

Betahistine as an add-on: The magic bullet for postoperative nausea, vomiting and dizziness after middle ear surgery?

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Abstract

Purpose: Patients undergoing middle ear surgery experience variable degrees of postoperative nausea and vomiting (PONV) despite prophylaxis and treatment with ondansetron or other 5HT₃ receptor antagonists. Furthermore vertigo or dizziness are not well controlled perioperatively. Role of betahistine was tested as an add-on to ondansetron in control of PONV and vertigo in middle ear surgery cases.

Materials and Methods: We conducted a prospective, randomized, double-blind, placebo controlled study, enrolling one hundred patients undergoing middle ear surgery under local anesthesia into two groups consisting of fifty ($n = 50$) patients each. Group A patients were given betahistine 16 mg plus ondansetron 8 mg and placebo plus ondansetron 8 mg were given to group B or placebo group, orally 3 hours before starting operation. The incidence of nausea, vomiting, and dizziness was noted during the intraoperative and postoperative 24 hours period. Chi-square test, unpaired 't' test, and Fisher's exact tests were performed for statistical analysis using SPSS version 16 and Open Epi version 2.3.1 softwares.

Results: Complete response was obtained in 90% patients in the betahistine group as compared to 66% in the placebo group. Vomiting in the intraoperative and postoperative period was noted in 4% and 8% cases, respectively, in the betahistine group as compared to 18% and 26%, respectively, in the placebo group. Overall, vertigo was 10% versus 32% in betahistine group and placebo group, respectively.

Conclusion: Betahistine as an add-on to ondansetron can significantly attenuate PONV and perioperative vertigo, following middle ear surgeries.

Key words: Betahistine, middle ear surgery, nausea, ondansetron, postoperative nausea and vomiting, vertigo, vomiting

Introduction

Postoperative nausea and vomiting (PONV) are among the most common adverse events following surgery, anesthesia, and opioid analgesia, with an estimated incidence of 25-30%.^[1] The aetiology is multifactorial that includes patient factors, type of surgery, and anesthetic technique.^[2]

Middle ear surgeries disturb the vestibular system and are associated with high incidence of PONV and vertigo, which are further aggravated by use of opioids. A 62-80% incidence of PONV following middle year surgery has been reported.^[3,4] Reduction in PONV and opioid-induced emesis is more with use of ondansetron and other 5HT₃ receptor antagonists (5HT₃RA) than other groups of antiemetics, but many patients still experience PONV and vertigo. No reduction of PONV occurs in patients with a history of motion sickness.^[4] Involvement of multiple types of receptors and factors like disturbances in the inner ear from surgical stimulation may be a reason for inadequate control of PONV with a single agent. Betahistine, a histamine agonist at H₁ receptor and antagonist at H₃ receptor, is widely used in Meniere's disease and other types of vertigo where disturbance or imbalance in vestibular system is considered as an etiological factor.^[5] We noticed that some of our patients, on betahistine pre-operatively for some indication, suffered from less incidence of PONV.

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Hyoscine (scopolamine), used for suppression of motion sickness due to the activity on the vestibular system, has been reported to successfully control PONV in middle ear surgeries.^[3] In this pilot study, we evaluated the effectiveness of betahistine as a routine add-on pre-medication in control of PONV and vertigo in middle ear surgeries.

Materials and Methods

After approval from the Hospital Research and Ethics committee, a prospective, randomized, double-blind, placebo controlled study was conducted on adult patients undergoing tympanoplasty or mastoidectomy under local anesthesia. Written informed consent was taken from all the patients and their legal guardian for participation in the study.

One hundred patients scheduled for either tympanoplasty or mastoidectomy (from July 2010 to November 2011) was divided in two groups of fifty each using web-based randomization. All patients consented to undergo surgery under local anesthesia (LA). The baseline data of hospital anxiety and depression was taken for all patients with Hospital Anxiety Depression Scale (HAD), a validated scale for this purpose. Only the patients with a baseline HAD data <7 were included in the study.^[6] Group A patients were given betahistine 16 mg and ondansetron 8 mg (orally) 180 min before the start of surgery. Group B patients were given placebo and ondansetron 8 mg (orally) 180 min before starting surgery. Riboflavin tablet 20 mg was used as placebo.

Inclusion criteria included American Society of Anesthesiologists (ASA) grade I and II patients, both males and females, aged 20-60 years, scheduled for tympanoplasty and/or mastoidectomy and with a HAD score <7. Patients not consenting for surgery under local anesthesia, lack of valid consent, patients with gastrointestinal disease, Meniere's disease, vertigo, dizziness, pregnant, menstruating, patients on regular anti-emetics, anti-vertigo, anti-psychotic drugs, having severe hypertension, coronary insufficiency, psychiatric disorders, and communication problems were excluded from the study.

After admission, detailed history was taken from the patients to exclude any other disease and they were subjected to routine investigations. History was taken regarding the regular use of antiemetics, motion sickness, or vomiting within 24 hours before operation.

All patients were advised to be nil per oral for solid food for 6 hours and for water for 2 hours before operation. Ranitidine 300 mg and lorazepam 1 mg were administered orally 4-5 hours before surgery. About 180 min before starting the

surgery, group A patients were given betahistine 16 mg and ondansetron 8 mg orally, while group B patients were given placebo and ondansetron 8 mg orally.

About 15 min prior to the surgery, all patients were given local block with bupivacaine 0.25%. Skin infiltration with lignocaine 0.1% with adrenaline (1 in 1,00,000) was done in all patients to reduce bleeding from the wound. The total volume of local anesthetic used was 10-12 ml. All patients were given midazolam 2 mg intravenous (IV) for sedation and anxiolysis. Monitoring of non-invasive blood pressure, heart rate, and pulse oximetry was done.

Postoperative pain was treated with diclofenac 1 mg/kg intramuscular (IM) in all patients ($n = 100$). Nausea in the operative period was recorded whenever complained voluntarily. Patients were asked to report any nausea and vertigo during the operative procedure. Patients were assessed intraoperatively and up to 24 hours postoperatively for the subjective complaints like nausea, vomiting (including retching), and vertigo by a trained nurse unaware of the study. Nausea in the postoperative period was recorded in a 100 mm VAS scale at 3, 6, 12, and 24 hours postoperatively. Vertigo was evaluated by categorical response of the patients to the question, "Are you feeling vertigo, yes or no?" or if the patient complained voluntarily. Incidences of postoperative severe nausea, retching, and vomiting occurring after 6 hours were treated with ondansetron 4 mg IV. Prochlorperazine 10 mg was given IM in case of vomiting during surgery in the first 6 hours after surgery and in case patient complained of dizziness and vertigo postoperatively. Adverse reaction to any drug was noted during the study period.

The primary efficacy parameters were complete response (CR), which included patients free from PONV and no rescue antiemetic in a defined period. Incidence of vomiting in the operative, postoperative 24 hours, and overall period (operation and postoperative 24 hours) were measured. The secondary efficacy parameter was incidence of nausea and/or vertigo during operation, at post operative 24 hours, and after overall period. Any association between nausea, vomiting, and vertigo was also to be noted. Use of rescue antiemetics and anti-vertigo medication was also noted.

The demographic data like age, sex, body weight, history of motion sickness, and duration of surgery in two groups were compared using unpaired 't' test and Chi square tests using statistical software SPSS, version 16. Data on complete response, nausea, vomiting, and vertigo were compared and analyzed using uncorrected and Yates

corrected Chi-square tests and Fisher’s exact tests with statistical software (SPSS version 16 and Open Epi version 2.3.1). A $P < 0.05$ was considered statistically significant.

Results

There was no significant difference in the age, sex distribution of the patients of both the groups, and duration of anesthesia or operation between two groups. \pm (Group data were presented as mean \pm SD) [Table 1].

Number of patients with CR, incidences of nausea, vomiting, and vertigo are shown in [Table 2]. The detail of the patients who had clinically significant nausea (VAS >50 mm), vomiting, and vertigo during surgery and first 24 hours of postoperative period in two groups and (shown and

Table 1: Demographic figures of the patients

Variable	Betahistine group (n=50)	Placebo group (n=50)	P value
Age	31.20 \pm 9.7	32.34 \pm 11.15	0.587
Weight	57.83 \pm 4.709	58.3 \pm 5.0477	0.631
Male/female	26/24	25/25	0.841
Motion sickness	12	9	0.461
Duration of surgery	51.02 \pm 11.494	49.16 \pm 9.734	0.385
Postoperative diclofenac	50	50	

Data in mean \pm standard deviation

Table 2: The incidences of nausea, vomiting, and vertigo in two groups of patients during surgery and then up to 24 hours of postoperative period

Variable	Betahistine group (n=50) n (%)	Placebo group (n=50) n (%)	P value
Operative period			
CR	47 (94)	41 (82)	0.03
Vomiting	2 (4)	9 (18)	0.05
Nausea	3 (6)	9 (18)	0.12
Vertigo	3 (6)	11 (22)	0.04
Rescue antiemetic	3 (6)	11 (22)	0.04
Post-op: 0-24 hours			
CR	46 (92)	37 (74)	0.03
Vomiting	4 (8)	13 (26)	0.03
Nausea	4 (8)	13 (26)	0.03
Vertigo	5 (10)	13 (26)	0.06
Rescue antiemetic	5 (10)	13 (26)	0.06
Over all: Operative+ Post-op 0-24			
CR	45 (90)	33 (66)	0.02
Vomiting	5 (10)	15 (30)	0.004
Nausea	5 (10)	17 (34)	0.007
Vertigo	5 (10)	16 (32)	0.006
Rescue antiemetic	5 (10)	17 (34)	0.007

CR=Complete response

compared) in [Figures 1-3]. Any patient with a VAS score for nausea >50 were considered as clinically significant and score >75 was taken as severe nausea.^[7] In the betahistine group, CR was observed in 90% cases as compared a CR 66% in the other group ($P < 0.5$) [Figure 4]. Rescue antiemetics were administered to all such patients ($n = 24$) [Table 2; Figure 5].

In the placebo group, 9 patients complained of nausea,

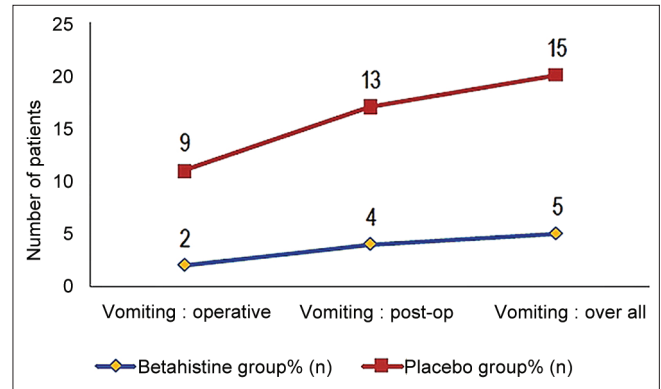


Figure 1: Comparative incidences of vomiting. Higher incidences were noted in the placebo group

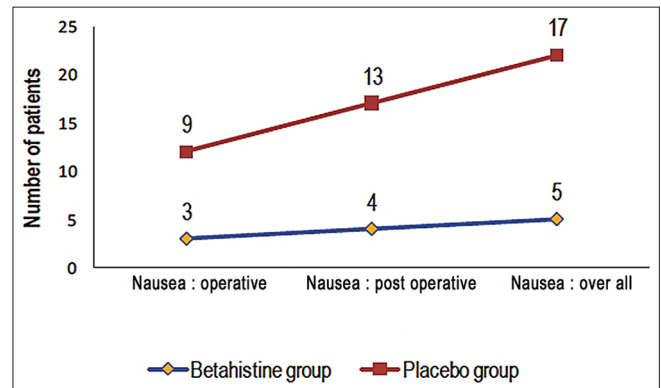


Figure 2: Comparative nausea in both groups of patients. Higher number of patients experienced nausea in the placebo group at all three time frames

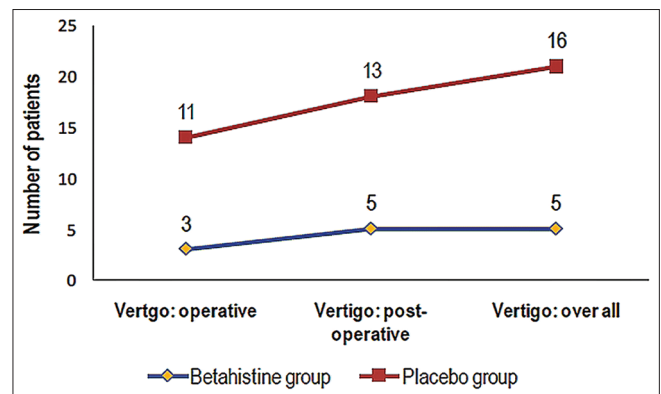


Figure 3: Comparative vertigo in both groups of patients. More number of patients experienced vertigo in the placebo group

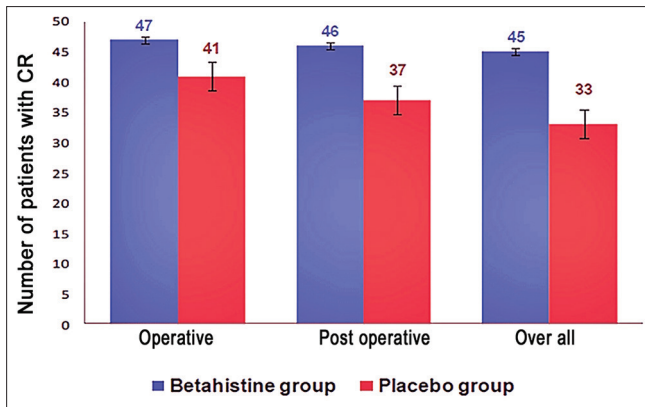


Figure 4: Complete response in two groups during surgery, postoperative 24 hours, and overall period. Numbers of patients are plotted along the “Y” axis (vertical axis) and time frame along the “X” axis (horizontal axis). The number of patients who had complete response was higher in the betahistine group in all the three time frames as compared to placebo group

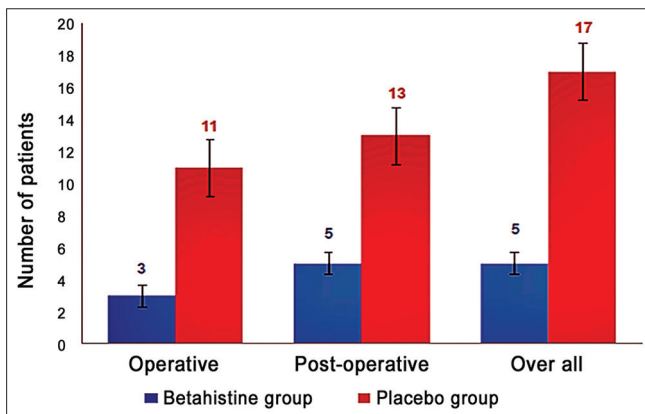


Figure 5: Rescue antiemetic use in two groups. (Vertical axis depicting number of patients and horizontal axis depicting different time frame)

retching, and vomiting during operation and 13 patients during 12 hours of postoperative period, however, emesis was present in 15 patients overall in the placebo group, indicating repeated occurrence of vomiting and nausea in same patients.

A strong association was noted between vertigo and emesis in these middle ear surgery cases. Most of the patients who had experienced vertigo or dizziness during surgery or within 24 hours after surgery also experienced clinically significant nausea and vomiting.

No adverse effects to any of the study drugs were noted in the study period.

Discussion

Addition of betahistine in the PONV prophylaxis regimen for middle ear surgery was superior to the placebo group in the control of nausea, vomiting and vertigo. Most patients who experienced vertigo in the operative or post-operative

period eventually developed PONV. Use of rescue antiemetic was less when betahistine was used in combination with ondansetron for prophylaxis of nausea and vomiting.

Tympanoplasty and mastoidectomy are two of the most common procedures performed on the middle ear. Both these surgeries are associated with a high incidence of PONV. Patients experiencing PONV consume more resources and require additional healthcare professional time.^[8]

A wide range of drugs are used to treat/prevent PONV that includes phenothiazines, anticholinergics, anti-histamines, butyrophenones, substituted benzamides, corticosteroids, 5-HT₃ receptor antagonists (5HT₃RA), and NK₁ receptor antagonists.^[9] Drug like hyoscine, primarily used in motion sickness and have been found to be effective in control of PONV and dizziness following middle ear surgery.^[3,10]

Ondansetron, a 5HT₃RA, is one of the most commonly used drugs for PONV prophylaxis and control. Combination of drugs is recommended for PONV, as it is superior to monotherapy.^[11] Although Ondansetron controls PONV effectively in diverse situations, it is not effective in motion sickness and vertigo.^[12]

Betahistine, a structural analog of histamine with H₁ agonist and H₃ antagonist activity, is effective in vertigo of both central and peripheral origin.^[13] H₁-mediated vasodilatation improves microcirculation in the inner ear and vestibular nuclei, a conventionally postulated theory for the mechanism of anti-vertigo action of betahistine. H₃ antagonism increases histamine synthesis and release from the vestibular nucleus, further augmenting H₁ action. Spike generation from the neurons of lateral and medial vestibular nucleus is also reduced. These actions along with a less specific action on alertness are supposed to improve vestibular compensation.^[14,15]

Uncontrolled change in resting discharge of vestibular nuclei, which is responsible for vertigo, is suppressed both by betahistine and its active metabolite.^[16] Betahistine has an established role as an anti-vertigo agent in Meniere's disease.^[17-20] It's use has also been found to benefit in motion sickness.^[21] However, there are no studies supporting the role of betahistine in PONV.

The exact mechanism of nausea, vomiting, and vertigo in middle ear surgery is not known, but physical stimulation in the form of drilling and irrigation in the bones adjacent to the inner ear at the time of surgery is a postulated mechanism. Physical stimulation leads to the generation of noises of different frequencies, producing low frequency sound (LFS) stimulation. LFS is a major contributing factor for instability in

Meniere's disease, chronic suppurative otitis media (CSOM) with vertigo, and vertigo of peripheral origin. This sound induced disequilibrium or "Tullio phenomenon" is due to activation of vestibulospinal response. Similarly, sound waves generated during middle ear surgery may lead to expression of "Tullio phenomenon."^[22] There is some similarity in the underlying mechanism of vertigo-dizziness in middle ear surgery and that due to Meniere's disease or vertigo of peripheral origin. Drugs that suppress vestibular stimulation or improve vestibular compensation might have some role in the control of dizziness and vomiting associated with middle ear surgery. Hyoscine, a drug that controls motion sickness, was found to be effective in control of PONV in middle ear surgeries.^[3,9] Many patients of middle ear surgery are noticed to complain of dizziness and vertigo in the intra and postoperative period and this could possibly be attributed to LFS and physical stimulation. There is considerable association between occurrences of vertigo-dizziness with nausea-vomiting in these cases. Complaints of vertigo and dizziness by a group of patients who eventually ended up with vomiting probably indicate some cross-link between vertigo-dizziness and nausea-vomiting in middle ear surgery cases. Betahistine probably acts by intersecting at this point.

Choosing local anesthesia provided some additional benefit in planning the study. Local anesthesia for middle ear surgery is feasible, cheap, safe and is one of the popular methods employed in such surgeries in some parts of the world.^[23] Free verbal communication with the patients is possible in the intra-operative period, which helped in assessment of symptoms of nausea, vomiting, and vertigo during this period and early postoperative period, which would have been impossible if patients are administered a general anesthetic.

The weakness of the study is a small sample size. Non-inclusion of cases under general anesthesia can be considered another limitation. Further the role of betahistine as an individual agent was also not assessed in this study.

The use of prophylactic betahistine preoperatively in conjunction with ondansetron for middle ear surgery was found to significantly reduce PONV and dizziness in patients after middle ear surgery, and it was also associated with superior control of perioperative vertigo and nausea and vomiting. Further study in this field is suggested with a larger sample size including both local and general anesthetics. Any possible direct antiemetic action of betahistine also needs further research. Larger sized randomized controlled trials may be conducted to justify the role of betahistine.

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