A Prospective Study To Compare Palonosetron Monotherapy with Palonosetron-Dexamethasone Combination for Prevention of PONV in Patients Undergoing Middle Ear Surgery

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ABSTRACT

Introduction: In middle ear surgeries especially mastoidectomy with tympanoplasty, postoperative nausea and vomiting is a major problem and in this modern era with the introduction of newer antiemetics it can be effectively controlled. One such drug introduced in recent times is palonosetron. The aim of this study was to find out whether addition of dexamethasone to palonosetron would be more effective than palonosetron monotherapy in prevention of this problem in patients undergoing middle ear surgery.

Material and Methods: The present double blind study was conducted in MLB Medical College, Jhansi. Materials and Methods: Eighty female patients with ASA grade I, II between 18-40 years of age undergoing elective middle ear surgery under general anaesthesia were randomised into two groups of 40 patients each. Group-A received 0.075 mg of palonosetron and Group-B received the same dose of palonosetron and 8 mg of dexamethasone before induction. Induction of anaesthesia was done with propofol and fentanyl while maintained with N2O, oxygen, sevoflurane and muscle relaxant rocuronium. All patients received i.v infusion of inj paracetamol for postoperative analgesia. Metoclopramide/ondansetron was used as rescue antiemetic. The number of patients having PONV were recorded at 0-2, 2-6, 6-24, 24-48 hours post-operatively and requirement of rescue antiemetic in 48 hrs. Chi square test of significance and *t*-test was used for statistical data assessment with *p* value of <0.05 considered as statistically significant.

Results: The incidence of early PONV in Group A was 75% (n=30) and in Group B 32.5%(n=13) was in was statistically significant (p value<0.001). During 24-48hrs late PONV the incidence in group A was 25% (n=10) and in group B it was 10% (n=4) which was statistically insignificant (p<0.05). Overall use of rescue medication is 37.5% (n=15) in group A and 5% (n=5) in group B (p<0.05).

Conclusion: Addition of dexamethasone to palonosetron offers an added advantage over the usage of palonosetron alone in treatment of early PONV.

Key words: Palonosetron, Dexamethasone, General Anesthesia, Middle Ear Surgery, Early and Late Postoperative Nausea and Vomiting.

INTRODUCTION

In this era of fast tract anaesthesia, PONV is a grave concern for an anesthesiologist. It is also the most common adverse event seen in postoperative ward which is the major factor in delaying the discharge from hospital.[1] It is a common occurrence after ENT surgeries, especially middle ear surgery (mastoidectomy with tympanoplasty) have a high incidence of postoperative emesis 60-80% when no prophylaxis is given.[2]

Recently introduced palonosetron is a newer 5HT3 receptors antagonist are found in the gut and CNS, in the CTRZ area postrema[3], is a single stereoisomer isoquinoline. It is moderately bounded to plasma proteins (62%) and has a long terminal half-life of approximately 40hrs[4], with less need for repeated dosage and marked reduction in the incidence and severity of PONV was reported during delayed postoperative period (24-72 h). However, the relative risk reduction in the incidence of early PONV (0-24 hrs) was 20% to 30% which is comparable with other single agent and combination of others.[5]

Dexamethasone on the other hand causes better control of late PONV (24-48hrs) commonly by inhibition of prostaglandin and 5HT levels[6], without any significant side- effects.[7] Previous studies have shown that dexamethasone when added to 5HT3 antagonist ondansetron, increases its efficacy.[8,9]

In this research work, we compared whether a combination of palonosetron and dexamethasone would be more effective than palonosetron monotherapy in the prevention of PONV, following middle ear surgery under general anesthesia (GA) without any increase in the incidence of side effects.

MATERIAL AND METHODS

After approval by the institutional review board an informed written consent was obtained from the patients. This study targeted 80 female patients with ASA I, II aged 18-40 years scheduled to undergo mastoidectomy with tympanoplasty were divided in two groups.

Group A (n=40) – received palonosetron(0.075mg) alone.

Group B (n=40) - received palonosetron(0.075mg) + dexamethasone(8mg) combination.

We included patients with two risk factors or more, among which were young age, female gender, non-smoking status, H/O PONV, and/or motion sickness, transferred to ward from a PACU after surgery. Patients were kept fasting for eight hours and were administered inj. glycopyrrolate(0.2mg) via intramuscular route 30 minutes prior to surgery and inj. fentanyl (1-2µg/kg) iv and inj.midazolam (0.3mg/kg) iv as premedication. Patients were then randomly allocated into two groups (n=40 each).

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Group A: palonosetron (0.075mg) in 3ml (0.9% saline was added to make it 3ml) and Group B palonosetron (0.075mg) + dexamethasone(8 mg) in 3ml.

The respective drugs were placed in sealed envelops prepared by anaesthetic technicians with the help of computer randomization.

Induction of anesthesia was done with lidocaine (40mg) and propofol (2mg/kg) i.v. Rocuronium (0.6mg/kg) i.v was used as a muscle relaxant for endotracheal intubation. Anaesthesia was maintained by sevoflurane (2-3%), N2O (1–1.5 L/min), oxygen (0.5-1 L/min) and rocuronium on closed circuit. EtCO2 was maintained at 35±3 mmHg and the patient's PR and MAP sustained within 20% of baseline. During surgery Ringer lactate solution was injected at a regular pace (10-20 ml/kg/hr) i.v infusion.

With injection of neostigmine and glycopyrrolate at the completion of the surgery, we counteracted the effect of the muscle relaxants. Patients who complaint of pain in PACU were given NSAIDS(inj. paracetamol 15mg/kg i.v infusion) on demand to control pain. All patients were observed postoperatively for any significant episodes of PONV or any other side effects.

Patient monitoring

All episodes of PONV were recorded for 0-2 hours in PACU and from 2-48 hours in the ward. Patient or their attendants were questioned directly to record incidence of nausea and vomiting at 2,6,12 and 48 hrs.

For rescue antiemesis the antiemetic drugs use were inj. Metoclopramide(10 mg)/inj. Ondansetron(4mg) i.v at 0-48 hours after surgery in the patients who complaint of PONV within 15 minutes of surgery. A complete response is defined as the absence of PONV and no use of rescue antiemetics.

STATISTICAL ANALYSES

The SPSS® statistical package was used for statistical analysis. The Student's t-test was used to compare intergroup differences and the $\chi 2$ or Fisher's exact tests were used for categorical variables. The p-value<0.05 was regarded as statistically significant.

RESULTS

A total of 80 patients were randomly assigned to receive either 0.075mg palonosetron (Group A) or 0.075mg palanosetron+8mg dexamethasone (Group B). Patients in all two groups had a similar demographic profile and no patients were later excluded from the study. Hemodynamic data (HR, MAP) (HR, MAP) were observed and monitored for any significant alteration from baseline.

Table 1 and 2 shows demographic distribution and risk factor distribution respectively between the two Groups. 40 female in Group A (mean [SD] age, 31.82 [7.08] years; height, 157.90 [4.77] cm; weight, 57.52 [14.39] kg) and Group B (mean [SD] age, 32.05 [7.22] years; height, 157.49[4.04] cm; weight, 56.23[12.81] kg;(Table 1). No statistically significant between-group differences were found in the patient's demographic variables. Table 2 shows PONV risk factors (duration of surgery

Demographic Data	Group A (n=40)	Group B (n=40)	p-value
Age in yrs	31.82±7.08	32.05±7.22	0.9
Weight in kg	57.52±14.39	56.23±12.81	0.7
Height in cms	157.90±4.77	157.49±4.04	0.7

Table-1: Demographic distribution

	Group A(n=40)	Group B (n=40)	p-value
Obesity n(%)	6(15%)	5(12.5%)	0.7
Non-obeses n(%)	34(85%)	35(87.5%)	
Non smoker n(%)	39(97.5%)	40(100%)	0.3
Duration of surgery (mins)	131.6±30.7	127.5±30.8	0.5
H/o motion sickness n (%)	12(30%)	14(35%)	0.6

Table-2: Risk factors

	Group A	Group B	P-value
0-2hrs			
Nausea n(%)	16(40%)	5(12.5%)	0.005
Vomiting	3(7.5%)	1(2.5%)	0.3
2-6hrs			
Nausea	5(12.5%)	3(7.5%)	0.4
Vomiting	2(5%)	1(2.5%)	0.5
6-24 hrs			
Nausea	3(7.5%)	2(5%)	0.6
Vomiting	1(2.5%)	1(2.5%)	1
Overall Early PONV(0-24hrs)	30(75%)	13(32.5%)	0.0001
24-48 hrs			
Nausea	7(17.5%)	3(7.5%)	0.2
Vomiting	3(7.5%)	1(2.5%)	0.3
Overall Late PONV(24-48hrs)	10(25%)	4(10%)	0.08
Rescue antiemetic n (%)	15(37.5%)	5(12.5%)	**0.01**

Table-3: Incidence of PONV during 48hrs post-operative in two groups

AEs	Group A	Group B	P value
Headache n(%)	5(12.5%)	3(7.5%)	0.4
Dizziness n(%)	10(25%)	5(12.5%)	0.1
Others n(%) (constipation, drowsiness, myalgia)	2(5%)	1(2.5%)	0.5

Table-4: Incidence of adverse events (AEs)

was 131.6±30.7, non-smokers 97.5%,non-obese 85%, H/O motion sickness 30%) in Group A. and in Group B (duration of surgery was 127.5±30.8, non-smokers 100%,non-obese 87.5%, H/O motion sickness 35%), statistically both the groups were comparable.(p>.05)

Table-3 shows the incidence of PONV (nausea + vomiting) during 0-2hrs was 47.5% (n=19) with Group A and 15% (n=6) with Group B and the incidence during 2-6 hrs postoperatively was 17.5% (n=7) with Group A and 10% (n=4) with Group B. During 6-24 hrs, the incidence was 10% (n=4) and 7.5% (n=3) in group A and B respectively. So, the difference of total early PONV in Group A was 75% (n=30) and in Group B 32.5% (n=13) was in was statistically significant (p value <.001).

During 24-48hrs (late PONV) the incidence of PONV in group A was 25% (n=10) and in group B it was 10% (n=4). The difference is statistically insignificant (p=0.08).

Overall use of rescue medication is 37.5% (n=15) in group A and 5% (n=5) in group B. (p<0.05) The use of rescue medication is about 25% less in group B than group A and statistically significant. During late post-operative period the antiemetic effect of group A shows improvement.

Headache, dizziness, drowsiness and constipation were the commonly observed adverse effects but those were not clinically serious or statistically significant between two groups (Table 4).

DISCUSSION

The problem of PONV enrolls various causative factors viz age, sex of patients, h/o motion sickness, smoking, duration and type of surgery, pain, opioid need, inhalation agents used, use of nitrous oxide.[10,11] PONV is a common occurrence after middle ear surgeries. Palonosetron in 2008 has been approved by FDA for prophylaxis of PONV. Prolonged duration of its action is due to higher receptor affinity and longer half life.[12] The dose used in our study is 0.075 mg which has been found to be the minimum ED in various studies.[13,14]

The use of dexamethasone in for PONV was suggested by Bisgaard et al[16] in 2003 who showed that the preoperative use of dexamethasone 8 mg reduced pain, fatigue, nausea and vomiting, and duration of convalescence in patients undergoing laparoscopic cholecystectomy.[15] It has a low cost, long acting antiemetic drug with an excellent side effect profile. Prophylactic use of dexamethasone has been found to be effective in reducing the incidence of PONV during 24 h after laparoscopic cholecystectomy. Dexamethasone when administered at the induction of anaesthesia is found to be more effective.[17]

The present study was formulated to compare the combination of palonosetron and dexamethasone is more beneficial than palonosetron to prevent PONV. Our selections of drug dosages are based on previous research works that demonstrated that these doses are effective. Kovac et al. demonstrated complete response rates of 56% and 70% between 0-24 h and 24-72 h respectively in palonosetron pre-treated patients after gynaecological surgeries. In a similar study, Candiotti et.al[14] reported a response rate of 43% between 0-24 hrs, 49% during 24-72 hrs after surgery in patients at dose of palonosetron 0.075 mg. Our complete response rate was 25% and 75% in palonosetron group A during 0- 24 h and 24-48 h respectively. Our study result show that the number of patients who responded and the nausea score in periods 2,6,24 hrs postoperative in two groups A and B the difference was statistically significant with (p value of 0.0001) in early PONV and insignificant (P=0.08) in late PONV(24-48hrs).

Recent study showed that ramosetron and dexamethasone combination was more superior than ramosetron alone after laparoscopic cholecystectomy in early PONV rescue.[18] In 2014 Bala et al.[19] found that in patients undergoing laparoscopic surgeries, the palonosetron with dexamethasone combination of drug was more efficient as compared to palonosetron alone for reducing PONV. No vomiting was seen in group DP as compared to group P between 0-24 hrs (P=0.004). Only 42.9% of patients had nausea and 33.3% patients had vomiting in group P while 14.4% patients had nausea and 11.9% patients complained of vomiting in group DP during 0-24 h. Two patients in group P reported nausea while none in group PD during 24-48 h. Our study results are in accordance with their study.

In another study, Blitz et.al.[20] compared 0.075mg palonosetron and 8mg dexamethasone combination therapy with palonosetron monotherapy in patients undergoing outpatient laparoscopic surgeries and reported low incidence of PONV in both the groups (Pal+Dex-1.7%; Pal-6.8%). The low incidence of PONV in these studies seems to be associated with the use of different anesthesia technique (no use of nitrous oxide) and patient selection.

In the present study analgesic requirement was also less in patients receiving palonosetron and dexamethasone combination than palonosetron monotherapy (P=0.01). Murphy et.al.[21] reported that the use of preoperative dexamethasone also reduced nausea and pain in the early postoperative period of 12 to 24 hrs. No serious adverse effects were found in any group in our study.

Limitations of the study

The main limitation of our study is that we did not include a placebo group which is required to calculate the absolute risk reduction of PONV.

CONCLUSION

We concluded that compared with palonosetron monotherapy, palonosetron and dexamethasone combination is more effective (highly significant p-value <0.001) in reducing the incidence of PONV during first 24hrs after surgery in patients undergoing ENT middle ear surgery. Combination of dexamethasone to palonosetron also reduces the requirement of rescue antiemetic and is associated with greater control in the management of PONV symptoms. This combination also does not have any significant increased incidence of side effects.

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