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Comparative evaluation of prevention of post-operative nausea and vomiting (PONV) by using Ramosetron and Ondansetron in high risk cases

Dr. Rupam Kamari
Assistant Professor, Department of Anaesthesia and Critical Care, Shree Krishna Medical College and Hospital, Muzaffarpur, Bihar, India

Abstract
Despite considerable effort in evaluating antiemetic strategies and the development of a new antiemetic class, postoperative nausea and vomiting (PONV) remains one of the most common and distressing complications after surgery. PONV not only increases physical and psychological discomfort but also causes wound dehiscence, dehydration, and electrolyte imbalance, which leads to delayed recovery, prolonged hospital stays, and life-threatening aspiration. [12-13] Published evidence suggests that prophylactic administration of antiemetic drugs should be considered for patients with two or more PONV risk factors, such as the female gender, nonsmoking, and the use of postoperative opioids. [14-15] Hence based on these findings the present study was planned for Comparative Evaluation of Prevention of post-operative nausea and vomiting (PONV) by Using Ramosetron and Ondansetron in High Risk Cases.

The present study was planned in Department of Anaesthesia and Critical Care, Shree Krishna Medical College and Hospital, Muzaffarpur, Bihar, India. The 25 cases enrolled in Group A received the Ramosetron 0.3 mg and the other 25 cases enrolled in Group B received ondansetron 8 mg. The study drugs were drawn in identical syringes with 4ml volume each, labelled ′antiemetic′ (ramosetron was diluted to 4 ml in normal saline) by a nurse who was not a part of the study and handed to the respective OT anaesthesiologist. The patient and investigators were blinded to the study medication.

The data generated Ramosetron is a very effective, safe antiemetic in the prevention of PONV and preoperative prophylactic administration of single dose IV Ramosetron (0.3 mg) has better efficacy than single dose IV Ondansetron (8 mg) in reducing the incidence of PONV over 12 hours postoperative period.

Keywords: post-operative nausea and vomiting, PONV, Ramosetron, Ondansetron, etc

1. Introduction

Postoperative nausea and vomiting (PONV) is the phenomenon of nausea, vomiting or retching experienced by a patient in the Post Anesthesia Care Unit (PACU) or 24-hours following a surgical procedure. It is an unpleasant complication that affects about 10% of the population undergoing general anaesthesia each year.

Emetogenic drugs commonly used in anaesthesia include nitrous oxide, physostigmine and opioids. The intravenous anaesthetic propofol is currently the least emetogenic general anaesthetic. These medications are thought to stimulate the chemoreceptor trigger zone (CTZ). This area is on the floor of the fourth ventricle and is effectively outside of the blood-brain barrier. This makes it incredibly sensitive to toxin and pharmacological stimulation. There are multiple neurotransmitters such as histamine, dopamine, serotonin, acetylcholine, and the more recently discovered neurokinin-1 (substance P).

A 2008 study compared 121 Japanese patients who experienced PONV after being given the general anesthetic propofol to 790 people who were free of post-operative nausea after receiving it. Those with a G at both copies of rs1800497 were 1.6 times more likely to experience PONV within six hours of surgery compared to those with the AG or AA genotypes. But they were not significantly more likely to experience PONV more than six hours after surgery [1]. Postoperative nausea and vomiting results from patient factors, surgical & anesthetic factors. Surgical factors that confer increased risk for PONV include procedures of increased length, gynecological, abdominal and laparoscopic procedures, ENT procedures, strabismus procedures in children. Anesthetic risk factors include the use of volatile anesthetics, Nitrous Oxide (N2O), Opioids, and longer duration of anesthesia.

Patient factors that confer increased risk for PONV include female gender, Obesity, age less than 16 years, past history of motion sickness or chemotherapy-induced nausea, high levels of pre-operative anxiety and patients with history of PONV in the past. Smokers and the elderly often have a decreased risk for PONV. A risk-stratification method created by Apfel *et al* has been developed to determine a patient's risk for PONV. The presence 0, 1, 2, 3, and 4 of any of the following risk factors corresponds to a PONV respective risk of 10, 20, 40, 60, and 80 percent [2].

Because there is currently no single antiemetic available is especially effective on its own, experts recommend a multimodal approach. Anesthetic strategies to prevent vomiting include using regional anesthesia whenever possible and avoiding medications that cause vomiting. Medications to treat and prevent postoperative nausea and vomiting are limited by both cost and the adverse effects. People with risk factors likely warrant preventative medication, whereas a "wait and see" strategy is appropriate for those without risk factors.

Fasting guidelines often restrict the intake of any oral fluid after two to six hours preoperatively. However, it has been

demonstrated in a large retrospective analysis in Torbay Hospital that unrestricted clear oral fluids right up until transfer to theatre could significantly reduce the incidence of postoperative nausea and vomiting without an increased risk in the adverse outcomes for which such conservative guidance exists [3].

A multimodal approach to treating a patient with PONV can be efficacious. Numerous patient factors as well as medication adverse effects must be taken into consideration when selecting a treatment regimen [4].

In conjunction with antiemetic medications, at least one study has found that application to the Pericardium Meridian 6 acupressure point produced a positive effect in relieving postoperative nausea and vomiting [5]. Another study found no statistically significant difference [6]. The two general types of alternative pressure therapy are sham acupressure and the use of the P6 point. A 2015 study found that there is no significant difference between the use of either therapy in the treatment or prevention of PONV. In a review of 59 studies it was found that both therapies significantly affected the nausea aspect, but had no significant effect on vomiting. Cannabinoids have also been used for treatment of PONV however its efficacy is controversial.

On average the incidence of nausea or vomiting after general anesthesia ranges between 25 and 30% [Cohen 1994]. Nausea and vomiting can be extremely distressing for patients and is therefore one of their major concerns [Macario 1999]. Vomiting has been associated with major complications such as pulmonary aspiration of gastric content and might endanger surgical outcomes after certain procedures, for example after maxillofacial surgery with wired jaws. Nausea and vomiting can delay discharge and about 1% of patients scheduled for day surgery require unanticipated overnight admission because of uncontrolled postoperative nausea and vomiting.

Ramosetron (INN) is a serotonin 5-HT3 receptor antagonist for the treatment of nausea and vomiting. Ramosetron is also indicated for a treatment of "diarrhea-predominant irritable bowel syndrome in male and women". In India it is marketed under the brand name of Ibset.

It is only licensed for use in Japan and selected Southeast Asian countries. In Japan it is sold under the trade name Irribow. and in India as Ibset. 'Elsewhere it is commonly sold under the trade name Nasea and in India as Nozia (150 μg/mL injection & 100 μg oral tablet) [7].

Ondansetron, marketed under the brand name Zofran, is a medication used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery. It is also useful in gastroenteritis. It has little effect on vomiting caused by motion sickness. It can be given by mouth or by injection into a muscle or into a vein [8].

Common side effects include diarrhea, constipation, headache, sleepiness, and itchiness. Serious side effects include QT prolongation and severe allergic reaction. It appears to be safe during pregnancy but has not been well studied in this group. It is a serotonin 5-HT3 receptor antagonist. It does not have any effect on dopamine receptors or muscarinic receptors [9].

Ondansetron was patented in 1984 and approved for medical use in 1990. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. It is available as a generic medication. The wholesale cost of the injectable form in the developing world is about US$0.10 to US$0.76 per dose. In the United States it costs about US$1.37 per tablet. In 2016 it was the 91st most prescribed medication in the United States with more than 8 million prescriptions [10].

Ondansetron is a highly specific and selective serotonin 5-HT3 receptor antagonist, with low affinity for dopamine receptors. The 5-HT3 receptors are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema in the medulla. Serotonin is released by the enterochromaffin cells of the small intestine in response to chemotherapeutic agents and may stimulate vagal afferents (via 5-HT3 receptors) to initiate the vomiting reflex. It is thought that ondansetron's antiemetic action is mediated mostly via antagonism of vagal afferents with a minor contribution from antagonism of central receptors [11].

Despite considerable effort in evaluating antiemetic strategies and the development of a new antiemetic class, postoperative nausea and vomiting (PONV) remains one of the most common and distressing complications after surgery. PONV not only increases physical and psychological discomfort but also causes wound dehiscence, dehydration, and electrolyte imbalance, which leads to delayed recovery, prolonged hospital stays, and life-threatening aspiration [12-13]. Published evidence suggests that prophylactic administration of antiemetic drugs should be considered for patients with two or more PONV risk factors, such as the female gender, nonsmoking, and the use of postoperative opioids [14-15]. Hence based on these findings the present study was planned for Comparative Evaluation of Prevention of post-operative nausea and vomiting (PONV) by Using Ramosetron and Ondansetron in High Risk Cases.

Methodology

The present study was planned in Department of Anaesthesia and Critical Care, Shree Krishna Medical College and Hospital, Muzaffarpur, Bihar, India. The 25 cases enrolled in Group A received the Ramosetron 0.3 mg and the other 25 cases enrolled in Group B received ondansetron 8 mg. The study drugs were drawn in identical syringes with 4ml volume each, labelled ′antiemetic′ (ramosetron was diluted to 4 ml in normal saline) by a nurse who was not a part of the study and handed to the respective OT anaesthesiologist. The patient and investigators were blinded to the study medication.

The standardized anaesthesia regimen was followed. All patients received general anaesthesia and were induced with propofol (2 mg/kg). Vecuronium (0.1 mg/kg) intravenous (IV) was used to facilitate tracheal intubation. Anaesthesia was maintained with 0.5-2% isoflurane, 33% oxygen in nitrous oxide (N 2 O). Intraoperative analgesia was provided with IV fentanyl (2-3 μg/kg) or morphine (0.1-0.2 mg/kg) and diclofenac (2 mg/kg) IV. At the end of surgery, residual neuromuscular block was reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) IV. The study drug was administered IV 30 min before the end of surgery by the attending anaesthesiologist. Post-operative analgesia was provided with paracetamol or diclofenac.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Exclusion Criteria

Patient refusal, any contraindication to any of the two drugs, history of allergy to any of the two drugs, pregnancy, lactation and children, subjects who vomited or received antiemetics within 24 hours before surgery, hepatic, renal or cardiac abnormality, alcoholism, diabetes, significant gastrointestinal disorders (e.g. peptic ulcer disease or gastro esophageal reflux disease) and motion sickness.

Results and Discussion

Postoperative nausea and vomiting (PONV) is an unpleasant, distressing, and exhausting experience for patients. The overall incidence of PONV has decreased from 60% when ether and cyclopropane were used, to 20% - 30% nowadays, with 0.1% of patients suffering intractable PONV [16].

Patients fear PONV more than postoperative pain, with 14% worrying about pain compared with 23% worry about PONV. If PONV does occur, this is a strong reason for the patient to rate the entire course of surgery negatively. PONV is common with rates of more than 50% associated with strabismus surgery, tonsillectomy, adenoidectomy, orchidopexy, hernia repair, laparoscopic cholecystectomy for cholelithiasis and major gynecologic surgery performed under general anesthesia [17].

PONV may prolong recovery, delay patient discharge and increase hospital costs. Prevention and treatment of PONV help to accelerate postoperative recovery and increase patient satisfaction. A number of pharmacological approaches (antihistamines, butyrophenones, dopamine receptor antagonists) have been investigated for the prevention and treatment of PONV, but undesirable adverse effects, such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, restlessness, changes in arterial blood pressure, and extra pyramidal symptoms have been noted [18].

The etiology of PONV is multifactorial, with risk factors that include age, sex, obesity, a history of motion sickness or previous PONV, smoking habits, anesthetic technique, and postoperative use of opioids [19]. Type of surgery as a risk factor is still debated; laparoscopic surgery is associated with a higher incidence of PONV when compared with open surgery due to CO2 insufflation, residual pneumoperitoneum, peritoneal distension, and diaphragm and visceral organ irritation [20]. Several meta-analyses report that ondansetron is one of the most effective antiemetic agents available for prevention and treatment of PONV, suggesting that intravenous ondansetron 4 mg was the optimal dose for treating established PONV [21].

Table 1: Characteristic in Both Groups

	Group A	**Group B**
Groups of	**Ramosetron**	**Ondansetron**
No. of Cases	25	25
Age	36 - 62 years	35 – 60 years
Sex:		
Males	7	5
Females	18	20
Surgery Duration	92 – 195 mins	85 – 183 mins
Anaesthesia Duration		
No. of Risk Factors:		
2	8	5
3	16	17
4	1	3
Risk Factors:		
Females	18	19
Non-Smokers	22	23
Motion Sickness	2	1
Perioperative Opioids	23	24
Intraoperative Fentanyl dose microgram	110 – 203	108 – 212
Surgery Type:		
Breast	8	9
Gynaecology	10	9
Thyroid	4	5
Parotid	1	0
TURBT	1	1
Neck dissection	1	1

Table 2: Outcomes

	Group A	**Group B**
Groups of	**Ramosetron**	**Ondansetron**
Nausea	8	9
Retching	2	3
Emesis	3	2
Rescue antiemetic	5	7

Ryu J *et al* (2009) [22] in 120 patients scheduled for Laparoscopic Cholecystectomy, were randomized (in double blind fashion) to receive 4 mg of Ondansetron(group O4), 8 mg of Ondansetron(group O8) or 0.3 mg of Ramosetron(group R) iv after surgery. The results were assessed at 2 hrs, 24 hrs, and 48 hrs after surgery. They concluded that Ramosetron 0.3 mg was as effective as Ondansetron 8 mg for the prophylaxis of PONV after Laparoscopic -Cholecystectomy.

Choi YS, *et al* (2008) [23], compared the effect of Ramosetron with that of Ondansetron on opioid-based IV patient-controlled analgesia (PCA) related postoperative nausea and vomiting (PONV) in highly susceptible patients after lumbar spine surgery and found that moderate to severe degree of nausea was significantly more in the group Ondansetron (34%) than in the group Ramosetron (13%) 6

to 24 hours after surgery. Overall incidence of vomiting 6 to 24 hours after surgery was significantly lower in the group Ramosetron (30% vs. 11% respectively). They concluded that Ramosetron was superior to Ondansetron in terms of preventing vomiting.

T. S. Hahm, *et al* (2010) [24]. compared the prophylactic anti-emetic efficacy of Ramosetron and Ondansetron in patients at high-risk for postoperative nausea and vomiting after total knee replacement surgery and found that more patients in the Ramosetron group had a complete response (no postoperative nausea and vomiting and no rescue anti-emetic) between 2 and 48 h. The incidence of nausea between 2 and 24 h was also less in the Ramosetron group. They concluded that Ramosetron was more effective than Ondansetron in preventing postoperative nausea and vomiting.

Kim Sl, *et al* (2009) [25]. studied the comparision of Ramosetron with Ondansetron for prevention of postoperative nausea and vomiting in patients undergoing gynaecological surgery. The incidence of nausea was lower in the Ramosetron (50%) and Ondansetron (44%) groups than placebo(69%) groups. Also, the incidence of vomiting was lower in both the Ramosetron (17%) and the Ondansetron (20%) groups than in the placebo group(44%) during the first 24 hrs after surgery($P< 0.05$). The visual analogue scale score for nausea was also lower in the Ramosetron and Ondansetron groups compared with the placebo group. They concluded that Ramosetron 0.3 mg IV was as effective as Ondansetron 8 mg IV in decreasing the incidence of PONV and reducing nausea severity in female patients during the first 24 hrs after gynaecological surgery.

In a study conducted on 120 patients it was found that Ramosetron 0.3 mg was more effective than ondansetron 4 mg and as effective as ondansetron 8 mg for the prophylaxis of PONV in patients undergoing laparoscopic cholecystectomy [26].

In a study conducted on 94 patients it was found out that Ramosetron was superior to ondansetron in terms of preventing vomiting and reducing the severity of nausea with less adverse events, in patients with high susceptibility, undergoing lumbar spine surgery [27].

In a prospective, randomized, double-blinded, placebo-controlled study, 162 healthy patients who were undergoing gynaecological operation under general anaesthesia it was found that Ramosetron 0.3 mg i.v. was as effective as ondansetron 8 mg i.v. in decreasing the incidence of PONV and reducing nausea severity in female patients during the first 24 h after gynaecological surgery [28].

In a study conducted on 84 patients showed that Ramosetron was more effective than ondansetron in preventing postoperative nausea and vomiting in patients at high risk undergoing unilateral total knee replacement [29].

In a study conducted on 80 patients it was shown that Prophylactic antiemetic therapy with ramosetron 0.3mg is efficacious against postoperative nausea and vomiting 0 to 24 hours after anaesthesia in patients undergoing total hip replacement. [30]

In the study on 50 patients it was proved that both drugs showed similar results in regard to chemotherapy-induced gastrointestinal side effects, emesis and appetite loss on day 1, but by day 5, ramosetron was significantly better than ondansetron in terms of controlling appetite loss. From days 3-5, ramosetron tended to be more effective than ondansetron in its antiemetic action [31].

Antiemetic drugs play an important role in therapy of PONV. Presently, there is no single PONV antiemetic medication or technique that is 100% effective for all patients [32]. And a search for better drug continues. The management of PONV has improved greatly in recent years with the introduction of 5-hydroxytryptamine (5-HT3) - receptor antagonists, which are widely regarded as most efficacious antiemetics available today and are currently recommended as the agents of first choice to control nausea and vomiting in most instances.4 Findings have demonstrated that several 5-HT3 antagonists (Ondansetron, granisetron, tropisetron, dolasetron, and ramosetron) currently available are highly efficacious for PONV [33].

Conclusion

The data generated Ramosetron is a very effective, safe antiemetic in the prevention of PONV and preoperative prophylactic administration of single dose IV Ramosetron (0.3 mg) has better efficacy than single dose IV Ondansetron (8 mg) in reducing the incidence of PONV over 12 hours postoperative period.

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