

## Evaluation of the Efficacy and Safety of Ramosetron versus Ondansetron for prevention of postoperative nausea and vomiting in gynaecological surgery

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### Abstract

**Context:** Postoperative Nausea and Vomiting (PONV) is a frequent and distressing complication after anaesthesia and surgery with a reported incidence of 20-30% and up to 80% in high-risk cases. It results in increased morbidity, prolonged hospital stay and increased healthcare costs. The multifactorial aetiology of PONV necessitates a combination of prophylactic antiemetic agents to prevent it.

**Aims:** In our study, we compared the efficacy of a combination of dexamethasone and 5HT<sub>3</sub> receptor antagonist (Ondansetron or Ramosetron) in preventing PONV in patients undergoing gynaecological surgeries under subarachnoid block.

**Settings and Design:** Prospective, randomised, double blind controlled clinical study. Methods and Material: 60 patients between the ages of 20 and 60 years with ASA physical status class I and II, undergoing elective total abdominal hysterectomy under subarachnoid block were selected and divided randomly into two groups of 30 members each. Group OD received Inj. Ondansetron 4 mg IV and Group RD received Inj. Ramosetron 0.3 mg IV, 20 minutes before completion of surgery. Inj. Dexamethasone 8 mg IV was given to patients in both groups immediately before spinal anaesthesia. PONV was assessed using a 4-point scoring system for 0-6, 6-12, 12-18 and 18-24 hours observational periods postoperatively. Incidence of nausea, vomiting, retching and other adverse effects were recorded.

**Statistical analysis used:** analysis of variance, x<sup>2</sup> test, two-tailed Fisher's exact probability test, or the Mann-Whitney U-test, as appropriate.

**Results:** Both groups of patients had significantly low incidence of PONV across all four observation periods with no statistically significant difference between groups OD and RD. In the overall 24 hour postoperative period, 84% of subjects in group OD and 94% in group RD showed a complete response to the prophylactic combination antiemetic therapy with no need for rescue antiemetic therapy.

**Conclusions:** Combination of 5HT<sub>3</sub> receptor antagonist with Dexamethasone reduces the incidence of PONV in the 24 hour period after elective gynaecological surgery under subarachnoid block. Combining Ramosetron with Dexamethasone showed a significantly higher complete response than Ondansetron and Dexamethasone.

**Keywords:** Ondansetron, Ramosetron, PONV, Dexamethasone, subarachnoid block, gynaecological surgery.

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### Introduction

Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications after anaesthesia and surgery, and may lead to serious postoperative complications.<sup>1</sup> The overall incidence of PONV has been reported to be between 20% and 30%, but can increase up to 80% in high-risk patients.<sup>1,2</sup> Patients undergoing gynaecological surgery have been associated with high risk for developing PONV.<sup>3,4</sup> Development of an effective antiemetic therapy has been hampered by the multifactorial nature of PONV.<sup>5</sup> None of the available antiemetics are entirely effective for preventing PONV, especially in high-risk patients.<sup>6</sup> Since at least four major receptor systems are involved

in the aetiology of PONV, a better prophylaxis might be achieved by using a combination of agents acting at different receptor sites.<sup>6</sup>

The most common prophylactic antiemetic combination used to prevent PONV in our institution is a combination of Intravenous Ondansetron, a 5-Hydroxy Tryptamine (5HT<sub>3</sub>) receptor antagonist with Dexamethasone. Ramosetron is a recently developed selective 5-HT<sub>3</sub> receptor antagonist. It exhibits significantly greater binding affinity for 5-HT<sub>3</sub> receptors with a slower dissociation rate from receptor binding, resulting in more potent and longer receptor antagonizing effects compared with older 5-HT<sub>3</sub> receptor antagonists.<sup>7,8</sup>

Therefore, we designed this prospective, randomized, double-blinded study to evaluate the efficacy and safety of Ramosetron for preventing PONV compared with that of Ondansetron in high-risk patients undergoing gynaecological surgery during the 24 h post operative period and to evaluate and record the incidence of adverse events like headache, dizziness, drowsiness, flushing and sedation if any.

## Subjects and Methods

After obtaining institutional ethical committee clearance and informed written consent, sixty patients aged between 20-60 years with body weight 40-60 kgs of ASA class I and II without any severe coexisting medical illness, posted for elective total abdominal hysterectomy under spinal anaesthesia were selected for the present study. Subjects suffering from gastrointestinal, liver and renal diseases, with history of motion sickness or PONV in previous anaesthetic exposure, receiving anti-emetic drugs or drugs with anti-emetic property during 24 hours before anaesthesia, prolonged Q-T interval on ECG were excluded from the study.

Pre anaesthetic evaluation was done on the previous day of surgery and patients were assessed for risk factors for PONV. Patients were advised to remain nil orally for solids after 10 pm and 2 hours for clear fluids. All of them received Diazepam 10mg & Ranitidine 150mg orally the night before surgery. On arrival in the operation theatre, after recording basal vital parameters (electrocardiogram, pulseoximetry, NIBP) subjects were administered 500ml (10ml/kg) of Ringer's Lactate before induction of spinal anaesthesia and premedicated with intravenous Inj Midazolam (1mg). Spinal anaesthesia was administered with 2.5ml of 0.5% Bupivacaine heavy and 0.5ml of Fentanyl (25µg) using 25G lumbar puncture needle in the lateral position. Immediately after spinal injection, 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. Estimated fluid deficit and maintenance fluid requirements were infused as required during the procedure. Intraoperatively, non-invasive blood pressure measured by an automated cuff blood pressure monitor, continuous pulse oximetry and electrocardiograph monitoring were done using multi parameter monitor. Duration of surgery and anaesthesia were noted. Hypotension (defined as decrease in systolic blood pressure > 20% from baseline values and or < 90 mmHg) immediately after spinal anaesthesia if present, was treated with 6mg mephentermine as required. Any patient having inadequate block, requiring supplemental analgesics or general anaesthesia and patients who had episodes of severe hypotension were dropped from the study.

Patients were randomly allocated to two groups to receive one of the two study anti-emetic drug combination therapy intravenously according to a closed sealed opaque envelope technique. Dexamethasone 8mg (2ml) was given immediately before spinal anaesthesia in all patients in both the groups. A trained anaesthesiologist not involved in the study process prepared 2 ml syringes (with Ondansetron for group OD and Ramosetron for group RD) for injection to be given 20 minutes before completion of surgery as per blinding .

Group OD [n=30] -20 minutes before completion of surgery Intravenous Ondansetron 4 mg (2ml) was given.

Group RD [n=30] -20 minutes before completion of surgery Intravenous Ramosetron 0.3 mg (2ml) was given.

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, 3hourly for the next 6 hours and 6th hourly for subsequent 12 hours using the following PONV scoring system.<sup>9</sup>

Score 0- No Nausea

Score 1- Nausea only

Score 2- Nausea with Retching

Score3-Vomiting

The results obtained were statistically evaluated after completion of the study. Monitoring of vital signs continued postoperatively. Inj. Diclofenac 75mg IM was administered for post operative pain relief. For the purpose of this study the following definitions devised by Watcha et al<sup>10</sup> were used:

Nausea: subjectively unpleasant sensation associated with an urge to vomit.

Retching: spasmodic, rhythmic contraction of respiratory muscle without expulsion of gastric contents.

Vomiting: forceful expulsion of gastric contents.

Nausea and vomiting occurring within first 6 hours is considered as early nausea and vomiting. Vomiting and retching episodes separated by less than 5 minutes as taken as single episode. Complete response is defined as absence of nausea, retching, vomiting and no requirement of rescue anti-emetic.

Patients with more than two episodes of nausea and vomiting in one hour period were given rescue anti emetic Inj Metoclopramide 10mg I V. Patients who received rescue antiemetics were excluded from the study. Patients were also monitored for adverse effects like headache, dizziness, drowsiness, flushing and sedation in the 24 hour post operative period.

Statistical analyses of data between the treatment groups were performed by using analysis of variance, x<sup>2</sup> test, two-tailed Fisher's exact probability test, or the Mann-Whitney U-test, as appropriate. A p value of less than 0.05 was considered significant. All values are expressed as mean ±sd, median (ranges) or number (%). We set  $\alpha = 0.05$  and  $\beta = 0.2$  and used a large magnitude of effect (effective size 0.8) to estimate a sufficient sample size. The analysis showed that 30 patients per group would be sufficient.

## Results

The two study groups were comparable with respect to demographic factors like age, weight and

body mass index (BMI) without any statistically significant difference observed between the groups. The duration of anaesthesia and duration of surgery in both

the study groups were comparable. Hemodynamic parameters were also comparable in both the groups and were statistically insignificant.

Mean±SD	GROUP OD	GROUP RD	P Value
Age in years	39.03(5.37)	39.3(7.96)	Not significant
Weight in Kgs	50.93(2.85)	51.3(6.78)	Not significant
BMI Kg/M <sup>2</sup>	22(1.38)	22(2.45)	Not significant
Duration of anaesthesia in minutes	103.63(19.77)	96.53(17.37)	Not significant
Systolic Blood Pressure mmHg	127.86(8.86)	128.06(8.87)	Not significant
Diastolic Blood Pressure mmHg	76.03(7.35)	72.76(6.44)	Not significant

### COMPARISON OF PONV SCORES:

PONV score	0-6hours			6-12 hours			12-18 hours			18-24hours			
	Group OD (n=30)	Group RD (n=30)	OD vs RD	Group OD (n=30)	Group RD (n=30)	OD vs RD	Group OD (n=30)	Group RD (n=30)	OD vs RD	Group OD (n=30)	Group RD (n=30)	OD vs RD	
0	27	28	p=0.637 Not significant	27	30	p=0.498 Not significant	29	30	p=0.79 Not Significant	29	30	p=0.685 Not Significant	
1	2	2		2	0		1	0		1	0		
2	0	0		1	0		0	0		0	0		0
3	1	0		0	0		0	0		0	0		0

Both the groups which received prophylactic anti emetic combination had a significantly low incidence of nausea, retching and vomiting in the initial six hours of post operative period with 90% complete response in group OD and 94% in group RD. In the 6 -12 hours period, complete response was noted in 90% of subjects in Group OD and in 100% of subjects in Group RD. Complete response in the next two observation periods was 97% in OD group and 100% in group RD.

### COMPLETE RESPONSE IN BOTH THE GROUPS IN 24 HOURS–

GROUP	PERCENTAGE
OD	84%
RD	94%

In overall 24 hours, the complete response was achieved in 84% of subjects in Group OD and in 94% of study population in Group RD. No patient in either Group OD or Group RD required rescue antiemetics in the study period.

### Discussion

PONV is defined as nausea and or vomiting that occurs within 24 hours after surgery and can occur following general, regional or local anaesthesia.<sup>11</sup> PONV has been a potential complication following surgery and anaesthesia since the “ether” era, with an occurrence of 75% to 80% at that time.<sup>12</sup> The overall incidence of PONV has been reported to be between 20% and 30%, but can increase up to 80% in high risk patients.<sup>1,2</sup> Patients undergoing major gynaecological surgeries are especially prone to PONV, with reported incidence of 50-75%.<sup>3,4</sup> A number of factors influence the occurrence of PONV.

Risk factors for PONV can be divided into 3 main groups<sup>13</sup>: Patient specific: Female sex, younger age, non-smoker, history of PONV or motion sickness, obesity, anxiety, gastroparesis. Surgical: Duration of surgery, with each 30-minute increase in duration increasing the risk of PONV by 60%. Laparoscopic ovum retrieval procedures have the highest incidence of PONV (54%), followed by laparoscopy (35%). Abdominal, gynaecological, ear, nose and throat, and strabismus surgeries are particularly emetogenic. In children, PONV is more common in strabismus surgery, orchidopexy, middle ear surgery and otoplasty. Anaesthetic: Patients receiving general anaesthesia

have an eleven fold increased risk for PONV compared with those receiving regional anaesthesia. Post-operative factors like pain, ambulation, oral in-take and opioids, determine the incidence of PONV.

Apfel et al. devised a simplified risk score for predicting PONV using four main risk factors<sup>14</sup>:

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

The estimated probability of PONV was 10%, 21%, 39% and 78% with 1,2,3 and 4 risk factors, respectively. The consequences of PONV may be surgical consequences like disruption of vascular anastomoses and increased intracranial pressure, physical effects like sweating, pallor, tachycardia, pain abdomen, increased chances of oesophageal tear, wound dehiscence and electrolyte imbalance and anaesthetic complications like aspiration pneumonitis.<sup>15</sup> PONV frequently results in prolonged postoperative stay, unanticipated admission and increased health care costs. This necessitates the use of prophylactic antiemetics.<sup>16</sup>

There is no uniform and consistent scoring system to assess PONV. As the scoring system employed by Kushwaha, et al<sup>9</sup> was simple and easy to follow we incorporated Kushwaha, et al scoring system of PONV for our study. Kushwaha, et al<sup>9</sup> used 4 point PONV scoring system-Score 0- No Nausea, Score 1- Nausea only, Score 2- Nausea with Retching, Score 3- Vomiting.

Development of an effective antiemetic therapy has been hampered by the multifactorial nature of PONV.<sup>5</sup> None of the available antiemetics are entirely effective for preventing PONV, especially in high-risk patients. Since at least four major receptor systems are involved in the aetiology of PONV, a better prophylaxis might be achieved by using a combination of agents acting at different receptor sites. Double and triple antiemetic combinations are recommended for patients with high risk for PONV.<sup>6</sup> The concept of combination antiemetic therapy was first introduced in chemotherapy induced vomiting.

Of the several drugs available to prevent or treat PONV, serotonin (5HT<sub>3</sub>) antagonists were found to possess significant antiemetic activity. They suppress nausea and vomiting by inhibiting serotonin binding to the 5HT<sub>3</sub> receptors present in several critical sites involved in emesis, including vagal afferents, the Solitary Tract Nucleus (STN), Chemoreceptor Trigger Zone (CTZ) and the area postrema. Introduced in 1990 they were found effective in prophylaxis of Chemotherapy Induced Nausea and Vomiting(CINV). They have also been proven safe and effective for treatment of PONV. Dexamethasone given concomitantly with a 5HT<sub>3</sub> receptor antagonist reduces the absolute risk of PONV to minimum. Combination

of 5HT<sub>3</sub> receptor antagonists and Dexamethasone has been recommended for prophylaxis in high risk group.<sup>17</sup> The most common prophylactic antiemetic combination used to prevent PONV in our institution is a combination of Intravenous Ondansetron, a 5HT<sub>3</sub> receptor antagonist with Dexamethasone. Ramosetron is a newly introduced 5HT<sub>3</sub> receptor antagonist with potential advantage of greater efficacy with prolonged duration of action. (Elimination half-life of Ramosetron is 9 hr).<sup>18</sup>

Type of anaesthesia: Of the various modes of anaesthetic techniques available, general anaesthesia is found to have the highest incidence of PONV. However, the incidence of intra operative nausea and vomiting under central neuraxial blockade is reported to be as high as 18% and postoperative vomiting is 21%.<sup>19</sup> Most of the gynaecological surgeries are done in our institution under central neuraxial blockade with local anaesthetic-opioid combination intrathecally. Fentanyl is highly lipophilic opioid, which is commonly being used in our institution as an intrathecal additive to local anaesthetics in spinal anaesthesia for its excellent intraoperative and post operative analgesia with better safety profile.<sup>20</sup>

The etiology of PONV under spinal anaesthesia may be the following<sup>20</sup>:

1. Hypotension – Rapid decline of arterial blood pressure (to < 80 mmHg) is often associated with nausea probably due to hypoxemia at the vomiting center acting as a stimulus to emesis.
2. Opioids as adjuvants to local anaesthetics in the subarachnoid space – More common with hydrophilic opioids like morphine.
3. Intrathecal Neostigmine – Spinal Neostigmine is highly emetogenic and PONV produced by neostigmine responds poorly to antiemetics.

There are several studies investigating PONV in gynaecological surgeries under general anaesthesia and only one study in gynaecological surgeries under spinal anaesthesia with morphine PCA. Dexamethasone has antiemetic properties in patients undergoing highly emetogenic chemotherapy, the mechanism of its antiemetic action is not well understood. Randomized placebo controlled studies have shown Dexamethasone to be useful in preventing nausea and vomiting associated with chemotherapy with the pronounced late efficacy.<sup>21</sup> Khalil, et al.<sup>22</sup> studied the association between the dose of Ondansetron and the duration of antiemetic efficacy and found the optimal dose of Ondansetron for prevention of PONV to be 4mg. Kovac, et al.<sup>23</sup> evaluated the prophylactic efficacy and safety of Ondansetron in male surgical outpatients and found 4mg doses to be more effective than placebo for prevention of PONV in this group. Ching-Liang Ho, et al.<sup>24</sup> demonstrated Ramosetron effectiveness in the dose of 0.3 mg in the control of CINV caused by Cisplatin

and non-cisplatin with a good safety profile. S. I. Kim, et al<sup>25</sup> have shown Ramosetron 0.3 mg to be effective in decreasing the incidence of PONV and reducing severity of nausea during the first 24 hours after gynaecological surgeries. The dosage of 0.3 mg Ramosetron was adequate in controlling PONV following laparoscopic cholecystectomy (Maulana M Ansari, et al<sup>26</sup>) and in total thyroidectomy in females (Dong Chul Lee, et al<sup>18</sup>).

The meta-analysis by Won Oak Kim, et al<sup>27</sup> has shown 0.3 mg Ramosetron to be effective in adults. Mokhtar Elhakim, et al<sup>28</sup> conducted study with various doses of Dexamethasone (2mg, 4mg, 8mg, and 16mg) and Ondansetron 4 mg in preventing PONV after laparoscopic cholecystectomy and concluded that 8 mg is the minimum dose of Dexamethasone that, combined with Ondansetron 4 mg will effectively prevent PONV in patients undergoing laparoscopic cholecystectomy. R. Thomas and N. Jones<sup>29</sup> in their study of prophylactic antiemetic therapy in day case gynaecological surgeries, have used Dexamethasone 8 mg alone and in combination with 4 mg Ondansetron and found the combination to be more effective. In a similar study, McKenzie et al<sup>30</sup> studied Ondansetron 4mg and Ondansetron 4mg with Dexamethasone 8mg in women undergoing major gynaecological surgery and concluded that combination was more effective than Ondansetron alone.

Jhi-Joung Wang JJ, et al<sup>31</sup> studied the timing effect of Dexamethasone 10 mg IV in preventing PONV and found that prophylactic I.V. administration of Dexamethasone immediately before the induction was more effective in preventing PONV. The onset time of Dexamethasone's antiemetic effect may be approximately two hours and more than 50% of patients experience PONV in 0-2 hours. Hence, Dexamethasone prophylaxis is useful if administered at beginning of surgery. Rui Sun, et al<sup>32</sup> and Jun Tang, et al<sup>33</sup> in their study in ENT surgeries and outpatient gynaecological laparoscopic procedures found that Ondansetron administered at the end of surgery significantly reduced the need for rescue antiemetics in the recovery room and was better in decreasing late nausea and emesis. Norma I. Cruz, et al<sup>34</sup> demonstrated that late administration of Ondansetron (within 30 minutes of completing the surgery) provided significantly better prevention of late PONV. Dong Chul Lee et al, 18 administered 0.3mg Ramosetron, 20 minutes before the end of surgery in female patients undergoing thyroidectomy and found that it was effective in PONV prevention in the first 6 hours.

In the present study, we have observed the study population for 24 hours in the postoperative period for incidence of PONV, the efficacy of anti emetic therapy and need for rescue anti emetics in four equal time periods within 24 hours (0-6 hours, 6-12 hours, 12-18 hours and 18-24 hours time periods). In our study, complete response in 0-6 hours time period was 90% in

the Ondansetron group and 94% in the Ramosetron group. These results tally with those of Thomas and N. Jones 30 (88% for Ondansetron and Dexamethasone combination). The 6% incidence of nausea and 3% incidence of vomiting in Ondansetron group in the early postoperative period was similar to those obtained by L.Lopez-Olaondo, et al<sup>35</sup> R. Thomas and N. Jones<sup>30</sup>, Mokhtar Elhakim, et al.<sup>29</sup> The lower incidence of nausea (6%) and no vomiting in the early postoperative period (0-6 hours) in Ramosetron group may be explained by its potency and the administration of prophylactic Dexamethasone 8 mg just prior to surgery which has antiemetic effect 2 hours after administration.

Complete response in 6-12 hours and later time periods in the Ondansetron group was 90%, while it was 97-100% in the Ramosetron group. These observations for Ondansetron and Ramosetron groups were significantly better than the previous studies by L.Lopez-Olaondo, et al, 35 Mokhtar Elhakim, et al,<sup>29</sup> Dong Chul Lee, et al.<sup>18</sup> and R. Thomas and N. Jones<sup>30</sup>. In our study, the incidence of nausea in the postoperative period (6-12 hours) in the Ondansetron group was 6% and there was no incidence of vomiting. There was no nausea and vomiting in the Ramosetron group. These observations were significantly better than the previous studies by L.Lopez Olaondo, et al,<sup>35</sup> Mokhtar Elhakim, et al<sup>29</sup>, Dong Chul Lee, et al.<sup>18</sup> and R. Thomas and N. Jones.<sup>30</sup> This may be explained by the different nature of surgeries, administration of dexamethasone and the use of central neuraxial blockade in our study, which in itself has lower incidence of PONV than general anaesthetic techniques. Also we have used a combination of Dexamethasone with 5HT3 receptor antagonists, and this may be the cause of lower incidence of PONV in our study. The use of different regimes of opioids for postoperative analgesia in their studies is associated with higher incidence of PONV. In our study, only NSAID (Inj Diclofenac sodium 75 mg) was used for postoperative analgesia and except for intrathecal Fentanyl 25µg, no other opioids were used perioperatively. We did not observe any adverse effects like headache, dizziness, drowsiness, flushing and sedation in any of the subjects in both study groups. Rescue antiemetics were not required in both Ondansetron and Ramosetron groups in the entire postoperative period. These are consistent with the observations of Mokhtar Elhakim, et al.<sup>29</sup> and of Dong Chul Lee, et al.<sup>18</sup> and significantly better than the previous studies by L.Lopez-Olaondo, et al,<sup>35</sup> and R. Thomas and N. Jones.<sup>30</sup>

The better complete response in Ramosetron group (94%) compared to the Ondansetron group (84%) coupled with reduction of retching and nausea in the 24 hour post operative period, and significant reduction in anti-emetic requirements suggests that Ramosetron Dexamethasone combination is a better antiemetic combination for preventing PONV.

## Conclusions

Combination of anti emetic 5HT<sub>3</sub> receptor antagonists, Ondansetron 4 mg or Ramosetron 0.3 mg with Dexamethasone 8 mg reduces the incidence of post operative nausea and vomiting and need for rescue anti emetics in early as well as late post operative period. However, combination of Ramosetron 0.3mg with Dexamethasone 8 mg has a significantly higher complete response than the Ondansetron 4mg with Dexamethasone 8 mg group in the 24 hour postoperative period, without significant adverse effects.

**Conflict of Interest: None**

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