.005	

N = patient numbers; n = number of complainants.

TABLE III   Time to onset of PONV (mean, standard deviation) and severity of vomiting (single vs multiple vomiters)

	iv Saline	im Prochlorperazine	iv Prochlorperazine	iv Ondansetron
Onset of PONV				
Number experiencing nausea or vomiting	27	16	21	14
Time to onset (hr)	4.63 (1.90)	7.28 (4.01)*	6.27 (3.69)	4.69 (2.6)
Severity of vomiting				
Patient numbers	37	37	37	37
Total number vomiting	25 68%	13 35%	20 54%	11 30%
− single episode	5 25%	6 46%	10 50%	7 64%*
− multiple episode	20 75%	7 54%	10 50%	4 36%*

*$P < 0.025$ compared with placebo.

sia occurred in 16% of the placebo group, 5% of those given im prochlorperazine and in 8% each of those given prochlorperazine iv or ondansetron iv ($P > 0.05$ all comparisons, Chi-squared).

Postoperative nausea, vomiting and headache
A failure on the part of a nine-year-old Arabic-speaking boy in the saline (placebo) group to reply unequivocally to questions at the postoperative interview regarding the occurrence of nausea or headache resulted in only 36 sets of nausea and headache data in this group. The incidences of nausea alone during the first 24 hr postoperative period were similar and infrequent (between 3 and 8%) in each treatment group. The incidences of vomiting alone (without accompanying nausea) during this time were also similar (11 to 24%). However, the incidence of nausea accompanied by vomiting was reduced from 53% (placebo) to 16% and 19% in those given prochlorperazine im and ondansetron iv respectively ($P < 0.0005$, both comparisons, Chi-squared), and to 30% in those given prochlorperazine iv ($P < 0.05$, Chi-squared). The number of patients experiencing no nau-

sea or vomiting in the four test groups were placebo 10(27%), prochlorperazine im 21 (57%), prochlorperazine iv 14(43%) and ondansetron iv 14 (62%), of which only the lower incidence in those given prochlorperazine im and ondansetron iv attained significance. ($P < 0.01$ and $P = 0.005$, Chi-squared, respectively; Table II).

The onset of any complaint of postoperative nausea or vomiting occurred later in those given prochlorperazine im ($P < 0.025$) and prochlorperazine iv ($P < 0.1$), but was unaffected by ondansetron iv. Both prochlorperazine treatments and ondansetron iv modified the severity of vomiting by reducing the incidence of patients experiencing multiple vomits, from 75% to 54, 50 and 36% respectively, but only the latter reduction attained significance ($P < 0.025$ Chi-squared; Table III).

The incidence of headache reported during the first 24 hr after surgery (placebo 56%, prochlorperazine im 41%,prochlorperazine iv 43% and ondansetron iv 49%) were similar in the four test groups.

Discussion
This double blind, placebo controlled, randomised

prospective study was conducted to determine the effects of prochlorperazine 0.2 mg·kg^{-1} im, prochlorperazine 0.1 mg·kg^{-1} iv and ondansetron 0.06 mg·kg^{-1} iv given with induction of anaesthesia on PONV and post-operative headache following general anaesthesia for tympanoplasty. Prochlorperazine im and ondansetron iv were similarly and powerfully efficacious in reducing the incidence of nausea with vomiting after middle ear surgery, while prochlorperazine iv caused a smaller reduction in this index of PONV. Neither of the prochlorperazine treatments was associated with iatrogenic extrapyramidal reactions, and ondansetron iv did not result in a higher incidence of postoperative headache. Prochlorperazine im delayed the onset of any symptom of PONV, and ondansetron reduced the severity of postoperative vomiting.

The failure of prochlorperazine 0.1 mg·kg^{-1} iv to demonstrate a more powerful antiemetic efficacy was surprising as previous studies have shown this treatment to be as effective as the larger dose given im.[4] The ineffectiveness may simply be attributable to the smaller dose administered iv. However, this dose lies within the range recommended in North America (Compazine; Smith Kline and Beecham; prochlorperazine edisylate; 5 to 10 mg iv or im,[14] and was chosen to avoid the possibility of hypertension, hypotension and extrapyramidal reactions which may have followed iv administration of the larger dose as recommended for im administration by its European manufacturers (Stemetil; Rhône Poulenc Rorer; prochlorperazine mesylate; 12.5 mg im).[11,14,15]

The size of the population studied provides sufficient power to suggest that failure of the smaller dose of prochlorperazine iv to exhibit more impressive antiemetic efficacy is a true indication of its relative lack of efficacy when so given. However, analysis of times of onset and severity of symptoms were performed on the small numbers of those who did become nauseated, retched or vomited. These sample sizes are too small to provide statistical significance to the observations that prochlorperazine iv delayed the onset of PONV and that either prochlorperazine treatment reduced the severity of vomiting. A delay in the onset of PONV in those given prochlorperazine, and not in those given ondansetron, may be anticipated as prochlorperazine has a half-life after parenteral administration of 23 hr,[16] whilst ondansetron has a half life after iv administration of 3.5 to 5.5 hr.[17]

Numerous surgical procedures on the head, neck and torso may reflexly stimulate the vagal brain stem nucleus to produce laryngospasm,[18] bradydysrhythmias[19–23] or emesis.[24–26] The sensory nerve supply of the auricle, external auditory meatus, tympanic membrane, middle ear cleft and inner ear is provided by the V (trigeminal),

VII (facial), VIII (vestibular, cochlear), IX (glossopharyngeal) and X (vagus) cranial nerves, and the second and third cervical nerves (C_2 C_3).[27,28] In this hospital, vomiting following ear, nose and throat surgery occurs most frequently aftere tympanoplasty (c. 60% of patients), less frequently after septorhinoplasty (c. 40% of patients), and least frequently after tonsilloadenoidectomy (c. 30% of patients). The high incidence of PONV in those undergoing middle ear surgery is very likely due to augmentation of the normal base vomiting rate expected after anaesthesia by vomiting reflexes mediated via the vagus.[3,26]

Headache following ear, nose and throat surgery in this hospital occurs most frequently following septorhinoplasty (c. 75% of patients), less frequently after tympanoplasty (c. 50% of patients and least frequently after tonsilloadenoidectomy (c. 33% of patients).[1,2] Ondansetron given as prophylactic antiemetic to patients undergoing chemo- and radiotherapy causes headache in 11% of patients,[6] but when given as prophylactic antiemetic to patients undergoing general anaesthesia does not appear to increase the incidence of postoperative headache.[8,10,29] In the present study the incidence of headache after tympanoplasty in patients given ondansetron (49%) was similar to that after placebo (50%), prochlorperazine im (41%), prochlorperazine iv (43%) and after tympanoplasty in our previous studies (50%).[1,2] These data suggest that ondansetron given with anaesthesia does not increase the incidence of postoperative headache.

Postoperative nausea and vomiting following microsurgery of the middle ear has been a problem since the introduction of this surgical technique in the early 1950s. Traditionally, hyoscine or promethazine im with premedication have been recommended for its prophylaxis,[30,31] and thiethylperazine, because of its effectiveness in vertigo,[11] for its treatment. More recently, with the decline in popularity of im pre-medication, transdermal hyoscine has been shown to be effective in reducing the incidence after tympanoplasty of postoperative nausea (from 27% to 10%), and of postoperative vomiting from (53% to 10%).[26]

This study confirms the observation that PONV is a frequent and debilitating complication after tympanoplasty,[1,2,26] and demonstrates that prochlorperazine 0.2 mg·kg^{-1} im and ondansetron 0.06 mg·kg^{-1} iv given during induction of anaesthesia are efficacious in reducing this morbidity. Depending on cost restraints and availability, it is suggested that patients undergoing tympanoplasty receive either prochlorperazine im or ondansetron iv with induction of anaesthesia or transdermal hyoscine with premedication to minimise PONV pending a comparison of these treatments.

Acknowledgements

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