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Original Research Article

An Assessment of Ramosetron Hydrochloride and Dexamethasone versus Ondansetron Hydrochloride in Prevention of PONV in Patients Undergoing Gynaecological Surgeries among Geriatric Women: A Randomized Double Blind Study

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Abstract

Aim: The aim of the present study was to compare the effectiveness of combination of Ramosetron 0.3mg and Dexamethasone 8mg v/s Ondansetron 4mg plus Dexamethasone 8mg among geriatric women.

Methods: A prospective, randomized double blinded comparative study of Ramosetron hydrochloride and Dexamethasone versus Ondansetron hydrochloride and Dexamethasone on 100 ASA class I/II patients posted for elective gynaecological surgeries under spinal anaesthesia was conducted in the Department of Anaesthesiology & Critical care, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar, India among geriatric women.

Results: The groups were comparable with respect to age and weight. There was no statistically significant difference observed between groups. There was no statistically significant difference in the ASA GRADING in all the two study groups. The complete response (Score-0) was 88%, 76%, 92%, 94%, 96% and 96% in first 3 hours, 4-6 hrs, 6-9hrs, 9-12hrs, 12-18hrs and 18- 24hrs respectively. PONV Score of Nausea 1 was seen in 5 patients in the first 3hr, 10 Patients in 4-6 hrs respectively. Therefore, the incidence of nausea (score 1) was 10% in first 3 hrs, 20% in 4-6 hrs, 0% in 6-9 hrs, 6% in 9-12 hrs, 2% in 12-18 hrs and 2% in 18-24hrs. Nausea with Retching (Score 2) was seen in 1 patient each in first 3hrs, 4-6hrs, and 2 in 6-9 hrs, 1 in 9-12 hrs and 18 -24 hrs respectively. Not seen any patient in 12-18hrs. The complete response (Score-0) in Ram+ Dexa was 84%, 74%, 88%, 92%, 94% and 96% in first 3 hours, 4-6 hrs, 6-9hrs, 9-12hrs, 12-18hrs and 18- 24hrs respectively. Majority of the patients had complete response during the study period. Complete response (Score-0) was 96% in first 3 hrs, 96% in 4- 6hrs, 100% in 6-9hrs, 98% in 9-12hrs, 100% in 12-18hrs and 98% in 18-24hrs. The incidence of nausea (score 1) was 4% in 1st 3hrs, 2% in 4-6 hours, 0% in 6-9hrs, 2% in 9-12hrs, 0% in 12-18hrs and 2% in 18-24hrs. Nausea with retching (score 2) was seen in 1 patient in 4-6hrs period. Vomiting (score 3) was not observed in 24 hour study period. Complete response (Score-0) in Ram+ Dexa was 94% in first 3 hrs, 94% in 4- 6hrs, 100% in 6-9hrs, 96% in 9-12hrs, 98% in 12-18hrs and 96% in 18-24hrs.

Conclusion: The study suggested combination of Dexamethasone (8mg) + Ramosetron (0.3mg) is a better alternative to combination of Dexamethasone (8mg) + Ondansetron (4mg) in preventing PONV in high risk patients.

Keywords: Ramosetron, Dexamethasone, Ondansetron, Dexamethasone, geriartic women

Introduction

Postoperative nausea and vomiting (PONV) is one of the most unpleasant and distressing symptoms which follow anaesthesia and surgery and lead to serious postoperative complications. [1] Postoperative nausea and vomiting, commonly abbreviated PONV, is defined as nausea and or vomiting that occurs within 24 hours after surgery and can occur following general, regional or local anaesthesia. [2] PONV has been a potential complication following surgery and anaesthesia since the "ether" era, with an occurrence of 75% to 80% at that time. [3] The overall incidence of PONV has been reported to be between 20% and 30%, but can increase up to 80% in high risk patients. [1]

Dexamethasone, when used with 5HT3 antagonist, reduces the absolute risk of PONV to minimum. For high risk group patients, 5HT3 receptor antagonists and dexamethasone combination has been recommended for prophylaxsis. [4] To reduce late PONV dexamethasone has been preferably used. [5-7] As a cost effective alternative to ondansetron, dexamethasone is also used prophylactically. [7] Dexamethasone and ondansetron combination therapy is the preferred choice for prevention of PONV after middle ear surgery. [8,9] In other surgeries for reducing early as well as late PONV, the newer 5-HT3 antagonist ramosetron, has been found to be more effective than ondansetron because of its long duration of action. [10]

The concept of combination antiemetic therapy was first introduced in chemotherapy induced vomiting. Its success prompted similar research in the field of PONV. [12] There is increasing evidence that the multimodal approach may improve the outcome. Double and triple antiemetics combinations are recommended for patients with high risk for PONV. [11,12] Several studies are being conducted with different drug combinations and different dosages. Combination of 5HT3 receptor antagonists and Dexamethasone has been recommended for prophylaxis in high risk group. [13] The most common prophylactic antiemtic combination used to prevent PONV in our institution is a combination of Intravenous Ondansetron, a 5HT3 receptor antagonist with Dexamethasone. Ramosetron is a newly introduced 5HT3 receptor antagonist with potential advantage of greater efficacy with prolonged duration of action. (Elimination half-life of Ramosetron is 9 hr). [14]

The aim of the present study was to compare the effectiveness of combination of Ramosetron 0.3mg and Dexamethasone 8mg v/s Ondansetron 4mg plus Dexamethasone 8mg among geriartic women.

Materials and Methods

A prospective, randomized double blinded comparative study of Ramosetron hydrochloride and Dexamethasone versus Ondansetron hydrochloride and Dexamethasone on 100 ASA class I/II patients posted for elective gynaecological surgeries under spinal anaesthesia was conducted in the Department of Anaesthesiology & Critical care, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar, India for two years among geriatric women. 100 normal adult female patients aged between 30-60 years with ASA class I and II were enrolled into the study in our hospital. Only patients undergoing elective gynaecological surgeries under spinal anaesthesia were enrolled in this study. Patients with known hypersensitivity or contra-indications to study drug, patients with history of nausea, vomiting or retching in 24 hours before anaesthesia, patients who received anti-emetic drugs or drugs with anti-emetic property during hours before anaesthesia, patients with diabetes mellitus, patients on chronic opioids use, patients with history of motion sickness, pregnant patients, Epileptic patients, patients with history of post operative nausea and vomiting in previous anaesthetic exposure, patients with significant cardiac, pulmonary, hepatic or renal dysfunction and patients having contraindications for spinal anaesthesia were all excluded from the study. The study population randomly assigned to two groups with fifty patients in each group received the following prophylactic anti emetic combination therapy.

Group Ond + Dexa [n=50]: Dexamethasone (8mg) + Ondansetron (4mg).

Group Ram + Dexa [n=50]: Dexamethasone (8mg) + Ramosetron (0.3mg).

Pre anaesthetic evaluation was done on the previous day of surgery and patients were assessed for risk factors for PONV. Written informed consent was taken from all patients selected for the study. A thorough history taking and general and systemic examination was done. Basic laboratory investigations (Hemoglobin level, total count and differential count, urine routine, and screening of chest x-ray, ECG, RBS, blood urea, serum creatinine and thyroid function tests) were evaluated. Patients were advised to remain nil orally for solids after 12 pm and 2 hours for clear fluids. All of them received tablet al prex 2.5mg and Ranitidine hydrochloride 150mg orally on the night before surgery. On arrival to operation theatre, routine monitors (electrocardiogram, pulse oximetry, NIBP) were connected and basal vital parameters were recorded. An 18G intravenous cannula was secured and an intravenous infusion of 500ml (10-15ml/kg) of Ringer's lactate was administered before induction of spinal anaesthesia. Patients were placed in the left lateral or sitting position and Subarachnoid block was performed in the L2-3 or L3-4 interspace using a midline approach with 25G Quincke's spinal needle. After confirming a free flow of cerebrospinal fluid, 2.5ml of 0.5% Bupivacaine heavy and 0.5ml of Fentanyl (25mcg) was injected. After injection of the anaesthetic solution, the patient was turned to supine position. Time of onset of action up to T6 level was noted using pin-prick method before surgical incision, and surgery was allowed to commence after 5 minutes. Supplemental oxygen 5L/min was administered via face mask during anaesthesia and surgery. Any patients having inadequate block, requiring supplemental analgesics or general anaesthesia and patients who had episodes of severe hypotension were dropped from the study. Intraoperatively, non-invasive blood pressure measured by an automated cuff blood pressure monitor, continuous pulse oximetry and electrocardiograph monitoring were done using multi parameter. Estimated fluid deficit and

maintenance fluid requirements were infused as required during the case. Duration of surgery was noted. Hypotension was defined as decrease in systolic blood pressure > 20% from baseline values and or < 90 mmHg immediately after spinal anaesthesia. Patients received increments 6mg mephentermine as required for hypotension. Patients randomly received one of the two study anti-emetic drug combination therapy according to a closed sealed opaque envelope technique:

Group Ond + Dexa [n=50] [Dexamethasone (8mg) + Ondansetron (4mg)]: Intravenous Dexamethasone 8mg (2ml) was given immediately before Spinal anaesthesia and Intravenous Ondansetron 4 mg (2ml) was given 20 minutes before completion of surgery.

Group Ram + Dexa [n=50] [Dexamethasone (8mg)+Ramosetron (0.3mg)]: Intravenous Dexamethasone 8mg (2ml) was given immediately before Spinal anaesthesia and Intravenous Ramosetron 0.3 mg (2ml) was given 20 minutes before completion of surgery. A specially designed proforma was used to collect the data including patient's particulars, patient's written informed consent, indication for surgery, the anesthetic details, intra-operative monitoring, post-operative follow up and PONV scoring system.[15] Thus there is no uniform and consistent scoring system to assess PONV. As the scoring system employed by Kushwaha, et al[16] was simple and easy to follow, so Kushwaha, et al[16] scoring system of PONV was used. Inj.Diclofenac75mg IM was administered 8th hourly for post operative pain relief. The incidence of nausea, vomiting and retching was studied for a period of 24 hours post operatively. All patients were assessed every hourly for the first 6 Hours, 3 hourly for the next 6 hours and 6th hourly for subsequent 12 hours using the following:

PONV scoring system[16]

Score 0: No Nausea

Score 1: Nausea only

Score 2: Nausea with Retching

Score 3: Vomiting

Statistical Analyses: The data was expressed as mean and standard deviation. The homogenicity in two groups of mean and standard deviation was analysed using SPSS version. Comparison between two groups at a time (inter-group comparison) was done using student's unpaired t- test. Statistical Software: The statistical software namely SPSS 15.0, Stata 8.0,MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have used to generate graphs, tables etc.

Results

Table 1: Demographic data

Age in years	**Ond+ Dexa**	**Ram+ Dexa**	**P Value**
Age In Years (SD)	62.88 (6.5)	64.56 (6.2)	0.634
Weight In KGS (SD)	59.16(5.7)	60.40(5.0)	0.334
ASA Grade			
I	30	34	0.444
II	20	16	

The groups were comparable with respect to age and weight. There was no statistically significant difference observed between groups. There was no statistically significant difference in the ASA GRADING in all the two study groups.

Table 2: Ponv scores in group ond+ dexa in 24 hours

Time	First 3 Hours	4to 6 Hours	6 To 9 Hours	9 To 12 Hours	12 To 18 Hours	18 To 24 Hours
Ond+ Dexa						
Score 0	44	38	46	47	48	48
Score 1	5	10	0	3	1	1
Score 2	1	1	2	1	0	1
Score 3	0	1	2	0	1	0
Ram+ Dexa						
Score 0	42	37	44	46	47	48
Score 1	6	11	0	2	2	1
Score 2	2	1	3	2	0	1
Score 3	0	1	3	0	1	0

The complete response (Score-0) in Ond+ Dexa was 88%, 76%, 92%, 94%, 96% and 96% in first 3 hours, 4-6 hrs, 6-9hrs, 9-12hrs, 12-18hrs and 18- 24hrs respectively. PONV Score of Nausea 1 was seen in

5 patients in the first 3hr, 10 Patients in 4-6 hrs respectively. Therefore, the incidence of nausea (score 1) was 10% in first 3 hrs, 20% in 4-6 hrs, 0% in 6-9 hrs, 6% in 9-12 hrs, 2% in 12-18 hrs and 2% in 18-24hrs. Nausea with Retching (Score 2) was seen in 1 patient each in first 3hrs, 4-6hrs, and 2 in 6-9 hrs, 1 in 9-12 hrs and 18 -24 hrs respectively. Not seen any patient in 12-18hrs. The complete response (Score-0) in Ram+ Dexa was 84%, 74%, 88%, 92%, 94% and 96% in first 3 hours, 4-6 hrs, 6-9hrs, 9-12hrs, 12-18hrs and 18- 24hrs respectively.

Table 3: Ponv scores in group ram +dexa in 24 hours

Time	First 3 Hours	4to 6 Hours	6 To 9 Hours	9 To 12 Hours	12 To 18 Hours	18 To 24 Hours
Ond+ Dexa						
Score 0	48	48	50	49	50	49
Score 1	2	1	0	1	0	1
Score 2	0	1	0	0	0	0
Score 3	0	0	0	0	0	0
Ram+ Dexa						
Score 0	47	47	50	48	49	48
Score 1	3	2	0	2	0	2
Score 2	0	1	0	0	0	0
Score 3	0	0	0	0	0	0

Majority of the patients had complete response during the study period. Complete response (Score-0) in Ond+ Dexa was 96% in first 3 hrs, 96% in 4-6hrs, 100% in 6-9hrs, 98% in 9-12hrs, 100% in 12-18hrs and 98% in 18-24hrs. The incidence of nausea (score 1) was 4% in 1st 3hrs, 2% in 4-6 hours, 0% in 6-9hrs, 2% in 9-12hrs, 0% in 12-18hrs and 2% in 18-24hrs. Nausea with retching (score 2) was seen in 1 patient in 4-6hrs period. Vomiting (score 3) was not observed in 24 hour study period. Complete response (Score-0) in Ram+ Dexa was 94% in first 3 hrs, 94% in 4- 6hrs, 100% in 6-9hrs, 96% in 9-12hrs, 98% in 12-18hrs and 96% in 18-24hrs.

Discussion

The consequences of PONV are surgical, physical and anaesthetic complications for patients and financial implications for the hospitals or institutions. [15,16] Surgical consequences include disruption of vascular anastomoses and increased intracranial pressure. Physical consequences include sweating, pallor, tachycardia, pain abdomen, increased chances of oesophageal tear, wound dehiscence and electrolyte imbalance. [17] The anaesthetic consequences are increased aspiration pneumonitis and discomfort in recovery. For institutions there is increased financial burden because of increased nursing care, delayed discharge and unexpected admissions. In ambulatory surgery too, PONV delays the hospital discharge. This necessitates the use of prophylactic antiemetics. [11]

The groups were comparable with respect to age and weight. There was no statistically significant difference observed between groups. There was no statistically significant difference in the ASA GRADING in all the two study groups. The complete response (Score-0) was 88%, 76%, 92%, 94%, 96% and 96% in first 3 hours, 4-6 hrs, 6-9hrs, 9-12hrs, 12-18hrs and 18- 24hrs respectively. PONV Score of Nausea 1 was seen in 5 patients in the first 3hr, 10 Patients in 4-6 hrs respectively. Therefore, the incidence of nausea (score 1) was 10% in first 3 hrs, 20% in 4-6 hrs, 0% in 6-9 hrs, 6% in 9-12 hrs, 2% in 12-18 hrs and 2% in 18-24hrs. Nausea with Retching (Score 2) was seen in 1 patient each in first 3hrs, 4-6hrs, and 2 in 6-9 hrs, 1 in 9-12 hrs and 18 -24 hrs respectively. Not seen any patient in 12-18hrs. The complete response (Score-0) in Ram+ Dexa was 84%, 74%, 88%, 92%, 94% and 96% in first 3 hours, 4-6 hrs, 6-9hrs, 9-12hrs, 12-18hrs and 18- 24hrs respectively. Majority of the patients had complete response during the study period. For PONV treatment and prevention, Ondansetron was the first 5HT3 receptor antagonist to become clinically available. But when compared with other 5HT3 antagonists Ondansetron is less selective for the 5HT3 receptor. It binds to 5HT1B, 5HT1C alpha adrenergic and opioid receptors with low affinity. It was revealed by a systematic review that Ondansetron's prophylactic effect on nausea was less pronounced when compared to vomiting. [18] The combination of Dexamethasone and Ondansetron was considered as the optimum choice for prevention of PONV after middle ear surgery. [19] This was because of the different mechanisms by which the drugs act in controlling PONV. Ramosetron is a recently developed 5HT3 receptor antagonist with a higher affinity and longer duration of action compared with other 5HT3 receptor antagonists. [20] The elimination half life of Ramosetron (9.3h) is longer in comparison to Ondansetron (3.5h), Granisetron (4.9h) and Alosetron(3.0h). [20,21] Ramosetron has a higher affinity (Ki = 0.091) and slower dissociation rate for 5HT3 receptors compared with other 5HT3 receptor antagonists. [22] The active metabolite M1

maintains a high receptor occupancy and prolongs the duration of action. [20]

Complete response (Score-0) was 96% in first 3 hrs, 96% in 4- 6hrs, 100% in 6-9hrs, 98% in 9-12hrs, 100% in 12-18hrs and 98% in 18-24hrs. The incidence of nausea (score 1) was 4% in 1st 3hrs, 2% in 4-6 hours, 0% in 6-9hrs, 2% in 9-12hrs, 0% in 12-18hrs and 2% in 18-24hrs. Nausea with retching (score 2) was seen in 1 patient in 4-6hrs period. Vomiting (score 3) was not observed in 24 hour study period. Complete response (Score-0) in Ram+ Dexa was 94% in first 3 hrs, 94% in 4- 6hrs, 100% in 6-9hrs, 96% in 9-12hrs, 98% in 12-18hrs and 96% in 18-24hrs. Rao GD and SC Basavaraj et al [23] in their study found complete response in 90% in OD Group and 100% in RD Group in 6-12 hour period and in the 12- 24 hour period complete response was 97% in OD Group and 100% in RD Group. These results were comparable with our study. We found complete response in 97% in DO and 100% in DR group in 6 - 12 hours and 97% and 100% in DO and DR Groups respectively in 12 – 24 hours.

Conclusion

The study suggested combination of Dexamethasone (8mg) + Ramosetron (0.3mg) is a better alternative to combination of Dexamethasone (8mg) + Ondansetron (4mg) in preventing PONV in high risk patients.

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