Comparing combination antiemetics of ramosetron and dexamethasone to ondansetron and dexamethasone in middle ear surgery in high risk patients: a prospective, randomized double-blind clinical study

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Abstract:

Context: Combination antiemetics are recommended as prophylaxis for PONV in moderate to high risk patients. Commonly dexamethasone and 5 HT3 receptor antagonists are used as combination antiemetics. There is questionable benefit of adding dexamethasone to ramosetron for PONV prophylaxis. There are no studies comparing efficacy of combination of dexamethasone with single dose of ondansetron and ramosetron.

Aims: To evaluate the efficacy of ramosetron and dexamethasone combination and compare it with ondansetron and dexamethasone in preventing PONV after middle ear surgery under general anaesthesia, in patients who are moderate to severe risk of PONV.

Settings and Design: Peri-operative and up to 48 hours postoperative. Prospective, randomised, double blind study.

Methods and Material: One hundred and forty four adult patients undergoing middle ear surgeries were allocated to receive either dexamethasone 8 mg and ondansetron 4 mg (n = 72) or dexamethasone 8mg and ramosetron 0.3 mg (n = 72). The incidence and severity of PONV, need of rescue antiemetics and the side effects of the antiemetics were noted for the first 48 h after surgery.

Statistical analysis used: Chi-square test or Fisher's exact test, independent sample t-test.

Results: There was no significant difference in the incidence and severity of nausea between groups at 2, 2-12, 12-24 and 24-48 hour interval. The incidence of vomiting and use of rescue antiemetic was also not different between groups at all the time intervals. Percentage of patients with no PONV in 48 hours was 78% and 76% in dexamethasone ondansetron and dexamethasone ramosetron groups respectively.

Conclusions: Combination of dexamethasone and ramosetron has equal efficacy as ondansetron with dexamethasone in reducing PONV after middle ear surgery.

Key-words: Postoperative nausea and vomiting, Middle ear surgery, Ondansetron, Ramosetron, Dexamethasone.

Key Message: Combination of dexamethasone and ramosetron has equal efficacy as ondansetron with dexamethasone in reducing PONV after middle ear surgery.

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Introduction

Incidence and severity of postoperative nausea and vomiting (PONV) is very high following middle ear surgeries, due to stimulation of labarynth.[1] Society for Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting, 2014, recommends that adults who are at moderate to severe risk for PONV should receive combination therapy with two or more prophylactic drugs, as combination therapy has superior efficacy compared with monotherapy for PONV prophylaxis.[2] It is advisable to use drugs with different mechanisms of action in the combination to optimise efficacy.[3] Because of better side effect profile dexamethasone along with 5 HT3 receptor antagonists are commonly preferred combination agents. Previous studies show ramosetron has similar or better efficacy compared to ondansetron for PONV prophylaxis. But to our knowledge, there are no studies comparing efficacy of combination of dexamethasone with single dose of 5HT3 antagonists, ondansetron and ramosetron.

In a previous study, we noted that combination of ondansetron with dexamethasone was superior to ramosetron for prevention of PONV following mastoid surgery.[4] We noted that, in group of patients who received ramosetron alone, 60% had some nausea/ vomiting compared to 29% in the group who received dexamethasone and ondansetron combination therapy. The better efficacy was attributed to the fact that combination antiemetics are more efficacious than any single antiemetic agent. Since for all moderate to severe risk category of patients, combination antiemetic are recommended, we wanted to compare the efficacy of combination of ramosetron and dexamethasone with the combination of ondansetron and dexamethasone for prevention of PONV. Hence the present study is

undertaken to evaluate the efficacy of ramosetron and dexamethasone combination and compare it with ondansetron and dexamethasone in preventing PONV after middle ear surgery under general anaesthesia, in patients who are moderate to severe risk of PONV.

Subjects and Methods

After approval from the hospital ethics committee, one hundred and forty four patients in the age group of 16-50 years with American Society of Anesthesiologists physical status classification I or II undergoing middle ear surgery were included in this study. Informed consent was taken from all the patients for this prospective, randomised, double-blind study. The patients who received other antiemetic medication or perioperative steroids as anti-edema therapy for facial nerve damage were excluded from the study. Risk factors for PONV, as identified by the simplified risk score system of Apfel were assessed.[5] This score system identifies high risk of PONV based on the 4 characteristics, which are: 1: female gender, 2: nonsmoking person, 3: past history of PONV or person with PONV and the 4: use of postoperative opioids. We included only the patients with 2 or more out of the total 4 risk factors, which puts them in medium to high risk for PONV as per Apfel's classification.

All the patients were premedicated with oral diazepam 10 mg given night before and on the morning of the surgery for anxiolysis. General anaesthesia was induced with Fentanyl (2-3 mcg/kg), propofol (2 mg/kg) and vecuronium (0.1 mg/kg) to and all the patients were intubated. General anaesthesia was maintained with isoflurane 1-1.5% with nitrous oxide 60% in oxygen. The patients received intravenous diclofenac 75mg infusion during the surgery. End tidal concentration of CO2 was maintained between 35 to 40 mmHg. To reduce the blood loss, anaesthetic depth was adjusted to keep mean arterial pressure about 20-30% below baseline. The patient's heart rate, mean arterial pressure, and minimum anaesthetic concentration (MAC) were noted every 30 min during surgery. At the end of surgery neuromuscular block was reversed with neostigmine and glycopyrrolate. The total amount of neostigmine used was noted. After the clinical assessment of adequacy of the reversal of neuromuscular block, trachea was extubated. After the end of surgery all the patients received 0.1mg/kg of morphine intravenously for the postoperative analgesia.

Patients were randomly allocated to receive a combination of dexamethasone 8 mg (given at the beginning of surgery) and ondansetron 4 mg (given near the end of surgery) (Group DO, n= 72) or dexamethasone 8 mg (given at the beginning of surgery) and ramosetron 0.3 mg (near the end of surgery) (group DR, n = 72) by a computer generated randomisation table. Primary efficacy variables assessed were the incidence of nausea and vomiting in the first 48 hours after the surgery. Use of rescue antiemetic was the secondary efficacy variable. These variables were assessed by an investigator who was blinded to the treatment group. Assessments were performed at the end of first 2 hours, 12 hour, 24 hours and 48 hours postoperatively. Vomiting was defined as the forceful expulsion of gastric contents and nausea was defined as subjectively unpleasant sensation associated with the urge to vomit. Retching was also counted as vomiting. The severity of nausea was graded as: 0= none, 1= mild, 2= moderate, 3 severe. The severity of postoperative pain was assessed by using a visual analog scale (VAS) that ranged from 0 as no pain to 10 as the worst pain imaginable. For patients who had grade 2-3 nausea or vomiting in the postoperative period, intravenous prochloperazine (stemetil) 25mg was given slowly as the rescue antiemetic. If patient's PONV persisted despite of rescue antiemetic, the physician was allowed to give any other antiemetic (including dexamethasone or ondansetron) as per their discretion. Patients received diclofenac tablets up to three times a day for the postoperative pain. If they complained of pain ≥ 5 on VAS, pethidine was used as a breakthrough analgesic. The incidences of common side effects of medication like headache, constipation, dizziness, drowsiness were noted.

Our previous study had shown the incidence of complete response (no PONV) as 71% in dexamethasone and ondansetron group. For additional 20% improvement in the complete response, presuming an α error of 0.05 and to achieve 80 % power, 71 patients were needed in each group. Sample size was calculated using statistical software package provided by medical University of Wien. Statistical analyses were performed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL). Categorical variables like Apfel score, incidence of PONV, rescue antiemetic use were compared using the chi-square test or Fisher's exact test. Continuous variables like weight, amount of neostigmine, morphine used and duration of anaesthesia were compared using independent t-test. Data are presented as mean ± standard deviation or as the number of patients and percentages. Value of *p* as less than 0.05 was considered statistically significant.

Results

All the 142 patients who were recruited completed the study and were analysed. There were no significant differences between groups with respect to the patient characteristics (age, weight, sex), duration of surgery or anaesthesia, amount of neostigmine used, vasopressor used. Patients were classified in to PONV risk score based on female sex, motion sickness/ PONV, non-smoking status and post-operative opioid use as Apfel score of 0-4. Apfel scores were comparable between the groups (Table 1). There was no significant difference in the measured mean arterial pressure, heart rate and depth of anaesthesia as noted by the MAC values between the groups.

There was no significant difference in incidence and severity of nausea between groups at 2, 2-12, 12-24 and 24-48 hour interval (Table 2).The incidence of vomiting and use of rescue antiemetic was also not different between groups at all the time intervals. The complete response was defined as patients who never perceived any nausea or vomiting in 48 hours of postoperative period. We noted 56 patients in DO group and 55 patients in DR group had complete response. Incidences of side effects were not different between the groups. Two patients who received ondansetron had headache and one patient had diarrhoea. There was no significant difference in the pain scores or analgesic requirement between the groups (Table 3). None of the patients needed rescue analgesic, pethidine.

Table 1: Patient characteristics, surgery and anaesthetic data

	Group DO	**Group DR**	***p***
n	72	72	
Age (yr)	30.4± 11	32.0± 13	0.43
Weight (Kg)	59.2± 11.6	57.0 ±14.3	0.29
Sex, M/F	42/30	37/35	0.42
Nonsmoker	60 (83%)	67 (93%)	0.07
h/o motion sickness or h/o PONV	20 (27%)	14 (19%)	0.21
Apfel's score 1	0 (0%)	0 (0%)	0.61
2	34(47%)	36 (50%)	
3	46(50%)	32 (44%)	
4	2 (3%)	4(6%)	
Anaesthesia Duration (min)	197 ± 69	196± 52	0.89
Duration of surgery (min)	163 ± 68	134 ± 149	0.22
Amount of neostigmine used (mg)	2.7 ± 0.35	2.4 ± 0.4	0.06
Dose of morphine (mg)	5.8 ± 1.0	5.3 ± 1.1	0.02
Ossiculoplasty	24 (33%)	14 (20%)	0.06
vasopressor used	10 (14%)	9(13%);'	0.36

Values are mean ± SD or the number of patients (percentages). Group DO: Dexamethasone and ondansetron group, Group DR: Dexamethasone and ramosetron group.

Table 2: PONV profile

	Group DO (n=72)	**Group DR(n=72)**	***p***
First 2hours			
Nausea: mild/ moderate/ severe	1/4/3	0/10/1	0.2
Vomiting	6(8.3%)	3(4.2%)	0.29
Rescue antiemetic	7(9.7%)	3(4.2%)	0.29
No PONV	64(88%)	61(84%)	0.46
2- 12hours			
Nausea mild/ moderate/ severe	3/5/3	5/10/0	0.15
Vomiting	9(12.5%)	8(12%)	0.17
Rescue antiemetic	13(18%)	9(12.5%)	0.66
No PONV	58(80%)	57(79%)	0.47
12-24hours			
Nausea: mild/ moderate/ severe	2/1/1	4/2/0	0.56
Vomiting	3(4.2%)	0(0%)	0.21
Rescue antiemetic	5(8%)	0(0%)	0.07
No PONV	65(90%)	67 (93%)	0.57
24-48 hours			
Nausea: mild/ moderate/ severe	2/1/1	2/0/0	.49
Vomiting	0	0	
Rescue antiemetic	1(2%)	0(0%)	0.31
No PONV	68(94%)	71(98%)	0.17
No PONV throughout 48 hours	56(78%)	55 (76%)	0.84
Side effects: headache	2(4%)	0 (0%)	0.16
diarrheaS	1 (2%)	0 (0%)	

Values are the number of patients (percentages). * $p \leq 0.05$. Group DO: Dexamethasone and ondansetron group. Group DR: Dexamethasone and ramosetron group

Table 3: Pain scores

	Group DO	Group R	*p*
VAS score in first 2 hours	1.9± 1.4	1.24± 0.74	0.09
VAS score 2-12 hours	2.7± 1.5	2.7 ± 1.1	0.77
VAS score 12-24 hours	1.4 ± 1.3	1.3 ± 1.1	0.75
VAS 24-48 hours	0.6 ± 0.9	0.9 ± 0.8	0.44

Values are mean ± SD.
Group DO: Dexamethsone and ondansetron group
Group DR: Dexamethasone and ramosetron group

Discussion

Four primary risk factors for PONV identified are: female gender, non-smoking, past history of motion sickness or PONV and use of postoperative opioids. Apfel classified patients with the presence of 0, 1, 2, 3, and 4 risk factors and noted incidence of PONV to be about 10%, 20%, 40%, 60%, and 80%, respectively.[5] In the present study we selected only patients with 2 or more risk factors, which put them in moderate to severe risk for PONV. As per the guidelines, patients with moderate to severe risk for PONV should receive combination therapy with two or more prophylactic drugs from different classes. Due to better side effect profile dexamethasone and 5HT3 antagonist are the commonly used antiemetics.

When ondansetron was the only 5HT3 antagonist available, the combination of dexamethasone and ondansetron was considered optimum choice for prevention of PONV after middle ear surgery.[6] In a previous study, we compared antiemetic efficacy of ramosetron to that of dexamethasone and ondansetron combination therapy and noted that combination of ondansetron with dexamethasone was still superior to ramosetron given alone for prevention of PONV following mastoid surgery. This was attributed to the fact that combination antiemetic are more efficacious than any single antiemetic agent, by blocking different receptors involved in the PONV pathway.

Ramosetron is a relatively new 5-HT3 receptor antagonist with a more potent and longer receptor antagonizing effect compared with older 5-HT3 receptors antagonists. In addition, the elimination half-life of ramosetron (9 hours) is longer than that of ondansetron (3.5 hours). Because of these pharmacological properties, ramosetron is expected to be more potent with a longer duration of action than older 5-HT3 receptor antagonists clinically. Several studies have shown ramosetron 0.3 mg is more effective than ondansetron 4 mg for PONV prophylaxis.[7,8,9] In few studies ramosetron 0.3 mg was as effective as ondanseton 8 mg in reducing the incidence of PONV after gynaecological surgery in high risk patients and following craniotomy.[10,11]

The benefit of adding of dexamethasone to ramosetron is doubtful when compared to ramosetron alone. While few of the studies show combination of dexamethasone with ramosetron to be superior to ramosetron monotherapy.[12] Few other studies did not find any difference in efficacy of combination of ramosetron and dexamethasone when compared to ramosetron alone.[13] Beneficial results are equivocal in few other studies.[14]

Not many studies have compared antiemetic efficacy of dexamethasone and ramosetron combination to dexamethasone and ondansetron combination. The only study comparing this combination was done by Choi YS et al, who used single bolus dose of dexamethasone followed by infusion of either ondansetron or ramosetron.[15] They did not find any significant difference in antiemetic efficacy of ramosetron plus dexamethasone when compared to ondansetron plus dexamethasone on preventing PONV following infusion of ondansetron or ramosetron infusion along with PCA. They concluded that adding dexamethasone to ramosetron might not be as beneficial as adding dexamethasone to ondansetron. Main limitation in generalising the results of this study is that continuous infusion of ondansetron and ramosetron may negate the better pharmacokinetic property of (long half-life) ramosetron. We could not find any study comparing antiemetic efficacy of dexamethasone with single bolus dose of ondansetron or ramosetron.

Ondansetron provides significant reduction in early PONV.[16] Dexamethasone has been used mainly to reduce late PONV. Ramosetron with long half-life is expected to reduce both early and late PONV. Few studies comparing ondansetron and ramosetron alone have noted no significant difference in the incidence of early PONV in the first 24 hours but noted significant difference in PONV in the 24-48 hours postoperative period.[9] Therefore adding dexamethasone to ondansetron may prolong the duration of PONV free period, but adding dexamethasone to ramosetron may not be beneficial, since ramosetron already has longer duration of action. This may be the reason why we did not find any difference in the PONV incidence both early or as well as late.

In the present study, we did not find any significant difference in the incidence of PONV in patients receiving either ramosetron and dexamethasone combination or ondansetron and dexamethasone. There was no difference in the severity of nausea or the

incidence of vomiting in either of the group in the present study. Percentage of patients with no PONV in 48 hours was 78% and 76% in dexamethasone ondansetron and dexamethasone ramosetron groups respectively. This rate is slightly higher than other studies which have noted no PONV in about 90-93% of patients receiving combination of ramosetron and dexamethasone. Slight higher incidence of PONV in our study may be due to high risk patient selected, longer duration of surgery, difference in the type of surgery (middle ear surgeries have high incidence), use of nitrous oxide and neostigmine for reversal during general anaesthesia.

From the previous studies we can conclude that ramosetron when used alone may be better than ondansetron for PONV prophylaxis, especially in the late postoperative period. But ondansetron and dexamethasone combination is superior to ramosetron alone. From the present study we can conclude that both ondansetron and ramosetron are having equal efficacy in reducing PONV when used along with dexamethasone.

Conclusion

Combination of dexamethasone and ramosetron has equal efficacy as ondansetron with dexamethasone in reducing PONV after middle ear surgery in high risk for PONV patients.

Conflict of Interest: None
Source of Support: Nil

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