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A Comparative Study of Ondansetron versus Ondansetron with Dexamethasone in Prevention of Postoperative Nausea and Vomiting (PONV) in Patients Undergoing Modified Radical Mastectomy with Axillary Node Dissection Under General Anaesthesia

Authors
Sahoo Alok Kumar[1], Das Prajnyananda[2], Danta Sachidananda[3]
[1]Assistant Professor, Dept of Anaesthesiology, S.C.B. Medical College. Cuttack. Odisha 753012 India
Email: *alokks108@gmail.com*
[2]Senior Resident, Dept of Anaesthesiology S.C.B. Medical College, Cuttack Odisha, India
Email: *drprajnya_das@rediffmail.com*
[3]Post Graduate Student, Dept of Anaesthesiology S.C.B. Medical College Cuttack, Odisha, India
Email: *drdantababa@gmail.com*

Abstract
Modified radical mastectomy surgeries used to have high incidence of nausea and vomiting. Ondansetron and Dexamethasone *both used to prevent postoperative nausea and vomiting .We evaluated the efficacy of Dexamethasone in combination with ondansetron verses ondensetron alone.*
Methods- *in a prospective double blind study of 80 patients scheduled for MRM with axillary node clearance taken in to consideration. Group O (n=40) given ondensetron 8mg alone and group D(n=40) given ondensetron 8mg with Dexamethasone 8mg. all patient have standard methods of anaesthesia and mastectomy. Episodes of PONV noted with standard 4 point scale.*
Observation and Results- *demographic profile in both group are comparable. The PONV lower in Dexamethasone group in first 6hr period(17.5% vs 40% p<0.05%).*
In 6-12 hr, the the PONV in Dexamethasone group is still lower (7.5% vs 20% p>0.05) but it is not statistically significant. In 12to 24 hr 100% patient in Dexamethasone group is completely free of PONV. There is minimal adverse effect of both of these drugs.
Conclusion- *Preoperative intravenous Dexamethasone (8 mg) in combination with ondansetron can significantly reduce the incidence of PONV in patients undergoing mastectomy with axillary dissection for breast cancer.*
Keywords *PONV, MRM, Dexamethasone , ondensetron.*

INTRODUCTION

Carcinoma breast is one of the common neoplasms in the developing country like India, with incidence of 145/1000 and mortality of 70/1000. Breast cancer is the most common cancer in women in India and accounts for 27% of all cancers in women[1]. Surgical resection with axillary lymph node dissection constitutes the treatment of choice assisted with neoadjuvant therapy and postoperative chemotherapy and/or

radiation therapy. PONV is one of the most distressing complications following MRM in these women with or without antiemetic therapy. The general incidence of vomiting is about 30%, the incidence of nausea is about 50%, and in a subset of high-risk patients, the PONV rate can be as high as 80%[2].Persistent nausea and vomiting is always distressing for patients and may result in electrolyte imbalance, dehydration, and delayed discharge. It can cause tension on suture lines, venous hypertension, increased bleeding under skin flaps and exposes the subject to increased risk of pulmonary aspiration of vomits. Serious complication like Esophageal rupture, bilateral pneumothorax subcutaneous emphysema are associated[3]. These justify the use of prophylactic antiemetics in women scheduled for mastectomy. The newest class of antiemetics used for prevention and treatment of PONV are serotonin ($5HT_3$) receptor antagonists—Ondansetron, granisetron, tropisetron, and dolasetron. These antiemetics do not have the adverse effects of the older, traditional antiemetics.

AIMS AND OBJECTIVES

The aim of the present study is to evaluate efficacy of prophylactic anti-emetics alone or in combination administered intravenously in Modified Radical Mastectomy (MRM) with axillary node dissection. The study is undertaken to evaluate the effect of ONDANSETRON 8 mg intravenously with combination of ONDANSE-TRON 8 mg AND DEXAMETHASONE 8 mg on postoperative nausea and vomiting (PONV)

METHODS

For the study, ninety two adult female ASA Grade I or Grade II patients of the age group 20 to 60 , who are posted for modified radical mastectomy selected, out of which eighty are taken into consideration after looking into exclusion criteria.

The patients were randomly allocated into two equal groups:

Group O (n=40): who received 8mg Ondansetron iv (4ml) and 5ml normal saline 5min before induction

Group D (n=40): who received 8mg Ondansetron iv (4ml) and Dexamethasone 8mg iv(made to 5ml) 5 mins before induction.

Patients with ASA Grade III & IV, patients on chronic steroid therapy ,pregnant/lactating women, patients having history of motion sickness ,patients who are obese (BMI>30), patients on preoperative chemotherapy ,patients having received antiemetic ,steroid within 24hrs of surgery, patients suffering from diabetes mellitus, intestinal obstruction, hiatus hernia, hepatic and renal diseases were excluded from the study.

The patients were examined day prior to surgery. Routine investigations depending on the ASA status; age and the clinical profile of the patient were done. All cases were kept NPO 8 hrs prior to surgery and given 0.5mg alprazolam tablet at night before surgery.

On the day of surgery,18 G IV canula was secured, standard monitors attached .Study medications was prepared by someone who is not related to the study in four identical syringes, two of each named A and B which will have Ondansetron 8mg, Dexamethasone 8 mg and Ondansetron 8mg and normal saline 5ml respectively.

Patient were pre-medicated with inj. Midazolam 2mg iv & inj. Glycopyrrolate 0.2mg iv and injection Butorphanol according to weight. General Anesthesia was induced by inj propofol 2-2.5 mg per kg body weight. Tracheal intubation was facilitated by inj. rocuronium 1mg per kg body weight. Anesthesia was maintained by N_2O: O_2 in 2:1 ratio and titrated dose of Isoflurane Vecuronium were given during anesthesia to maintain adequate muscle relaxation. Intra operative HR, BP, SpO_2, ECG, EtCO2, temperature and urine output was monitored. Patient was extubated after surgery. In the post-operative period patients vitals were monitored.

Assessment

All post operative cases will be followed up at 0 to 6 hrs, 6 to 12 hrs and 12 to 24 hrs for post operative nausea and vomiting. (PONV SCORE) will be evaluated on a four point scale:

0 = None 1 – Nausea 2 - Nausea with Retching 3 = Vomiting. Rescue antiemetic consisted of 0.15 mg./kg. Metoclopramide IV. An episode of emesis was defined as vomiting or retching or any combination of these events occurring in rapid sequence (<1 min between events). When the interval between episodes of vomiting or retching was >1 min were considered separate episodes. If the patient experienced repeated episodes (two or more) of emesis, or moderate nausea (>=2 score) held for 15 min or more, or if requested antiemetic. The primary efficacy outcome in this study was defined as a complete response to antiemetic prophylaxis.[9] This in turn was defined as no vomiting, no moderate nausea sustained for 15 min or more and no application for administration of rescue antiemetic medication. Rescue analgesic consisted of 75 mg. diclofenac sodium infusion.

Statistical Analysis

The quantitative variables were summarized as mean ± SD (standard deviation), while the qualitative variables were summarized as percentage. Age, weight, duration of surgery and duration of anesthesia were analyzed by using student t-test, while gender, frequency of nausea and vomiting and use of rescue antiemetic were analyzed by using chi-square test. For Table 8(A), 8(B) and 8(C),we performed a t-test with alternative hypothesis that average score of group O is more than average score of group D. A p-value of <0.05 was considered significant and a p-value of >0.05 was considered to be insignificant.

1. Demographic Characteristics:

Demographic Data and Age Range in both study groups:

Age in Years	Group – O	Group – D	
30-40	4	3	
40-50	16	18	
50-60	20	19	
Age in Yrs	50.225 (SD 7.16)	50.4 (SD 5.35)	P>0.05
Weight (in Kg)	56.25 (SD 7.44)	56.52 (SD 5.95)	>0.05
Smoking history	2	1	

2-Surgical time and duration of anaesthesia -

	Group – O	Group – D	P-Value
Duration of Surgery (SD) in Minutes	94.475 (8.11)	96.42 (6.48)	>0.05
Duration of Anaesthesia in min	103.1 (9.273)	105.125 (6.82)	>0.05

3-Haemodynamic Parameters-

	Group – O	Group – D	P-Value
Systolic Blood Pressure(mmHg) Mean (SD)	121.404 (9.16)	124.32 (5.99)	>0.05
Diastolic Blood Pressured (mmHg) Mean (SD)	78.8 (4.0)	78.88 (3.78)	>0.05
Heart Rate per Minute Mean (SD)	71.2 (4.72)	71.92 (4.91)	>0.05

The mean blood pressure and heart rate was comparable between two groups and the difference was not significant (p > 0.05).

Comparison of PONV Scores:

Nausea, Retching and vomiting occurring within first 6 hrs in the post operative period were defined as early PONV. Scores were tabulated and compared.

4(A). PONV SCORE IN FIRST 6 HRS:

PONV Score	Group – O (n=40)	Group – D (n=40)	
0	24(60%)	33(82.5%)	
1	8(20%)	4(10%)	
2	5(12.5%)	2(5%)	
3	3(7.5%)	1(2.5%)	
Average Score	0.625 (0.9)	0.2 (0.52)	p-value <0.05

4(B) PONV SCORE IN FIRST 6 - 12 HRS

PONV Score	Group – O (n=40)	Group – D (n=40)	
0	32(80%)	37(92.5%)	
1	6(15%)	2(5%)	
2	2(5%)	1(2.5%)	
3	0	0	
Average Score (SD)	0.25 (0.54)	0.1 (0.38)	p-value >0.05

4(C)-PONV SCORE IN FIRST 12 - 24 HRS :

PONV Score	Group – O (n=40)	Group – D (n=40)	
0	38(95%)	40(100%)	
1	2(5%)	0	
2	0	0	
3	0	0	
Average Score (SD)	0.05 (0.22)	0 (0)	p-value >0.05

REQUIREMENT OF RESCUE ANTIEME-TIC

Group	
Gr – O	10
Gr – D	3

22.5% of patients in Group A and 7.5% of Group B required antiemetics.

5-Comparison Of Adverse Effects

Adverse Events	Group – O	Group – D
Headache	1	0
Drowsiness	0	0
Sedation	0	0
Flushing	0	1
Dizziness	0	0

In Group – A one patient (Patient No.16) had headache and one had in Group – B.

DISCUSSION

PONV is a common, unpleasant experience for patient undergoing modified radical mastectomy surgery.

In this prospective, randomized double blind study, we found combination of Dexamethasone 8 mg and Ondansetron 8mg is most effective in control of nausea and vomiting.

The etiology of PONV after breast surgery depends on many variables that include surgery related, patient related and anesthetic technique and the postoperative care. Complicated formulations were simplified establishing four predictor factors: a) female sex; b) a history of motion sickness and/or PONV; c) absence of a smoking habit and d) any use of opioids. If none, one, two, three or four of these factors were present, the incidence of PONV was 10%, 23%, 39%, 61% and 79% respectively[4,5].

Breast surgery inherently caters to high-risk patients and being female was an independent predictor for PONV in multivariate analysis [6,7]. In our study patients with history PONV and/or of motion sickness were not included and only 2 of our patients were active smokers.

As established by Sinclair et al.[8] each 30 min increase in the duration of surgery increases the incidence of PONV by 60% but in our study surgical time in both group are comparable.

Our study found that Ondansetron and Dexamethasone administered before induction of anesthesia was associated with a reduction in the incidence of PONV as compared to Ondansetron alone is by 12.5% in first 6hour.

Mc Keniez[9] et al studied Ondansetron 4mg and Ondansetron 4mg with Dexamethasone 8mg in women undergoing major gynecological surgery and concluded that combination was more effective than Ondansetron alone

Our study shows that Dexamethasone 8 mg plus Ondansetron 8mg iv administered in combination to female patients undergoing modified radical mastectomy surgeries under general anesthesia does significantly decrease the incidence, of PONV than Ondansetron 8mg used alone

Kirn,et al[10]. choose 8 mg dose of Ondansetron for their study based on the meta-analysis by Tramer and colleagues[9] .We chose 8 mg of Ondansetron as monotherapy because it is the standard antiemetic in our institution. This dose prevents PONV after Cesarean delivery, abdominal, laparoscopic, and day case surgery.

The onset time of Dexamethasone antiemetic effect may be approximately 2 hours and more than 50% of patients experience PONV in 0-2 hours. Hence, Dexamethasone prophylaxis is useful if administered at beginning of surgery. Therefore, in the present study 8 mg Dexamethasone was administered immediately before induction of anesthesia

In the present study we used Inj Metoclopramide 10 mg IV as rescue antiemetic. L.Lopez-Olaondo[12], et al and Maulana M. Ansari, et al[13] has used Inj Metoclopramide l0 mg as rescue antiemetic when Ondansetron was used as a primary antiemetic.

In our study the demographic profile was similar in both groups with respect to age, weight and body mass index. There was no statistical significant difference noted in the above mentioned parameters.

In the present study, we have observed the study population for 24 hours in the postoperative period for incidence of PONV, the efficacy of antiemetic therapy and need for rescue antiemetics in three time periods within 24 hours 0-6 hours, 6-12 hours, 12-24 hours. This is similar time interval used by Mokhtar Elhakim et al[14].

In our study, complete response in 0-6 hours time period in the Ondansetron group was 60% and in the Ondansetron plus Dexamethasone group was 82.5%. Nausea during this time period was noted in 20% subjects & nausea with retching was 12.5 % cases and vomiting was 7.5% in Ondansetron group while nausea was 10%, nausea and retching is 5% and there is one case of vomiting (2.5%) in combination group. These results are similar to the complete response obtained by Thomas and N. Jones[15] (88% for Ondansetron and Dexamethasone combination). Rajeeva et al[16] also found that a combination of Dexamethasone and Ondansetron is more effective as prophylaxis for postoperative nausea and vomiting with overall incidence of 8%.

In our study, complete response in 6-12 hours time period in the Ondansetron plus Dexamethasone group was 92.5% and in the Ondansetron group was 80 %. Nausea in this time period was observed in 15% patients and nausea with retching noted in 5% patients in Group O while 5% have nausea, and 2.5% have nausea with retching in group D. No cases of nausea & vomiting seen in either group. The average p value in this group is statistically not significant, this was similar to findings of Lopez et al[17], where less cases of delayed nausea was seen in combination group in comparison to Ondansetron group. But we don't found any statistically significant differences.

In our study, complete response in 12-24 hours time period in the Ondansetron plus Dexamethasone group was 100% and in the Ondansetron group was 96%. R.Thomas et al[15] also found that vomiting was 0% in 12-24hr time period in the Ondansetron and Dexamethasone-combination group and complete response was 86% during this time period in the combination group.

Opioids for postoperative analgesia are associated with higher incidence of PONV. In our study, only NSAID (Inj. Diclofenac sodium 75 mg) was used for postoperative analgesia. Hence the incidence of PONV in our study is less than others.

In our study, the requirement of rescue antiemetics in the early postoperative period (0-6 hours) in the Ondansetron plus Dexamethasone group was 7.5% .The requirement of rescue antiemetics in 6-12 hours and 12 to 24 hours postoperative period was 2.5% in combination group. This was similar to Lopez-oleando et al[17], and Rush D et al[18] findings.

In our study, we observed adverse effects like headache in one patient of Group A and flushing in one patient of Group B. These adverse effects were mild and did not require any medications. S. I. Kirn et al [19]also reported adverse events were dizziness and headache .Rush D et al[18] also found similar incidence of side effects in both study groups.

Limitation of our study is number of patient is only 80 and concerns that there are no established parameters to measure nausea severity. Also, because nausea is a subjective symptom, it is difficult to accurately judge the development of nausea.

SUMMARY & CONCLUSION

The following conclusion was drawn from our study

1. Ondansetron in a dose of 8 mg I.V is effective in reducing the incidence of postoperative nausea and vomiting.
2. Combination of Dexamethasone 8 mg and Ondansetron 8mg more effective than Ondansetron 8 mg alone in first 6hr after surgery.
3. The present study showed that neither Dexamethasone nor Ondansetron was associated with significant side effects.

As nausea and vomiting are distressing to the patient and increase the risk of delayed discharge from the hospital, we recommend that antiemetic prophylaxis should be given to all the patients undergoing modified radical mastectomy surgeries to achieve comfort and highest level of satisfaction as the important outcome measures. If we aim for total elimination of 'unpleasant' PONV, any improvement in patient satisfaction with prophylactic antiemetic is a worthwhile step towards the goal. In view of the present study, it is prudent to administer Dexamethasone and Ondansetron at the beginning of surgery for prevention of postoperative nausea and vomiting after modified radical mastectomy.

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