Original Article

Randomized Double-Blind Comparison of Two Different Low Doses of Ondansetron in Combination with Dexamethasone for Prophylaxis of Postoperative Nausea and Vomiting in Middle Ear Surgery

Varun Seth, Geetanjali Tolia Chilkoti, Vibhor Gupta, Medha Mohta and Ashok Kumar Saxena

Department of Anaesthesiology and Critical Care, University College of Medical Sciences and GTB Hospital

ABSTRACT

Background: Ondansetron is associated with more side effects and is expensive when compared to dexamethasone; thus, mandating a need to identify the optimal dose of 5- HT3 antagonist like ondansetron when used in combination with dexamethasone for PONV prophylaxis.

Aim: The present study was undertaken with the aim to assess and compare the efficacy of two low-doses of ondansetron i.e. 50µg/kg and 25µg/kg in combination with 8mg dexamethasone for prophylaxis of postoperative nausea and vomiting in middle ear surgery.

Method: Following approval from Institutional Ethics Committee-Human Research (IEC-HR) and prospective CTRI registration, this randomized, double blind interventional study was conducted following informed consent from each participant. Patients aged 16-65 years of either sex, with ASA physical status I or II, undergoing middle ear surgery (tympanoplasty or mastoidectomy) under general anaesthesia were included and divided into group C and L. Group C and L received 50µg/kg and 25µg/kg ondansetron in combination with 8mg dexamethasone, respectively. The incidence of PONV, haemodynamic parameters, rescue antiemetic and rescue analgesia were recorded.

Results: A total of 120 patients were included with 60 in each group. In the first two hours of postoperative period, there was a significantly higher number of patients in Group L having PONV score between 1-3 than Group C (p value<0.05). Among group C, six out of 60 patients required metoclopramide in first 2 hours. There were significantly higher number of individuals in Group L requiring anti-emetic than in Group C. (p-valu <0.05).

Conclusions: We observed that 50µg/kg dose combination of ondansetron was more efficacious than 25µg/kg dose combination with 8mg dexamethasone for PONV prophylaxis following middle ear surgery.

Key Words: Dexamethasone, Middle ear surgery, Ondansetron.

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Corresponding Author: Vibhor Gupta, Department of Anaesthesiology and Critical Care, University College of Medical Sciences and GTB Hospital, **Tel.:** 9971068804 , **E-mail:** vibhor817@gmail.com

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BACKGROUND

Postoperative nausea and vomiting (PONV) is one of the common distressing complication postoperatively leading to prolonged hospital stay[1]. Its incidence is 20-30% amongst various surgeries but it may be as high as 50-80% in middle ear surgery[2], 50-70% in laparoscopic cholecystectomy[3], 60-80% in breast surgery with axillary dissection[4] and 54-92% in laparoscopic gynaecological procedures[5]. The risk of PONV following middle ear surgery has been found to be very high in comparison to other surgeries and has been reported to be between 60-80%[6-9]. Thus emphasizing upon the routine use of prophylactic antiemetics in middle ear surgery[10].

Dexamethasone 8mg and ondansetron 4mg is most widely studied for the prophylaxis of PONV in middle ear surgery. Ondansetron, a 5 HT3 antagonist is known to decrease the incidence of PONV in the early postoperative period and dexamethasone decreases the incidence of the late PONV. The most commonly used adult dose is 4mg i.e. approx 100µg/kg. Various studies evaluating ondansetron with dexamethasone also have used 4mg standard dose of ondansetron for PONV prophylaxis for various surgeries[11-13].

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The cost effectiveness is one of the primary considerations in PONV prophylaxis as it is preferred to be administered to all patients undergoing surgery under general anaesthesia (GA). Therefore, there is a need to decrease the dose of ondansetron when used in combination with dexamethasone.

Literature search revealed only single article where combination of low dose ondansetron 50ug/kg and 150ug/kg dexamethasone is compared to higher dose of ondansetron i.e. 150ug/kg only for PONV prophylaxis and they concluded that low dose ondansetron plus dexamethasone is more effective prophylactic antiemetic combination for children undergoing strabismus surgery[14]. Thereafter, no further study was conducted to evaluate the combination of low dose of ondansetron with dexamethasone for PONV prophylaxis for any other surgeries.

We hypothesized that the two low doses of ondansetron i.e. 50ug/kg and 25ug/kg in combination with 8mg dexamethasone to be equally efficacious for prevention of PONV in middle ear surgery. Therefore, we undertook the present study with the aim to assess and compare the efficacy of two low-doses of ondansetron i.e. 50µg/kg and 25µg/kg in combination with 8 mg dexamethasone for PONV prophylaxis in middle ear surgery.

METHODS

Following approval from Institutional Ethics Committee-Human Research (IEC-HR) and prospective CTRI registration (CTRI/2019/02/017523), the present randomized, double blind interventional study was conducted in a tertiary care centre from Nov 2018 to April 2020. Written informed consent was obtained from all the patients. Patients aged 16-65 years of either sex, with American Society of Anaesthesiologists (ASA) physical status I or II, undergoing middle ear surgery (tympanoplasty or mastoidectomy) under GA were included. The patients were excluded if pregnant, had received any antiemetic medication or perioperative steroids as anti-edema therapy for facial nerve damage. Patients were randomly allocated into one of the two groups. Patients in both groups received dexamethasone 8mg given at the beginning of surgery. Patients in group C and L received ondansetron 50µg/kg and 25µg/kg near the end of surgery, respectively.

Randomization was done using a computer-generated random number tables. The allocation concealment was done using sequentially numbered opaque-coloured sealed envelopes. The study drug was prepared by the third person not involved in the study and the patient as well as the investigator were blinded to the study drug used.

For premedication, tablet alprazolam 0.5mg was given as premedication, the night before the surgery. General anaesthesia was induced with morphine (0.1mg/kg), propofol (2mg/kg), and vecuronium (0.1mg/kg) to facilitate endotracheal intubation. Dexamethasone 8mg IV was given after induction of anaesthesia. Anaesthesia was maintained with isoflurane 1%-1.5% with nitrous oxide 60% in oxygen. Ventilation was mechanically controlled and adjusted to maintain an end-tidal concentration of CO_2 between 35 and 40mmHg.

The haemodynamic parameters and minimum anaesthetic concentration (MAC) were noted every 15min during the surgery. Depending on the group allocation, ondansetron 50µg/kg or 25µg/kg was administered 30min before the completion of surgery. The study drug was prepared by the third person not involved in the study. Neuromuscular blockade was reversed with neostigmine and glycopyrrolate at the end of surgery and trachea was extubated. Towards the end of surgery, all patients had received intravenous Paracetamol 1gm infusion intravenously.

Haemodynamic parameters i.e. heart rate (HR), systolic blood pressure (SBP) and mean blood pressure (MBP) and SPO_2 were recorded at pre induction as baseline, post induction and after tracheal intubation at thereafter every 15 minutes till the end of surgery. Patients were kept under observation in the postoperative period for at least 4hr. All haemodynamic variables i.e. HR, SBP, DBP, MAP were recorded every hour for 4 hours. All the patients had received injection paracetamol 1gm IV every 8 hourly for postoperative pain management.

The incidence of PONV was assessed by an investigator who was blinded to the treatment group. The evaluations were performed at various time intervals i.e. first 2h, 2-6h, 6-12h, and 12-24h postoperatively. Nausea is defined as subjective unpleasant sensation associated with the urge to vomit. Vomiting is defined as the forceful expulsion of gastric contents.

Postoperative nausea and vomiting was evaluated using numeric scoring system for PONV score[15]. No nausea or vomiting= 0; Nausea but no vomiting= 1; Vomiting once in 30min or more =2; Persistent nausea >30min or two or more vomits in 30min= 3. The severity of postoperative pain was assessed by using a numerical rating score (NRS) that ranged from 0 (no pain) to 10 (worst pain imaginable).

If the patient develops nausea for more than 15min or vomiting in the postoperative period, then metoclopramide 10mg was given slowly intravenously as rescue antiemetic. If the patients' PONV persisted despite administering rescue antiemetic, the anaesthesiologist was allowed to give ondansetron or any other antiemetic as per their discretion and the patient is excluded from the study.

If patient complains of pain ≥3 on NRS pain score, injection diclofenac 75mg IV was used as a breakthrough analgesic. The patients were enquired about the common side effects of medication, namely headache, dizziness, drowsiness, constipation, and flushing.

The primary outcome was PONV score at various designated intervals in the first 0-2hrs and Secondary outcomes were PONV scores at 2-6hr, 6-12 and 12-24hrs, total rescue antiemetic consumption in 24hr, NRS pain score in the postoperative period and side effects, if any.

Sample size calculation:

Our pilot study on 50 patients has shown the incidence of complete response i.e. no PONV as 72% with dexamethasone 8mg and ondansetron 50µg/kg combination for middle ear surgery. Considering a difference of 20% to be statistically significant, presuming an α-error of 0.05 and to achieve a power of 0.8, the sample size calculation revealed 57 patients in each group. To consider the dropouts, a sample size of 120 patients was taken with 60 patients in each group.

Statistical analysis:

Statistical analyses was performed using SPSS version 21.0. Data was presented as mean±standard deviation or as the number of patients or percentages. Categorical variables was compared using the chi-square test or Fisher's exact test. Continuous variables was compared using independent *t*-test. *P*-value less than 0.05 was considered statistically significant.

RESULTS

A total of 127 patients were assessed for eligibility. Out of 127, seven didn't meet the inclusion criteria. Finally, 120 patients were included with 60 in each group (Figure 1).

Both the groups were comparable with respect to weight, gender and ASA status. The duration of surgery in the Group C was observed to be significantly longer than Group L, this finding could be incidental (Table 1).

Table 1: Patients' Characteristics:

Parameters Weight of the patient (in kgs)	Group C (n= 60)	Group L (n= 60)	p-value
(Mean±SD)	60.45(±9.03)	62.91(±12.06)	0.269
Gender (M: F)	28:32	17:43	0.077
ASA Grade (1:2)	52:8	48:12	0.327
Duration of surgery (in mins) (Mean±SD)	183.51(±40.91)	149.78(±47.55)	0.001*

Group C- Ondansetron 50µg/kg+ Dexamethasone 8mg; Group L- Ondansetron 25µg/kg+ Dexamethasone 8mg; * p-value <0.05: Statistically significant.

In the first two hours in the postoperative period, a significantly higher number of patients in Group L had PONV score 1-3 than in Group C. (p value <0.05). Between 2-6 hours postoperatively, both groups had a comparable proportion of patients experiencing PONV.

There was no significant difference between the two groups in the incidence of PONV between 2-6 hrs and 6-12 hrs postoperatively. No participant experienced PONV between 12-24 hrs time interval (Table 2).

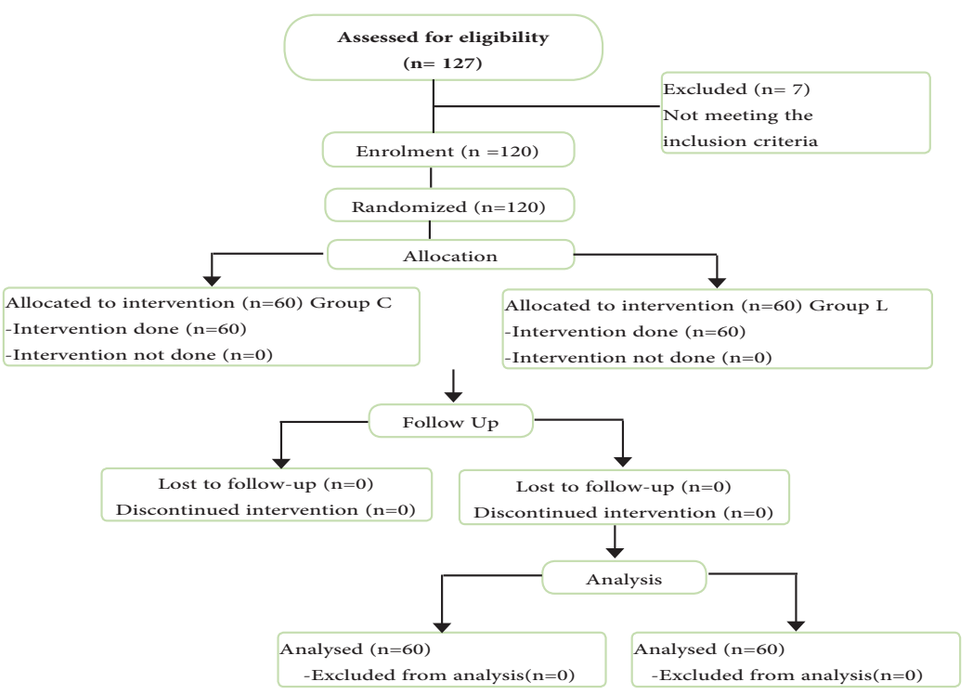

Fig. 1: Consort Flow diagram.

Table 2: Post-operative Nausea Vomiting (PONV) score at various time intervals:

PONV score (0-2hr)	Group C (*n*= 60)	Group L (*n*= 60)	*p*-value
0	47 (78.3%)	33(55%)	0.009*
1	10 (16.7%)	14(23.3%)	
2	2 (3.3%)	13(21.7%)	
3	1 (1.7%)	0	
PONV score (2–6)hr)			
0	50 (83.3%)	49(81.7%)	0.924
1	10 (16.7%)	11(18.3%)	
PONV score (6–12hr)			
0	58(96.7%)	57(95%)	0.975
1	2 (3.3%)	3(5%)	
PONV score (12-24hr)			
0	0	0	----
1	0	0	----

Group C- Ondansetron 50µg/kg+ Dexamethasone 8mg; Group L- Ondansetron 25µg/kg+ Dexamethasone 8mg; * *p*-value <0.05: Statistically significant; *n*= number of patients.

A significantly higher number of individuals in Group L required antiemetic than in Group C. (*p*-value <0.05) No significant difference was observed between the two groups in terms of the need for rescue antiemetic between 2-6 hrs and 6-12 hrs time intervals, postoperatively. Amongst patients requiring metoclopramide, none of the patient needed any other antiemetic after that. No patient required rescue antiemetics at 12-24 time interval (Table 3).

The mean NRS-pain score was observed to be higher in Group L in the 0-2hr and 2-6hr interval when compared to Group C; however, the difference was not significant. Similarly, NRS score was comparable in 6-12 and 12-24hr time intervals (Table 4).

The need for rescue analgesic was observed in first 2hrs only and was higher in group L than in group C; however, not statistically significant (Table 5).

Table 3: Patients requiring rescue antiemetics at various time intervals:

Rescue Antiemetic (0–2hr)	Group C (*n*= 60)	Group L (*n*= 60)	*p*-value
Administered	6(10%)	24(40.0%)	0.001*
Not Administered	54(90%)	36(60.0%)	
(2–6hr)			
Administered	9(15%)	8(13.3%)	0.830
Not Administered	51(85%)	52(86.7%)	
(6–12hr)			
Administered	1(1.67%)	2(3.3%)	0.975
Not Administered	59(98.3%)	58(96.7%)	
(12-24hr)			
Administered	0	0	
Not Administered	60(100%)	60(100%)	

Group C- Ondansetron 50µg/kg+ Dexamethasone 8mg; Group L- Ondansetron 25µg/kg+ Dexamethasone 8mg (figure 8); * *p*-value <0.05: Statistically significant.

Figure (2) shows the hemodynamic parameters at various time points starting as baseline, post induction, post-intubation and every 15mins, thereafter till the end of surgery. The mean SBP was observed to be lower in group L then group C at various time intervals; however, this decrease was found to be significant at immediately after induction of anaesthesia till first 15mins and then from 90th min till the end of 135th mins. Similarly, the mean MAP was reduced in group L; however, no particular trend was observed. The mean HR was found to be comparable between the two groups at various time intervals.

Table 4: Numerical Rating Score (NRS-Pain) at various time intervals:

Numerical Rating Score (NRS)	Group C (*n*= 60)		Group L (*n*= 60)		*p*-value
	N	Mean (±SD)	N	Mean (±SD)	
NRS 0–2	60	0.83(±1.71)	60	1.41(±1.93)	0.133
NRS 2–6	60	0.04(±0.29)	60	0.02(±0.15)	0.688
NRS 6–12	60	0.00	60	0.04(±0.30)	0.304
NRS 12–24	60	0.00	60	0.00	-

Group C- Ondansetron 50µg/kg+ Dexamethasone 8mg; Group L- Ondansetron 25µg/kg+ Dexamethasone 8mg; N= Number of patients.

Table 5: Distribution of patients according to the need for rescue analgesic at various time intervals:

Rescue Analgesic (0–2hr)	Group C (*n*= 60)	Group L (*n*= 60)	*p*-value
Administered	7(11.7%)	11(18.3%)	0.304
Not Administered	53(88.3%)	49(81.7%)	
Rescue Analgesic (2-6hr , 6-12hr, 12-24hr)			
Administered	0	0	
Not Administered	60(100%)	60(100%)	
Total	60	60	

Group C- Ondansetron 50µg/kg+ Dexamethasone 8mg; Group L- Ondansetron 25µg/kg+ Dexamethasone 8mg.

In group C, four patients (6.6%) out of 60 patients experienced side effects; whereas, in group L also, four patients (6.6%) out of 60 experience side effects due to either drug. No adverse effect was observed in any other patients. The side effects were mild and did not require any intervention. Both the groups were comparable with respect to side effects.

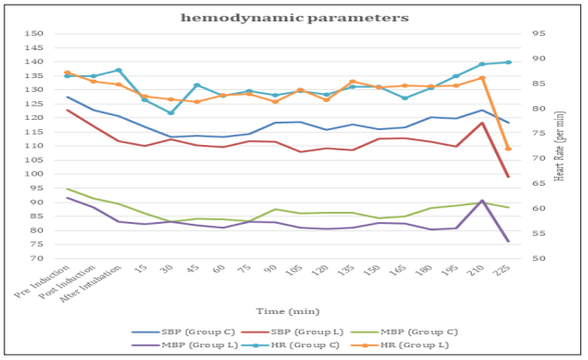

Fig. 2: Group C- Ondansetron 50µg/kg+ Dexamethasone 8mg; Group L- Ondansetron 25µg/kg+ Dexamethasone 8mg.

DISCUSSION

In the present study, a significantly higher proportion of patients developed PONV and required higher rescue antiemetic in the first 2hrs in group L when compared to group C; however, the NRS-pain score, rescue analgesic requirements and side effects were comparable between the two groups.

Amongst the different combination of pharmacological agents used for PONV prophylaxis, dexamethasone 8mg and ondansetron 4mg is most widely studied for the prophylaxis of PONV in middle ear surgery[11]. Typical dosing of ondansetron is 4mg, but a meta-analysis found no difference in efficacy between 1mg, 4mg, and 8mg for postoperative therapy for PONV prophylaxis[13]. Ondansetron, a 5 HT3 antagonist is known to decrease the incidence of PONV in the early postoperative period and dexamethasone decreases the incidence of the late PONV Therefore, the use of combination of drugs for the prophylaxis of PONV against the sole antiemetic drug is always considered superior[16].

Dexamethasone has the advantage of being cost effective, longer duration and minimal to no side effects when administered for PONV prophylaxis[17]. In addition, it has anti-inflammatory and analgesic action[18,19].

Various researchers have recommended to identify the optimal dose of 5- HT3 antagonist like ondansetron when used in combination of dexamethasone in PONV prophylaxis[20,21]. Literature search revealed only single study where combination of low dose ondansetron 50ug/kg and 150ug/kg dexamethasone has been compared to high dose ondansetron i.e. 150ug/kg and they concluded that low dose ondansetron plus dexamethasone is more effective prophylactic antiemetic combination for children undergoing strabismus surgery[14].

Ondansetron is more effective in preventing early PONV; whereas, dexamethasone was found to have more pronounced action in the late postoperative period[20]. This is in concordance to the result of the present study reflecting the higher PONV score in first 2hrs in group L utilizing further lower dose i.e. 25µg/kg dose of ondansetron; however, 50µg/kg dose of ondansetron was found to be less efficacious than the 25µg/kg dose in terms of prophylaxis of PONV. The finding of our study is in accordance to the study by Splinter *et al.,* which concluded that low-dose ondansetron plus dexamethasone group had a lower incidence of vomiting, 9% (95% ci= 4-17%) versus 28% (95% ci= 20-38%; $p<0.001$). The aforementioned study compared the standard dose combination i.e. 50µg/kg ondansetron with 8mg dexamethasone with high dose ondansetron 150µg/kg alone.

Dexamethasone in the same dose i.e. 8mg was used in both the groups and it is known to have analgesic properties along with anti-inflammatory and prevention of PONV[22]. Dexamethasone is a useful adjunct in multimodal pain management[23]. This could probably explain the comparable NRS pain scores in both groups and requirement of rescue analgesic between the two groups.

Both PONV and rescue antiemetic requirement was observed to be lesser with 50µg/kg ondansetron dose when compared to 25µg/kg dose only in the initial 2hrs. Ondansetron is known to reduce PONV in the early postoperative period; whereas, dexamethasone reduces late PONV[14]. Thus, this difference in results only in the first 2hrs can clearly be implicated to the change in the dose of ondansetron in the study.

We observed a higher incidence of PONV scores with the use of 25µg/kg dose of ondansetron group to the significantly lower SBP in the same group intraoperatively. This higher PONV incidence may be attributed to the hypovolemia and also in the postoperative period when compared to the 50µg/kg dose of ondansetron i.e. group C. Hypovolaemia after overnight fasting is believed to exacerbate PONV and intraoperative fluid administration has been proven to be an important factor determining the PONV occurrence[24,25].

The study is dealt with few limitation. Firstly, we didn't follow any specific protocol for fluid administration and also didn't record the IV fluid administered intraoperatively. Secondly, no risk stratification using a simple scoring system like Apfel was attempted.

CONCLUSIONS

We observed lesser PONV incidence and rescue antiemetic requirement only in the initial 2hrs with 50µg/kg ondansetron dose in combination with dexamethasone when compared to low dose i.e. 25µg/kg ondansetron dose in combination with dexamethasone for PONV prophylaxis following middle ear surgery. We recommend further studies with a larger sample size to validate the findings of the present study.

ABBREVATIONS

PONV: Postoperative nausea and vomiting, **µg/kg:** microgram per kilogram.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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