Comparative study of efficacy of combination of palonosetron hydrochloride & dexamethasone sodium phosphate versus dexamethasone sodium phosphate alone for postoperative nausea & vomiting after modified radical mastectomy

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Abstract

Background: Post-operative nausea & vomiting is a common and distressing complaint observed after Modified Radical Mastectomy surgery performed under General Anaesthesia.

We compare the effect of combined palonosetron (0.075 mg) & dexamethasone (8mg) versus dexamethasone(8mg) administered i.v. alone for controlling post-operative nausea & vomiting in MRM Patients by means of a Randomized double blind control study.

Materials & Method: In a prospective randomized study 50 patients of ASA I and ASA II undergoing elective Modified Radical Mastectomy under general anaesthesia were allocated in two groups(25 patients in each).

Group A (Dexona Group) received 8 mg dexona before induction of anaesthesia.

GroupB (Palonosetron +dexona Group) received IV DEX 8mg+Palonosetron 0.075 mg before induction of anaesthesia

The incidence of PONV, need for rescue antiemetics and complete response was recorded at the end of 0,2,4, 6 hr,12 hrs,24 hrs.

Results: The incidence of complete response (no PONV, no rescue medication) was 88% (p=0.025) for the early post-operative period (0-6 h) in the combination P+D group and 84% (p=0.032)for the late (6-24 hr) period as compared to 56% and 52% in the dexona only group in the early (0-6h) and the late (6-24h) post-operative period respectively.

Conclusion: Palonosetron –DEX combined regimen given before anaesthesia induction is an effective regimen for early (0-6 hr) and late (6-24 hr) PONV with significantly lower incidence of PONV, higher incidence of complete response and better patient satisfaction.

Key words: Palonosetron, Dexamethasone, Modified radical mastectomy

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Introduction

Post-operative nausea and vomiting (PONV) is a distressing and common symptom seen after Modified Radical Mastectomy surgery performed under general anaesthesia. Patients very often rate nausea and vomiting worse than post-operative pain. Vomiting may cause dehydration, electrolyte imbalance, wound dehiscence, disruption of surgical repair, esophageal rupture, increased risk of pulmonary aspiration, subcutaneous emphysema.[1]

Post-operative nausea and vomiting results in increased patient discomfort and dissatisfaction and increased costs related to length of hospital stay. Among high risk patients, the incidence of PONV can be as frequent as 70-80%[2]. The reported incidence of PONV in patients undergoing breast surgery with axillary dissection is about 60-80%. Hence, there is a continued interest in methods to reduce the incidence and severity of PONV.

Apfel[3] et al devised a simplified risk score for predicting PONV. They concluded that there are 4 main risk factors:

1. Female sex
2. Prior history of motion sickness or PONV
3. Non smoker
4. The use of post-operative opioids

The estimated probability of PONV was 10%, 21%, 39% and 78% with 1, 2, 3 and 4 risk factors respectively. Additional patient related factors include patients with increased body weight. A complete response (CR) was defined as no vomiting and no rescue medication for any time interval.[4] More than 1000 randomized controlled trials have evaluated pharmacological methods of preventing and treating PONV. Most trials have compared a single intervention with placebo. Serotonin antagonists, dexamethasone and droperidol are among the best studied anti emetic agents. Alternatively, the avoidance of emetogenic factors during anaesthesia can reduce the baseline risk of post-operative nausea and vomiting. This strategy includes the use of propofol instead of volatile anaesthetics, the substitution of nitrogen for nitrous oxide and the use of remifentanyl, an ultra-short acting opioid instead of fentanyl. Current

medical practice entails the use of a combination of antiemetic acting on multiple receptor sites to reduce the risk of PONV in high risk patients. A recent meta-analysis on prevention of PONV suggested that a combination of dexamethasone with 5-HT3 receptor antagonists is likely to be the best antiemetic prophylactic regimen among the drugs currently available.

Post-operative nausea & vomiting is an adverse event of surgery caused by use of inhaled anaesthetics and opioid analgesics.

Dexamethasone is a 21 carbon compound having a cyclopentanoper hydro-phenanthrene(steroid) nucleus. It is a very potent and highly selective long lasting gluco corticoid. It has a long life of 36-48 hours after a single dose of 8 mg i.v. given before induction of anesthesia. The precise mechanism of action is not well understood, but may be due to prostaglandin antagonism, serotonin inhibition in gut and release of endorphins that elevate mood and stimulate appetite[5].It augment efficacy of other primary antiemetic drugs like metoclopramide, palonosetron and granisetron. It also serves to reduce certain side effects of the primary antiemetics. Serotonin receptor antagonists are widely used as one of the first line therapeutic agent for the prevention of PONV because of their good efficacy and minimal side effects.[6] Palonosetron is a novel, long lasting second generation 5-HT3RA with a strong receptor binding affinity and long elimination half-life. Palonosetron is the most recently developed 5-HT3receptor antagonist. It is the only drug of its class approved for prophylaxis against both acute and delayed chemotherapy induced nausea and vomiting(CINV). It binds at the allosteric site of 5-HT_3 receptor and this binding may prevent attachment of 5 HT at the orthosteric site of the receptor explaining its long lasting effects.[7] A higher binding affinity to the 5-HT3 receptors than the other drugs of this group and its extended half-life contributes to its efficacy in PONV.

We compare the effect of combined Palonosetron (0.075 mg) & Dexamethasone (8mg) versus dexamethasone (8mg) alone administered i.v. for controlling post-operative nausea & vomiting in MRM Patients.

Materials & Method

The study protocol was approved by Institutional Ethical Committee and informed consent was taken by every patient. 50 female patients of ASA I and II with carcinoma breast stages 1-3 undergoing Modified Radical Mastectomy were included in study. Patients with history of motion sickness and previous history of PONV, history of smoking, full stomach, gastro esophageal reflux disease, pregnant and lactating women and those who had taken antiemetic medication within 48 hrs. were excluded from study.

All the patients were kept fasting 6-8 hrs.and pre-medicated with tablet alprazolam 0.25 mg at night and in morning .In operation theatre, I.V. line was started in the hand opposite to the side to be operated. Basic monitors in form of cardiogram, BP, pulse oximetry were connected to the patient. Baseline pulse, BP and spo2 were recorded. Patients were randomly allocated in 2 Groups(n=25).

Group A: IV Dexamethasone 8mg alone

GroupB: IV Dexamethasone (8 mg)+ Palonosetron (0.075mg)

Both the groups received the drugs 15 mins. before the induction of anesthesia. All patients were pre oxygenated with 100% 0_2 for 3 mins. Anaesthesia was induced with fentanyl (2 ug/kg) and thiopentone (5-7 mg/kg). Endotracheal intubation was facilitated by the use of vecuronium bromide(0.1mg/kg). After completion of surgery, patients were smoothly reversed and post operatively, the timing of nausea & vomiting episodes were recorded at 0, 2, 4, 6, 12 and 24 hrs. post-operatively. Complete response (CR) of the drug was defined as no PONV and no administration of rescue antiemetic during the study period. Adverse effects like headache, dizziness, myalgia, constipation and extrapyramidal manifestations were recorded. This prospective randomized study was designed to compare the efficacy of combined palonosetron and dexamethasone versus dexamethasone alone for controlling post-operative nausea and vomiting in Modified radical mastectomy patients.

Statistical Analysis

The results were analysed using Graphpad.com.(Graph pad prism version 5.00 for Windows, San Diego, California). Power analysis indicated that 25 patients are required per each group based on 85% incidence of PONV in MRM surgery if no prophylaxis given with an anticipated reduction in the incidence of emesis upto 25% which was the Therapeutic outcome for dexamethasone when given as a sole prophylactic agent. The alpha error was set at 0.05 and Type 2 error was set at Statistical analysis was done using Fischer T test(paired) for comparing 2 different groups. For all tests $P < 0.05$ was considered to be significant. Data was presented as a mean and standard deviation or number and percentage.

Table 1: The Age and weight Data is presented as mean and SD

Demography	Group A (Dexona alone)	Group B (Dexona+Palonosetron)
Age (in years)	47.24±12.65	44.76±10.24
Weight (in kg.)	54.88±9.22	51.71±8.44
Duration of surgery (in mins)	124±7 mins	118±8 mins

Table 2: Incidence of post-operative nausea and vomiting

Time intervals & events	Group A(Dexona alone)	Group B(Dexona +Palonosetron)	P Value
0-2 hrs.			
(A) Nausea	32%(8)	4%(1)	0.0232
(B) Vomiting	24%(6)	4%(1)	0.0983
(C) Nausea+Vomiting	36%(9)	4%(1)	0.0106
(D) Rescue Treatment	24%(6)	4%(1)	0.0983
(E) Complete Response	64%(16)	96%(24)	0.0106
2-4 hrs.			
(A) Nausea	36%(9)	8%(2)	0.0374
(B) Vomiting	28%(7)	4%(1)	0.0488
(C) Nausea+Vomiting	40%(10)	8%(2)	0.0181
(D) Rescue Treatment	28%(7)	4%(1)	0.0488
(E) Complete Response	60%(15)	92%(23)	0.0181
4-6 Hrs			
(A) Nausea	40%(10)	12%(3)	0.0500
(B) Vomiting	44%(11)	8%(2)	0.0083
(C) Nausea+Vomiting	44%(11)	12%(3)	0.0255
(D) Rescue Treatment	36%(9)	8%(2)	0.0374
(E) Complete Response	56%(14)	88%(22)	0.0255

Table 3: Incidence of post-operative nausea and vomiting

Time intervals & events	Group A (dexona alone)	Group B(Dexona+palonosetron)	P Value
6-12 Hrs			
(A) Nausea	44%(11)	12%(3)	0.0255
(B) Vomiting	52%(13)	12%(3)	0.0054
(C) Nausea+Vomiting	48%(12)	16%(4)	0.0322
(D) Rescue Treatment	40%(10)	12%(3)	0.0507
(E) Complete Response	52%(13)	84%(21)	0.0322
12-24 Hrs			
(A) Nausea	48%(12)	16%(4)	0.0322
(B) Vomiting	52%(13)	4%(1)	0.0003
(C) Nausea+Vomiting	48%(12)	16%(4)	0.0322
(D) Rescue Treatment	40%(10)	16%(4)	0.1137
(E) Complete Response	52%(13)	84%(21)	0.0322
24-72 Hrs			
(A) Nausea	52%(13)	16%(4)	0.0157
(B) Vomiting	56%(14)	8%(2)	0.0006
(C) Nausea+Vomiting	56%(14)	20%(5)	0.0186
(D) Rescue Treatment	44%(11)	20%(5)	0.1284
(E) Complete Response	44%(11)	80%(20)	0.0186

Table 4: Incidence of adverse events and patient's satisfaction

Complications	Group A (Dexona) alone	GroupB(Dexona+Palonosetron)
(A) Extrapyramidal symptoms	0	0
(B) Headache	2(8%)	4(16%)
(C) Dizziness	2(8%)	2(8%)
(D) Constipation	2(8%)	0
(E) Myalgia	4(16%)	2(8%)
Patients Satisfaction	48%	88%

Result

The groups were comparable according to age, weight and duration of surgery. During 0-2 hrs., 32% (8) patients had nausea in the dexona group while only one (4%) had complaint of nausea in the P+D Group. Similarly, 24%(6) patients had vomiting in the dexona group while only 1 (4%) had vomiting in the P+D group.

During 2-4 hrs, 36% (9) patients had nausea in the dexona group while 28% (7) had vomiting. But comparatively only 8%(2) had nausea while 4%(1) had vomiting in the P+D Group. At 4-6 hrs, 40%(10) patients had nausea while 44%(11) had vomiting in the dexona group. But comparatively only 12 %(3) had nausea while 8%(2) had vomiting in the P+D group. At 6-12 hrs, 44%(11) Patients had nausea while 52%(13) had vomiting in the dexona group while 12%(3) had nausea while 12%(3) had vomiting in the P+D group. Similar effects were seen in the 12-24 hrs. and 24-72 hrs. study period in the patients.

The number of patients who showed CR(complete response) to antiemetic prophylactic therapy was higher in group B (Palonosetron+dexamethasone).The overall incidence of PONV and rescue antiemetic therapy over the 24 hr. period was significantly lower in the Dexona+Palonosetron group as compared to the other group. At the end of 24 hr. study period, the number of patients who were totally satisfied with the antiemetic regimen was significantly higher in the Dexona+palonosetron group in comparison with Dexona alone.

Discussion

Post-Operative nausea and vomiting is one of the most distressing experiences associated with surgery and many patients find it troublesome than post-operative pain itself. The occurrence of intractable vomiting can prolong the hospital stay and hence the economic complications also assume even greater significance.

The strategies for the prevention of early and late PONV have changed considerably over the last decade, with the focus having moved from single Drug therapy to combination antiemetic therapy or balanced antiemesis. The first such evidence that such combination therapy is more beneficial came in 1994. Since then several combinations have been tried and many of them have proved to be more efficacious than single drug therapy.

KOVAC et al(2008)[8] undertook a study to evaluate the efficacy of palonosetron. A complete response (CR) rate (no nausea and no vomiting at any interval) was observed in 56% of patients who had received a dose of palonosetron 0.075mg. During the first 24 hrs. of surgery, palonosetron 0.075 mg reduced the incidence of nausea (from 71 to 50%) and vomiting (from 60% to 40%) compared to placebo. He reported that only 27% of patients who had received 0.075mg of palonosetron required rescue therapy. He suggested that palonosetron's efficay appeared to be mainly in the first 24 hrs. This finding is in accordance with our study where after addition of palonosetron to dexamethasone, the incidence of complete response increases upto 84% as compared with dexamethasone alone in which complete response is only 52%.

Henzi et al(2010)[9] compared the combination of dexamethasone with 5-HT3receptor antagonists to the monotherapy of 5-HT3 receptor antagonist. He reported that the occurrence of nausea was 4% and 11% over 6hrs.post-operatively, and the occurrence of vomiting was 2% and 7%. In addition, the occurrence of nausea during 6-24 hrs. was 28% for the combination therapy and 41% for the monotherapy, and the occurrence of vomiting was 23% and 35% respectively, reported a significant difference. Similarly, in our study, the occurrence of nausea & vomiting was only 8% during the first 6 hrs. post-operatively with combination therapy as compared to 20% with dexamethasone administered alone.

Bala et al (2014)[10] reported that combination of palonosetron 0.075 mg and dexamethasone 8 mg was more effective than palonosetron 0.075 mg alone in reducing PONV after laparoscopic cholecystectomy. Nausea occurred in 42.9% and vomiting in 33.3% of patients who received palonosetron alone while nausea occurred in 14.3% and vomiting in 11.9% who received combination of palonosetron and dexamethasone during the first 24 hrs. after surgery. The requirement for rescue antiemetic was significantly less in the combination treatment group which is in accordance with our study.

This study is in concordance with the above study. The study is performed in Indian females. We also compared the efficacy of combination of palonosetron and dexamethasone versus dexamethasone alone for prevention of PONV in female patients undergoing Modified radical mastectomy. Episodes of nausea and vomiting were recorded for 0-2, 2-4, 4-6, 6-12, 12-24 and 24-72 hrs. post-operatively in both the groups.

During 0-2 hrs, 32% (8) patients had nausea in the dexona group while only one (4%) had complaint of nausea in the P+D Group. Similarly, 24%(6) patients had vomiting in the dexona group while only 1 (4%) had vomiting in the P+D group. $P<0.05$ which is statistically significant.

During 2-4 hrs, 36% (9) patients had nausea in the dexona group while 28%(7) had vomiting. But comparatively only 8% (2) had nausea while 4%(1). had vomiting in the P+D Group. $P<0.05$ which is statistically significant.

At 4-6 hrs, 40%(10) patients had nausea while 44%(11) had vomiting in the dexona group. But comparatively only 12%(3) had nausea while 8%(2) had vomiting in the P+D group. $P<0.05$ which is statistically significant.

At 6-12 hrs, 44%(11) Patients had nausea while 52%(13) had vomiting in the dexona group while 12%(3) had nausea while 12%(3) had vomiting in the P+D group. $P<0.05$ which is statistically significant.

Similar effects were seen in the 12-24 hrs. and 24-72 hrs. study period in the patients.

A complete response (no PONV and no need of rescue antiemetic) during 0-2 hrs. after surgery was 96% and 92% in 2-4 hrs. after surgery respectively in the combination P+D group. The corresponding incidence was 80% and 76% in the dexamethasone only group in 0-2 hrs. and 2-4 hrs. time period post operatively. Adverse effects like dizziness, constipation and myalgia were more common in the dexamethasone group as compared to the combination therapy group.

In Our Study in 50 patients undergoing Modified radical mastectomy, Dexamethasone effectively reduced the incidence of early PONV (0-6 hrs postoperatively) but failed to reduce the incidence of late PONV(6- 24 hrs. postoperatively) in relation to the combination therapy. The Palonosetron–Dexona prophylactic regimen significantly reduced the incidence of PONV over the whole 24 hrs. postoperative period.

Hence we can say that the administration of palonosetron and dexamethasone together had significantly reduced the incidence of PONV as compared to dexamethasone alone in patients undergoing MRM.

Conclusion

Palonosetron (0.075 mg) when combined with Dexona (8 mg) and given immediately before anaesthesia induction is an effective regimen for the prevention of early (0-6)hrs. and late (6-24 hrs) PONV in high risk patients scheduled for modified radical mastectomy. Palonosetron–Dexona combination therapy is superior to Dexona alone with regard to overall outcome of PONV prophylaxis over 24 hrs. Post-operatively, as shown by the significantly lower incidence of PONV, higher incidence of complete response and greater overall patients satisfaction.

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