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Comparison of Ramosetron and Palonosetron for Prevention of Post Operative Nausea and Vomiting in Adult Patients Undergoing Middle Ear Surgery Under General Anaesthesia

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Abstract: ***Background: Postoperative Nausea and Vomiting (PONV) is one of the most distressing adverse effects following anaesthesia and surgery. High incidence of PONV has been demonstrated after middle ear surgery. 5-Hydroxytryptamine (5-HT$_3$) receptor antagonists are used commonly due to higher efficacy and lesser side effects. Ondansetron is most commonly used for prevention of PONV. Both palonosetron and ramosetron have been reported to be superior to ondansetron for PONV prevention. This study is being undertaken to compare the efficacy of palonosetron and ramosetron for the prevention of PONV in middle ear surgeries. Objectives: Primary Objective: Number of episodes of PONV in 24 hours following conclusion of anaesthesia. Secondary Objectives: 1) Rescue antiemetic, if required 2) Overall satisfaction of patient with nausea and vomiting experience 3) Incidence of adverse effects like headache, dizziness, drowsiness, injection site reaction etc. All the above 3 parameters were observed over 24 hours following conclusion of anaesthesia. Methods: In this Single blinded Randomised Controlled study, 60 adult patients undergoing middle ear surgery were randomised into 2 groups of 30 each to receive Palonostreon or Ramosetron. PONV Score, Rescue Antiemetic requirement, Adverse effects and Overall patient satisfaction were assessed at time of reversal and during the time interval of 0-2 hours, 2-6 hours, 6-12 hours and 12-24 hours after completion of surgery. RESULTS: Both groups were comparable with respect to age, sex, BMI, ASA grade and duration of anaesthesia. Higher incidence of PONV and PONV score was seen at 6 – 12 hours time-interval with ramosetron. Use of rescue antiemetic was seen only with ramosetron. Overall patient satisfaction was higher with palonosetron. Conclusion: In our study palonosetron was found to be superior to ramosetron for PONV prophylaxis. It has similar safety profile as ramosetron but longer duration of action which can have implications in providing a better and longer duration of prophylaxis.***

Keywords: postoperative nausea and vomiting, middle ear surgery, palonosetron, ramosetron, antiemetics

1. Introduction

In the past several years, multiple advances have been made to minimise adverse events following anaesthesia. Still, the most common and distressing adverse effects that the patient experiences following anaesthesia and surgery are pain and vomiting.[1] Postoperative nausea and vomiting (PONV) has been related to anaesthetic agents, especially ether, chloroform and other inhalational agents. During the ether era, incidence was as high as 75-80%.

Postoperative nausea and vomiting not only decreases patient satisfaction but also relates to several adverse consequences, including pulmonary aspiration, wound dehiscence, esophageal rupture, subcutaneous emphysema, and bilateral pneumothoraces.[2]

Risk factors for PONV can be broadly divided into 3 categories: patient risk factors, anaesthetic technique and surgical procedure.[3]

Patient Risk Factors	Surgical Risk Factors[4]	Anaesthesia Risk Factors
• Young age • Female gender • Non-smoking status • Previous history of PONV/motion sickness • Preoperative anxiety • Genetic predisposition	• Duration of surgery • Type of surgery (laproscopic surgery, middle ear surgery, strabismus surgery)	• Intraoperative use of opoids, nitrous oxide and inhalational agents

While knowing the control measures of PONV, identification of patients at high risk for PONV during pre-anaesthetic checkup helps in better management.

Apfel et al[4] identified four risk factors that form the basis of the Apfel Scoring System. Each risk factor increases the likelihood of PONV by 18-22%[4]. The score consists of 4 predictors:

1) Female gender
2) History of PONV and/or motion sickness
3) Non-smoking status
4) Postoperative use of opioids

The ear is made up of three basic parts: outer ear, middle ear and inner ear.

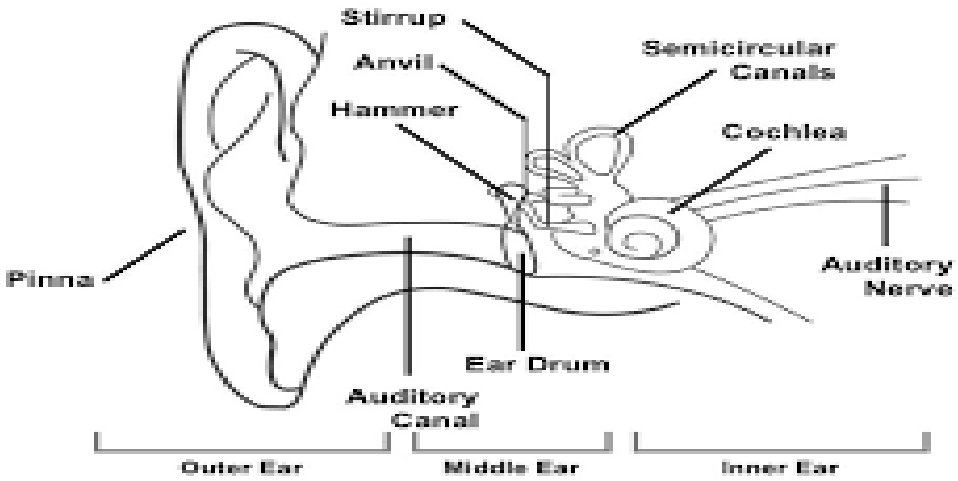

Figure 1: Parts of Ear

Middle ear is an air-filled cavity which consists of tympanic membrane and three tiny, interconnected bones called ossicles: malleus (hammer), incus (anvil) and stapes (stirrup). Middle ear surgery is done to treat a variety of disorders in any of these parts.

Types of middle ear surgeries include stapedectomy, tympanoplasty, myringotomy and mastoidectomy. Stapedectomy is replacement of a middle ear bone with a prosthesis which leads to improved hearing. Tympanoplasty is the reconstruction of the eardrum after partial or total conductive hearing loss. Myringotomy is a surgical incision into the eardrum done to drain ear fluid, prevent infection and normalise middle ear pressure.

Mastoidectomy is the surgical removal of mastoid air cells. It can be done for treatment of mastoiditis, chronic suppurative otitis media (chronic inflammation of middle ear) or cholesteatoma (abnormal, non-cancerous skin growth in middle ear). Air cells are open spaces containing air that are located throughout the mastoid bone. Infections in the middle ear can easily spread into the mastoid bone via mastoid antrum (air space in petrous part of temporal bone), making surgery necessary if antibiotics don't work.

It has been demonstrated that after middle ear surgery, the incidence of nausea and vomiting can be as high as 62% - 80%, when no prophylactic antiemetic is used. Such high incidence is attributed to the direct physical stimulus to vestibular system in the ear which leads to activation of vestibular afferent pathway (as involved in motion sickness)[5].

The interventions for management of PONV are both pharmacological and non-pharmacological. Non-pharmacological interventions include patient and family education preoperatively, protection of airway to prevent aspiration intraoperatively and providing non-stimulating environment postoperatively (minimise unpleasant smells, sight and sounds)

Various pharmacological agents are coming up rapidly to prevent and treat PONV. The newer class of antiemetics are NK-1 receptor antagonists (aprepitant, casopitant, rolapitant etc.) and Serotonin ($5\text{-}HT_3$) receptor antagonists (e.g. ondansetron, granisetron, palonosetron, ramosetron etc.)[6]. These have replaced the traditional antiemetics like phenothiazines (promethazine), antihistaminics (diphenhydramine), butyrophenones (droperidol) and benzamides (metoclopramide) as the latter have side effects and limited efficacy[7]. It should be noted that no single drug is 100% effective in prevention of PONV and no therapy is devoid of adverse effects.

Various studies suggest that multiple drug therapy resulted in lesser incidence of PONV than single drug therapy[8]. This led to the formulation of multimodal approach for prevention of PONV. Multimodal approach extends far beyond intraoperatve pharmacotherapy and starts with non-pharmacological interventions in the preoperative period[9].

The 5-Hydroxytryptamine ($5\text{-}HT_3$) receptor antagonists are used commonly due to higher efficacy and lesser side effects[10]. Among these, ondansetron is most commonly used for prevention of PONV. Other alternatives to ondansetron include granisetron, tropisetron, dolasetron, ramosetron and palonosetron.

Palonosetron is a newly developed $5\text{-}HT_3$ receptor antagonist, which has been proved as an effective anti-emetic. It has high receptor binding affinity and a half-life of 40 hours. Thus, duration of action exceeds 24 hours. Palonosetron has been reported to provide better prophylaxis of early and late postoperative nausea (PON) and late postoperative vomiting (POV), compared to ondansetron in elective surgeries performed under general anaesthesia.[11]

Ramosetron is a relatively newer 5-HT3 antagonist with a higher affinity, prolonged activity and also the ability to prevent early and late postoperative vomiting (POV) better than previously used drugs such as granisetron and ondansetron.[12]

2. Review of Literature

Ear is called the organ of hearing and balance. It is primarily divided into three parts: outer, middle and inner ear. Middle ear is the portion of ear internal to tympanic membrane and external to the oval window of inner ear.

Middle ear includes a hollow space called Tympanic cavity; Eustachian tube, which connects the tympanic cavity to nasopharynx; and Mastoid air cells, which surround the middle and inner ear and protect them from any trauma.

Other contents are the three ossicles: malleus, incus and stapes, which help in sound transmission; two muscles: stapedius and tensor tympani; and two nerves: chorda tympani and tympanic nerve plexus.

Middle ear cxploratory surgeries are myringoplasty, ossiculoplasty, tympanoplasty and mastoidectomy.

Myringoplasty is the surgical closure of tympanic membrane perforation. Ossiculoplasty is the reconstruction of ossicular chain. Tympanoplasty is the surgical procedure performed for the reconstruction of tympanic membrane and/or ear ossicles with the aim to close the perforation as well as restore hearing ability. It is most commonly done in chronic suppurative otitis media, which is an infection characterised by recurrent middle ear discharge through a persistant middle ear perforation. It can be performed through the ear canal (transcanal approach), through an incision in the ear (endaural approach) or through an incision behind the ear (postauricular approach). A graft may be taken from temporalis fascia or tragus and placed over the perforated tympanic membrane using underlay (medial grafting) or overlay (lateral grafting) technique. The underlay technique is widely used and is relatively simple to perform, as the graft is placed entirely medial to the remaining tympanic membrane and malleus[13].

Mastoidectomy is the surgical removal of mastoid air cells. Modern mastoid surgery was pioneered by a German otologist, Schwartze in 1873. It can be perfomed as a part of treatment for mastoiditis, chronic suppurative otitis media or cholesteatoma. In addition, it is sometimes performed as a part of other procedures (cochlear implant) or for access to middle ear[14].

It has been demonstrated that after middle ear surgery, the incidence of nausea and vomiting can be as high as 62% - 80% when no prophylactic antiemetic is used[5].

Definition and Classification of PONV

PONV comprises of three main symptoms that may occur separately or in combination after surgery: nausea, vomiting and retching.

Nausea is an unpleasant sensation associated with the awareness of the urge to vomit but without any expulsive muscular movement or painful sensation to the pharynx and upper abdomen.[15]

Vomiting or Emesis is the forceful expulsion of gastric contents from the mouth and is brought about by powerful, sustained and coordinated contraction of abdominal, intercostal, pharyngeal and laryngeal muscles, along with descent of diaphragm, opening of gastric cardia and closure of glottis. It is associated with tachycardia, tachypnea and sweating.[15, 16]

Retching is defined as laboured, spasmodic and rhythmic contractions of respiratory muscles including diaphragm, chest wall and abdominal wall muscles without the expulsion of gastric contents.[15]

PONV may take place in single or multiple episodes, that may last minutes, hours or even days[17]. It is classified as Early PONV, occurring within 2 to 6 hours after surgery, or Late PONV, occurring up to 24 or 48 hours after surgery[3].

Physiology of Nausea and Vomiting

Vomiting involves vomiting reflex which comprised of three major components:

a) Emetic detectors
b) Integrative mechanisms
c) Motor outputs

a) Emetic Detectors

1) **Abdominal Visceral Afferents:** The gut has detection systems, capable of activating the vomiting reflex. Electrical stimulation of abdominal course of vagus is capable of inducing emesis within 20 seconds[18].

Two types of vagal afferent fibers are involved in emetic responses:

- **Mechano-receptors:** These are located in the muscular wall of gut and activated by both contraction and distension.
- **Chemo-receptors:** These are located in the mucosa of upper gut and respond to mucosal stroking, acid, alkali, hypertonic, solutions, temperature, irritants and enterotoxins[19]. The substrates for the polymodal mucosal chemoreceptor have not yet been fully explained, but current studies point towards a variety of cell receptors responding to a range of chemicals and stimuli. In the gastrointestinal tract, the enterochromaffin cells play a vital role.

2) **Central Mechanisms:** The vomiting centre is located in the dorsal reticular formation of the Medulla oblongata, close to the Nucleus of Tractus Solitarius (NTS). Afferents from gastrointestinal tract (GIT) travel via vagus to area postrema and NTS. Area postrema, the locus of chemoreceptor trigger zone (CTZ), is one of the circumventricular organs located outside blood brain barrier (BBB). Lack of BBB allows CTZ to monitor blood and CSF constantly for toxic substances and to relay the stimulus to the vomiting centre deep in medulla causing nausea and emesis. Ablation of CTZ inhibits the effect of centrally acting emetics and prevents motion sickness. CTZ is refractory to electrical stimuli, but very sensitive to emetogenic drugs. Apomorphine can cause emesis by exciting the receptors in the CTZ which stimulates the deep lying vomiting center. Both NTS and area postrema are rich in 5-HT (5-Hydroxytryptamine) receptors located at presynaptic terminals.

Afferents from vestibular labyrinth reach vomiting centre through CTZ. Those from head and neck region pass through the 5th cranial nerve to NTS. Emetic stimuli from viscera

traverse via splanchnic nerves to reach central nervous system (CNS). In 1981, Thusmus experimented on the dogs and showed that vomiting centre is a set of neurons and is situated in dorsal reticular formation of medulla oblongata in close proximity to other visceral control centres; vestibular centre, vasomotor centre and vestibular nuclei. The vomiting integrating centre is sensitive to numerous pathological stimuli like enteric toxins and increased intracranial tension. It may give rise to emetic symptoms through special sense of sight, smell and taste[20].

There are mainly 4 types of receptors involved in the emetic response – Dopaminergic, Histaminic, Cholinergic and Serotonergic[7]

The latest antiemetic is the neurokinin (NK1)-receptor antagonist Aprepitant. While its efficacy is well known in the chemotherapy literature it has now also been demonstrated for PONV. Specifically, a study by Diemunsch P et al[21] shows that it is at least as effective as ondansetron against nausea, but much more effective against vomiting.

Therefore, at least through five different mechanisms, vomiting reflex could be triggered.

5-Hydroxytryptamine (serotonin) is a widely distributed endogenous vasoactive substance that also serves as an inhibitory neurotransmitter in the CNS. 90% of serotonin is present in enterochromaffin cells of the GIT; rest 10% in the CNS and platelets. 5-HT mediates its emetic sequel by acting on 5-HT_3 receptors located both centrally (in the area postrema) and peripherally on the nerve plexus (vagal and splanchnic) within the wall of the small intestine. There are 4 types of 5-HT receptors ($5HT_{1-4}$). 5-HT_3 receptors are found in high density in the area postrema and NTS, mostly on the vagus nerve terminals. Receptors have also been found on the peripheral sections of the vagus nerve in the GI tract. Emetogenic stimuli result in the release of 5-HT in the small intestine and initiate a vomiting reflex (via vagal afferents). Vagal afferents may also result in the release of 5-HT in the area postrema, hence 5-HT_3 receptor antagonists are supposed to block the initiation of emetic reflex peripherally in the GIT and centrally in the area postrema and CTZ.

b) Integrated Mechanism

Vomiting can be considered to be a stereotyped motor programme involving coordination between many physiological systems and between the autonomic and somatic components of nervous system. The motor components of the reflex are mediated by both autonomic and somatic nerves. All these motor pathways have non-emetic functions. For example, vagus mediated gastric relaxation and phrenic nerve contracts the diaphragm for inspiration. The term vomiting centre has been used widely to describe the central emetic coordinating mechanism. The coordination of the motor components of the vomiting reflex occurs in the brainstem. It is here that the vagal motor neurons supplying the gut and heart, the dorsal and ventral respiratory groups regulate the phrenic nerve. The output of these nuclei is coordinated partly by Nucleus Tractus Solitarius and partly by dorsal respiratory neuronal group.

c) Motor Components of Vomiting Reflex (Mechanism)

The ejection of upper gastrointestinal contents represents the culmination of a series of motor events involving both autonomic and somatic division of nervous system.

- **Pre-ejection Phase:** It is characterized by prodromal symptoms of nausea associated with autonomic sensations such as cold, sweating, cutaneous vasoconstriction, pupillary dilation, salivation and tachycardia. Immediately before the ejection of vomitus there is profound relaxation of stomach (proximal part) mediated by vagal efferent using vasoactive intestinal polypeptide (VIP) as neurotransmitter. In conjunction with this, a retrograde giant contraction originates in the mid small intestine and travels toward the stomach. This is controlled by vagus using acetylcholine as neurotransmitter. The pre-ejection phase is usually, but not invariably followed by the ejection phase.
- **Ejection Phase:** This phase comprises retching and vomiting. During retching the abdominal muscles and the entire diaphragm contract rhythmically and synchronously while the mouth and glottis are kept closed, whereas during vomiting the periesophageal diaphragm relaxes, the stomach is compressed by descending diaphragm and the abdominal muscles contract. The typical posture of the patient optimizes compression of the stomach by somatic muscles and minimizes strain on muscle groups. There is flushing of face, salivation, inhibition of normal respiration, flaccid relaxation of stomach with opening of the cardiac end and relaxation of oesophagus, rise of intragastric pressure above 20mmHg, closure of glottis and elevation of soft palate. Finally, mouth is opened up; there are sharp spasmodic contractions of diaphragm and abdominal muscles resulting in ejection of the contents of flaccid stomach through relaxed passage. It is associated with marked tachycardia, hypertension and pallor.

Consequences of Postoperative Nausea & Vomiting

Postoperative nausea and vomiting have got certain number of detrimental effects on the patient which are as follows:

a) Physical:
- Stress and strain
- Aspiration pneumonitis
- Wound dehiscence
- Muscular strain and fatigue
- Intraocular bleeding
- Rupture of cutaneous vessels
- Gastric herniation
- Rupture of oesophagus

b) Metabolic:
- Anorexia
- Dehydration
- Alkalosis

c) Psychological:
- Aversion to further surgeries
- Single experience of postoperative nausea and vomiting may create an apprehension of repeat postoperative nausea and vomiting during

Etiology of Post-Operative Nausea & Vomiting

1) Patient Factors

a) **Age:** The incidence of PONV changes with age[22]. It is very low in infants, increases at about 5% through childhood to about 20% in children under 5 years of age. Incidence rises to a peak of about 34-51% in the 6-16 years age group depending on the surgical procedure[23]. The incidence falls in adulthood to about 14-40%. In general, children are twice as likely as adults to experience PONV.

b) **Gender:** Adult women are 2-4 times more likely to suffer PONV than men and the symptoms in them are more severe. A higher incidence of sickness 38.4% in females than males 17% in a ratio of 2.3:1 was reported by Apfel et al[4]. Female gender was the strongest overall predictor of PONV[24]. The incidence of PONV varies with the phase of the menstrual cycle[25], but menstrual hormonal fluctuations are unlikely to be responsible for PONV. This has been confirmed in an RCT of 5000 patients, which demonstrated no link between menstrual cycle phase or menopausal status and incidence of PONV[26]. That prepubescent girls apparently lack increased likelihood of PONV[23], could imply that the risk relates to hormonal factors. The exact mechanism relating female gender to increased incidence of PONV is as yet unknown[24]. Risk of PONV in the prepubertal children shows no gender difference.

c) **History of PONV & Motion Sickness:** PONV is 3 times more likely in patients who have experienced emesis after a previous operation. Patients who are susceptible to motion sickness are particularly predisposed to PONV[27].

d) **Obesity:** Earlier it was thought that chances of PONV increases in obese patients and probably it was presumed that excessive adipose tissue serves as a storage site for anaesthetic drugs which are later released leading to PONV but now obesity has been disproved as a patient-related PONV risk factor[28].

e) **Delayed Gastric Emptying:** Decreased gastric motility due to any cause increases the risk of PONV. Common conditions associated with delayed gastric emptying include gastrointestinal obstruction, pyloric stenosis, diabetes mellitus, hypothyroidism and pregnancy[18].

f) **Non-Smoker:** The underlying mechanism for the reduced incidence of PONV in smokers compared with non-smokers is also not well understood. One theory suggests that chronic exposure to polycyclic aromatic hydrocarbons in cigarette smoke might induce the cytochrome P450 isoenzymes (CYP2E1)[22] responsible for phase 1 (first pass) metabolism of volatile anaesthetics[29]. However, given that only a small percentage of volatile anaesthetics gets metabolized (e.g. 0.2% of isoflurane, 0.02% of desflurane), it appears unlikely that liver enzyme induction could account for such large variation in the incidence of PONV between smokers and non-smokers. Thus, the protective effect of smoking may be due to functional changes in neuroreceptors from chronic exposure to nicotine, and thus nicotine withdrawal rather than nicotine exposure reduces smoker's susceptibility to PONV[30].

2) Preoperative Factors

a) **Food:** The induction of anaesthesia shortly after a meal is well known to be associated with emesis during induction and postoperative period. Even if adequate time is given for emptying, that doesn't ensure that the stomach is empty. Further, emptying rate is dependent upon the volume and chemical composition of meal. In addition, physical trauma decreases gastric emptying through sympathetic activation. It is self-evident that the presence of food promotes PONV[31] but as such, food is not emetogenic. The gut release hormones like gastrin, motilin which activate neurons in area postrema.

b) **Psychological Stress:** Patients are usually apprehensive about the forthcoming surgery and have some degrees of stress. Stress stimulates cerebral cortex and induces emesis[32]. In addition, anxious patients tend to hyperventilate which causes distension of GI tract due to aerophagy.

c) **Reason for Surgery:** The reasons for surgery have a strong impact on PONV. In cases of raised intracranial tension, upper GI tract obstruction, the central emetic apparatus is already sensitized. This argument holds good for abortions during first trimester of pregnancy where the patient is already within her vomiting phase. Influence of sex hormones on emetic reflex in females is substantiated by an increase in reflex of PONV after tubal ligation in the first 8 menstrual days.

d) **Premedication:** Premedication does have certain influence on PONV e.g. atropine can delay gastric emptying and cause PONV. Regarding morphine and pethidine, their intrinsic emetic and antiemetic effects are dose related. It is thought that the emetic effect of morphine and related opioids are via an action on opioid receptors, which is present in area postrema. With gradual increase in doses of morphine, the antiemetic centre located in the reticular formation is activated leading to increased emetic drive. The type of opioid receptor for antiemetic centre cannot be identified with certainty. Opioid analgesia primarily involves central mu, kappa, and delta receptors in the rostral anterior cingulate cortex and the brainstem[33]. However, opioid activity at peripheral receptors in the gut inhibits the release of acetylcholine from the mesenteric plexus and stimulates mu receptors, which reduces muscle tone and peristaltic activity. Consequent delayed gastric emptying and gastric distension activate visceral mechanoreceptors and chemoreceptors, which trigger nausea and vomiting via a serotonergic signalling pathway[24]. Other studies using loperamide implicate the presence of delta receptors[34]. The causes of PONV with the use of morphine appear to be due to:

- Morphine molecule stimulates area postrema
- Morphine and other narcotics slow down the gastric emptying.
- Narcotics increase the sensitivity of the emetic reflex to activation by labyrinthine stimulation as indicated by the increase in the incidence of nausea and vomiting in ambulatory patients.
- Morphine and other opioids enhance the release of 5-HT from enterochromaffin cells and induce PONV.

- Morphine and its congeners release ADH from posterior pituitary which causes nausea and vomiting.

However, some contradictory findings have been reported with respect to postoperative opioid use in adults[32].

Benzodiazepines, such as midazolam and temazepam when used as premedication, have shown promising effects by decreasing PONV.

3) Intra-Operative Factors

The two main intraoperative contributors of PONV are the anaesthetic and surgical procedure.

a) **Anaesthesia:** Recumbent posture of the patient during anaesthesia and prolonged muscular relaxation inhibits tonic discharge from vestibular labyrinth when the patient awakens from anaesthesia; the head is the first to move, leading to sudden vestibular discharge and increased chance of PONV. Anticholinergic premedication leads to vestibulo-visual mismatch leading to PONV (Compton, 1989).

b) **Anaesthetic Agents and Drugs**

- **Pharmacological Effects of Anaesthetics:** Agents such as cyclopropane and others are associated with a high incidence of PONV due to increased concentration of circulating catecholamines which act on area postrema. The release of adrenaline due to sympathetic stimulation has also been implicated in the mechanism of emesis induced by hypotension and pain. Attention should also be focused on the action of anaesthetics on antiemetic centre. The depressant effect of anaesthetics virtually inactivates this centre resulting in more incidence of PONV. Animal studies indicate that influence of 5-HT metabolism in brain can contribute to the pathogenesis of PONV. Nitrous oxide may contribute to PONV in several ways, it may act upon dopamine and opioid receptors in the brain, produce changes in middle ear pressures, and/or cause bowel distention as it diffuses into closed cavities[35, 36].
- **Physical Effects of Volatile Anaesthetic Agents:** The incidence of PONV is greater with volatile than with intravenous anaesthetics[37]. An increase in middle ear pressure has been implicated, but the main effects are suggested to be on the gut. Manual ventilation with mask leads to distension of stomach which leads to emetic reflex. The impact on small intestine is much greater. The belching reflex is likely to be suppressed under general anaesthesia. Such gastrointestinal distension with loss of intestinal motility adds to PONV.
- **Endocrine Effects of Anaesthetics:** These are complex and complicated. A large number of peptide hormones e.g. angiotensin-II, gastrin, insulin, etc. have been shown to induce emesis via area postrema.
- **Cardiovascular Effects of Anaesthesia:** Hypotension induces nausea and vomiting by release of catecholamines. Another possible mechanism is by activation of vagal afferent mechanoceptors in the ventricles of heart. Hypotension during spinal anaesthesia carries more significant risk towards PONV. The incidence of emesis would be greater when systolic blood pressure is reduced to < 80mmHg.
- **Gastrointestinal Effects of Anaesthetics:** Anaesthetics may induce nausea and vomiting by causing disruption of gastrointestinal tract. Effects of anaesthetics on lower esophageal sphincter (LES) bear special significance, because it is the LES which prevents reflux of gastric contents. In general, inhalational anaesthetics produce reduction in LES tone. This is seen with nitrous oxide in oxygen, and enhanced by the presence of halothane and enflurane. Studies in animals and humans by monitoring Migrating Motor Complex (MMC), indicate that the reduction in gastric motility under anaesthesia maybe contributed by vagal mechanisms. Anaesthetics modify the vagal drives probably by involving area postrema. During anaesthesia, reduction of gastric antral motility associated with relaxation of pyloric sphincter, promotes reflux of bile into the stomach. Bile causes gastric irritation and contributes to PONV.

Some anaesthetic agents reduce mesenteric perfusion and induce brief periods of ischemia, which sensitizes gut afferent to natural stimuli. The mechanisms involve local release of 5-HT, substance P, bradykinin and prostaglandin. In the postoperative period as normal gut functions return, the CNS is stimulated by abnormal levels of afferent activity adding further to emetic drive.

An additional factor that should be considered is the effect of anaesthetic on the release of 5-HT from the enterochromaffin cells in the mucosa of upper intestine. Opioids, adrenaline, ischemia and mechanical stimulation of gut enhances the release of 5-HT. Release of 5-HT induces emesis, mechanism applies to radiation and anticancer drug induced vomiting.

- **Effect of Anaesthetics on Intracranial Pressure:** Raised intracranial pressure causes headache, nausea, vomiting and inhibition of gastric motility. Ketamine, halothane, enflurane and isoflurane cause vasodilatation and an increase in intracranial pressure thus contributing to emesis[9].
- **Propofol and Postoperative Nausea and Vomiting:** Propofol use is associated with a low incidence of PONV (1-3%) compared to the usual (10-15%) with other IV anaesthetics[38]. This has been confirmed in numerous prospective studies, including studies in children. Although some authors have suggested that propofol has specific antiemetic effects, there are no data confirming that Total IV anaesthesia may be associated with less nausea and emesis[7]. Grace Brooke Huffman (2002) showed propofol used only as induction agent is not effective in preventing PONV, but acts only when used as continuous low dose IV infusion[39].

c) **General Effects of the Surgical Procedure:** The contribution of surgery is two-fold, the general effects of surgical procedure and the effects of specific types of surgical procedures that are reported to be associated with a high incidence of PONV [9]. In one of the systematic review and analysis in 2012, Apfel et al mentioned that only cholecystectomy, laparoscopic procedures, and gynaecological surgery reached statistical significance as independent predictors of PONV[24]

Gastrointestinal Motility: Effects of surgery on the GI tract are profound and outlast the duration of surgery. The significance of delayed gastric emptying and reduced intestinal motility induced by anaesthesia and surgery is two-fold. Firstly, during surgery, the delay or stasis leads to accumulation of fluid secretions and facilitates the reflux of bile into the stomach; all of which serve as stimuli for distention in the postoperative period. Therefore, when patient regains consciousness, even a normal quantity of meal received by an atonic stomach may result in vomiting.

The endocrine effects of surgery are complex and may contribute to PONV. The release of vasopressin due to surgery itself (e.g. Gastric manipulation) bears some relationship with occurrence of nausea and subsequent vomiting.

d) **Specific Effects of Surgery:** Certain types of surgical procedures are reported to be associated with a high incidence of PONV[35].

- **Ophthalmic Surgery:** Ocular surgery is associated with a high incidence of PONV. The incidence of early emesis is higher with squint surgery (10%) than with non-squint ocular (1.8%) and orbital surgery (2.7%). Manipulation of the eye, oculoemetic reflex, oculocardiac reflex and vestibulovisual mismatch are suggested causes of PONV.
- **Ear Nose and Throat Surgery:** High incidence of emesis associated with surgery of middle ear is caused by activation of glossopharyngeal afferents[5]. PONV in middle ear surgeries can be due to drilling by ontologist near to inner ear and the sound waves generated by drilling by tullio phenomenon may activate vestibular part of inner ear[5].
- **Abdominal Surgery:** Intra-abdominal operations are more emetogenic than extra-abdominal operations irrespective of patient's gender. During abdominal surgery; displacement, manipulation and traction upon the gut stimulate the vagal afferents contributing to PONV[19].
- **Gynaecological Surgery:** Women are more sensitive than men to all emetic stimuli; hence, gynaecological surgery should be associated with a high incidence of PONV[40].
- **Laparoscopic Surgery:** In laparoscopic cholecystectomy there are several factors which increase the intra-abdominal pressure and predispose to regurgitation like initial steep head down tilt, insufflation of peritoneum by CO_2 which irritates vagus nerve endings and effect of CO_2 on emetic centre[7].

e) **Duration of Surgery:** Increasing duration of surgery has been shown to be an independent PONV risk factor by a few well conducted studies in adults[4, 27] or children[23]. An outpatient study found that each 30 minutes increase in surgery duration increased baseline PONV risk by 60% [27].

f) **Regional Anaesthetics and Postoperative Nausea & Vomiting:** The first step is to evaluate whether regional anaesthesia can be used instead of general anaesthesia. The incidence of PONV is lower in both children and adults with regional anaesthesia; in some cases, the incidence is reduced 9-fold[41]. The incidence of postoperative emesis following regional nerve block procedure is usually lower than with general anaesthesia. Use of concomitant IV sedation during regional anaesthesia or intrathecal/epidural administration of opioids may contribute to PONV[42]. Emesis with central neuraxial block is greater than that with peripheral nerve blocks because of associated sympathetic blockade which contributes to hypotension induced nausea. A rapid decline in arterial BP to <80mmHg during spinal anaesthesia is often associated with the onset of nausea. It can be decreased by administering 100% oxygen, blood pressure raising drugs and I.V atropine (counteracts vagal effects).

In women undergoing laparoscopic procedures, postoperative emesis is lower with epidural than general anaesthesia. However, the epidural blockade is also not free form emesis. Incidence of 17% emesis is seen with caudal epidural blockade for paediatric anaesthesia[41]. Epidural pain-relieving techniques with opioids are associated with nausea and vomiting.

The evidence of nausea after epidural opioid administration may be lower with the more lipid soluble agents e.g. fentanyl and sufentanil[43]. Drugs with antagonistic action at opioid receptors can be used to reverse the side effects of intrathecal opioids including emesis without significantly decreasing the quality of analgesia. Intravenous nalbuphine (2.5-5mg) can reverse the respiratory depressant and emetic effects of epidural morphine[44].

4) Postoperative Factors

a) **Pain:** Visceral or pelvic pain is a common cause of postoperative emesis. Relief of pain is frequently associated with a relief of nausea. The relationship between pain and vomiting is supported by the increased emesis following naloxone reversal of opioid mediated pain relief.

b) **Dizziness:** PONV is increased in patients who feel dizzy. Postural hypotension and unrecognized hypovolemia may all contribute to decreased blood flow to CTZ leading to dizziness and vomiting.

c) **Ambulation:** Sudden motion, changes in position and patient transport precipitates nausea and vomiting mainly in those who have received opioids. This suggests that opioids sensitize the vestibular system to motion-induced nausea and vomiting.

d) **Oral Intake:** The timing of oral intake after surgery can influence the incidence of emesis in the postoperative period. Martin et al. found that restricting oral intake during the first 8 hours postoperatively significantly decreased emesis compared to that in a group that ingested fluids prior to discharge[45].

e) **Opioids:** The incidence of PONV is similar with opioids irrespective of route of administration. Most studies have not found differences in the incidence of nausea and vomiting in patients who have received IV via a PCA delivery system compared to standardized fixed interval IM injections[46]. There are conflicting reports regarding the incidence of emesis in patients receiving epidural opioids compared to IV, PCA or IM opioid therapy.

Patient Risk Assessment for PONV

For objective risk assessment, it is recommended to focus on those that independently predict PONV after accounting for other confounding factors. The two most commonly used risk scores for in-patients undergoing balanced inhaled anaesthesia are the Koivuranta score[47] and the Apfel score[4]. Koivuranta et al and Apfel et al came to the conclusion that inclusion of more than a few risk factors attains little to no improvement in accuracy.

Apfel et al[4] identified four risk factors that form the basis of the Apfel Scoring System. Each risk factor increases the likelihood of PONV by 18-22%[4]. The score consists of 4 predictors:

- Female gender
- History of PONV and/or motion sickness
- Non-smoking status
- Postoperative use of opioids

Number of Risk Factors	PONV Incidence
0	9%
1	20%
2	39%
3	60%
4	78%

Table 1: Risk Factors for PONV in Adults[30]

Evidence	Risk Factors
Positive overall	Female sex History of PONV or motion sickness Non-smoking Younger age General versus regional anaesthesia Use of volatile anaesthetics and nitrous oxide Postoperative opioids Duration of anaesthesia Type of surgery (cholecystectomy, laparoscopic, gynaecological)
Conflicting evidence	ASA physical status Menstrual cycle Level of anaesthetist's experience Muscle relaxant antagonists
Disproven or of limited clinical relevance	BMI Anxiety Nasogastric tube Supplemental oxygen Perioperative fasting Migraine

*Source: Tong J. Gan, et al Consensus Guidelines for the Management of Postoperative Nausea and Vomiting[30]

Strategies Recommended to reduce Baseline Risk include[60]

1) Avoidance of general anaesthesia by the use of regional anaesthesia.
2) Use of propofol for induction and maintenance of anaesthesia[38].
3) Avoidance of nitrous oxide[28, 48, 49]
4) Avoidance of volatile anaesthetics[38, 51]
5) Minimization of intraoperative and postoperative opioids[4, 48, 51]
6) Adequate hydration[50]

The IMPACT study evaluated six strategies to reduce PONV in 5199 high-risk patients[38]. They found that a combination of propofol and air/oxygen (total IV anaesthesia [TIVA]) had additive effects, reducing PONV risk by approximately 25%[38]. These findings are supported by 2 meta-analysis demonstrating that avoiding nitrous oxide reduced PONV risk[48, 49] and a randomized, placebo-controlled trial showing that volatile anaesthetics were the primary cause of early PONV (0–2 hours after surgery), but that they did not have an impact on delayed PONV (2–24 hours after surgery)[51]. However, nitrous oxide had little impact when the baseline risk for PONV is low[49].

Baseline risk for PONV can also be reduced by minimizing postoperative opioids[4, 48, 51]. The decrease in opioid consumption by using analgesic adjuncts has been demonstrated to decrease the incidence of opioid-related nausea and vomiting. A small dose (2 mg) of midazolam when given toward the end of surgery is effective in reducing PONV[30].

Prophylactic and Combination Antiemetic Therapy

Clinically approved drugs that are recently introduced in practice since the earlier guidelines are[30]:

1) $5HT_3$ receptor antagonists: ramosetron and palonosetron.
2) NK-1 receptor antagonist: aprepitant, casopitant, and rolapitant.
3) Corticosteroid: methylprednisolone.
4) Butyrophenone: haloperidol.
5) Antihistamine: meclizine.

The recommended pharmacologic antiemetics for PONV prophylaxis in adults currently include the 5-hydroxytryptamine (5-HT_3) receptor antagonists (ondansetron, dolasetron, granisetron, tropisetron, ramosetron, and palonosetron), neurokinin-1 (NK-1) receptor antagonists (aprepitant, casopitant, and rolapitant), corticosteroids (methylprednisolone and dexamethasone), butyrophenones (droperidol and haloperidol), antihistamines (dimenhydrinate and meclizine), and anticholinergics (transdermal scopolamine [TDS]).

Antiemetic Doses and Timing for Prevention in Adults[30]

Aprepitant 40 mg per os At induction
Casopitant 150 mg per os At induction
Dexamethasone 4–5 mg IV At induction
Dimenhydrinate 1 mg/kg IV
Dolasetron 12.5 mg IV End of surgery; timing may not affect efficacy
Droperidol 0.625–1.25 mg IV End of surgery
Granisetron 0.35–3 mg IV End of surgery
Haloperidol 0.5–<2 mg IM/IV At Induction
Methylprednisolone 40 mg IV
Ondansetron 4 mg IV End of surgery or at induction
Palonosetron 0.075 mg IV At induction
Perphenazine 5 mg IV
Promethazine 6.25 - 12.5 mg IV At induction
Ramosetron 0.3 mg IV End of surgery
Rolapitant 70–200 mg per os At induction
Scopolamine Prior evening or 2 h before surgery (Transdermal patch)
Tropisetron 2 mg IV End of surgery

New Antiemetic Combination Therapies

These include midazolam and dexamethasone, dexamethasone 8 mg IV at induction plus ondansetron 4 mg IV at the end of surgery plus ondansetron 8 mg PO postoperatively[52] and haloperidol 2.5 mg plus dexamethasone 5 mg IV after induction[53]. Among the NK1 receptor antagonists, aprepitant (40 mg) in combination with dexamethasone 10 mg proved superior to ondansetron 4 mg and dexamethasone 10 mg in preventing vomiting in neurosurgical patients up to 48 hours after surgery[54]. The combination of casopitant and ondansetron proved more effective than ondansetron alone[55].

Combination therapy for PONV prophylaxis is preferable to using a single drug alone[38]. Apfel et al[38] demonstrated that the effects of antiemetics acting on different receptors are additive.

Modern multivariable risk factor studies have strengthened the belief in the multifactorial nature of PONV and led to the development of a so-called “multimodal approach” to better address this issue[50]

It is not recommended to give prophylactic antiemetics to all patients who undergo surgical procedures[30]. Multiple interventions should thus generally be reserved for patients at moderate to high risk for postoperative nausea and vomiting or those in whom nausea and vomiting would be especially dangerous.

Other Methods and Alternative Therapies

Adequate IV fluid hydration is an effective strategy for reducing the baseline risk for PONV[56]. However, there was no difference in efficacy between crystalloids and colloids when similar volumes were used in surgeries associated with minimal fluid shifts[57].

Lack or Limited Evidence of Effect

Neostigmine had been implicated as a risk factor for PONV. But recent data disputed the clinical importance of neostigmine’s effects on PONV[58]. Hence, minimization of neostigmine dosage has been removed from the list of strategies to reduce the baseline risk.

Multiple studies show that supplemental oxygen had no effect on nausea or overall vomiting, although it may reduce the risk of early vomiting[59].As a result, supplemental oxygen is not recommended for the PONV prevention in these guidelines.

Other disputed strategies for PONV prophylaxis include music therapy, isopropyl alcohol inhalation, intraoperative gastric decompression, the proton pump inhibitor esomeprazole, ginger root, nicotine patch to nonsmokers, cannabinoids (nabilone and tetra-hydrocannabinol), and intraoperative supplemental oxygen[30].

In 2 RCTs, the phenothiazines, promethazine, 12.5 to 25 mg IV, administered at the induction of surgery, and prochlorperazine, 5–10 mg IV, given at the end of surgery were shown to have some antiemetic efficacy[60, 61]. Similarly, it is suggested that the phenylethylamine, ephedrine, 0.5 mg/kg IM, has an antiemetic effect when administered at the end of surgery[62]. However, due to a paucity of data, evidence is not as strong as for the other well-documented antiemetic drugs; therefore, further research is warranted before these drugs or techniques can be recommended as first-line therapy

Cost-Effectiveness (C/E)

The C/E of therapy is one of the major considerations in determining whether to use PONV prophylaxis. Willingness to pay is a recommended measure in cost benefit analysis. Reducing baseline risk can be a cost-effective strategy. It is estimated that each episode of emesis delays discharge from the PACU.

Hill et al found that prophylaxis in high-risk patients is more cost-effective than placebo due to increased costs associated with nausea and vomiting[63].

The decision about whether or not to use PONV prophylaxis, or to treat patients with established symptoms, not only depends on the efficacy of the drug but also on the baseline risk for PONV, adverse effects of the antiemetics, and drug acquisition costs, which will vary among different setting[30].

5-HT_3 Receptor Antagonists

The discovery and introduction of 5-HT_3 receptor antagonists in the early 1990s has rekindled interest in the mechanisms of nausea and vomiting and their use has revolutionized the

management of chemotherapy induced vomiting. Subsequently, 5-HT_3 receptor antagonists were introduced into anaesthesiology to prevent and treat PONV.

Ondansetron is the prototypical drug in this class. It and other 5-HT_3 antagonists have become some of the most widely used drugs for chemotherapy induced nausea and vomiting (CINV)[64]. Other agents in the class now are available including granisetron, dolasetron, tropisetron, ramosetron and palonosetron. The differences among these agents are mainly related to their chemical structures, 5-HT_3 receptor affinities and pharmacokinetic profile.

Mechanism of Action

Their effects at both central and peripheral locations contribute to their efficacy. 5-HT_3 receptors are present in several critical sites involved in emesis, including vagal afferents, the nucleus of tractus Solitarius (NTS) (a nucleus of vagus nerve which receives signals form vagal afferents), and the area postrema (located in the floor of 4th ventricle, outside the blood brain barrier). Serotonin (5-HT) is released by the enterochromaffin cells of the small intestine in response to GI tract insult and pneumoperitoneum. Chemotherapeutic agents can stimulate vagal afferents via 5-HT_3 receptors to initiate the vomiting reflex. Experimentally, vagotomy has been shown to prevent cisplatin induced emesis. However, the highest concentrations of 5-HT_3 receptors in the CNS are found in the NTS and CTZ (Chemotactic Trigger zone, located in the area postrema) and 5-HT_3 receptor antagonists suppress nausea and vomiting by acting at these sites.

Pharmacology of Serotonin Receptor Antagonists

Palonosetron

The empirical formula of palonosetron hydrochloride is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single stereo isomer and has the following structural formula:

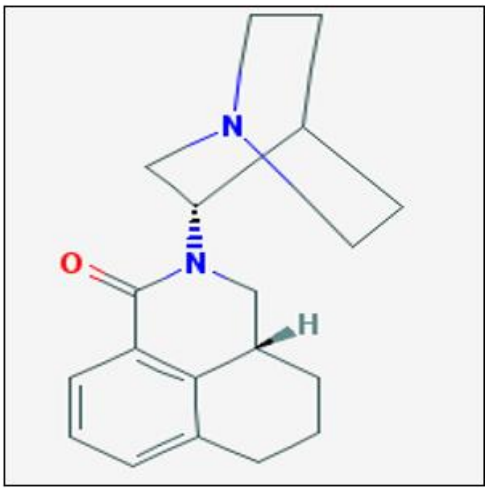

Figure 2: Chemical Structure of Palonosetron

Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Palonosetron injection is a sterile, clear, colorless, nonpyrogenic, isotonic, buffered solution for intravenous administration. Palonosetron injection is available as 5 ml vial.

Each mL in the vial contains palonosetron hydrochloride equivalent to 0.05 mg palonosetron in sterile water for intravenous administration. The pH of the solution in the 5 mL vial is 4.5 to 5.5.

Palonosetron is a second-generation serotonin (5-HT_3) receptor antagonist. Unlike other antagonists, it is a potent 5-HT_3 receptor antagonist developed to prevent chemotherapy-induced nausea and vomiting. It is unique structurally, pharmacologically, clinically.

Indication in Adult

- Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses.
- Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses.
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

Recent receptor binding studies suggest that palonosetron is further differentiated from other 5-HT_3 antagonists by interacting with 5-HT_3 receptors in an allosteric, positively cooperative manner at sites different from those that bind with ondansetron and granisetron[65]. Also, it may have long lasting effects on receptor ligand binding and functional responses to serotonin[66]. Also, it blocks the response associated with substance P, has negative cooperativity with neurokinin-1 receptors by cross-talk, and creates an antiemetic effect[67].

Salient Features

1) Long half-life: 40 Hrs,
2) Much more potent at 5-HT_3 receptors (pKi = 10.45),
3) Strong binding to 5HT_3 receptors (53% with palonosetron, 15% with granisetron and 4% with ondansetron),
4) Allosteric binding at receptors,
5) Long lasting inhibition of calcium channels,
6) Positive cooperativity at 5HT_3 receptors (Not seen with granisetron or ondansetron),
7) Receptor internalization

Table 2: Half-Life and Binding Affinities of 5-HT_3 Receptor Antagonists

5-HT_3 Receptor Antagonists	Half-life (Hrs)	Binding affinity (pki)
Palonosetron	40	10.45
Ramosetron	5.78	8.5
Ondansetron	4	8.39
Granisetron	9	8.91
Dolasetron	7.3	7.6

Adult Dosage

A single 0.075 mg intravenous dose administered over 10 seconds at the induction of anaesthesia. Dosage forms and

strength is 0.25 mg/5mL (free base) vial (concentration: 0.05 mg/mL, 50 mcg/mL).

In the inpatient surgical setting, a single 0.075 mg IV dose of palonosetron significantly reduced emesis, intensity of nausea and the use of rescue antiemetic in addition to delaying the time to emesis and treatment failure, particularly during the first 24 h after surgery[68]. "The 1 mcg/kg dose was comparable to 0.075 mg which was chosen as the highest dose studied in the current trial[68]".

Pharmacodynamics

Palonosetron is a selective 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and a little or no affinity for other receptors.

Pharmacokinetics

After intravenous dosing of palonosetron, an initial decline in plasma concentrations is followed by slow elimination from the body. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in cancer patients.

Distribution: The pharmacokinetics and metabolic disposition revealed extensive distribution volume (8.34 ± 2.5 L/kg) and mean plasma elimination half-life of 37 hours. Plasma protein binding rate of palonosetron is 62%.

Metabolism: Palonosetron is eliminated by multiple routes. Approximately 50% of the drug is metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites are largely inactive. *In vitro* metabolism studies show that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron.

Elimination: Renal elimination is the primary excretion route and palonosetron circulates in plasma mainly as the parent drug. After a single intravenous dose of 10 mcg/kg of palonosetron, approximately 83% of the dose was recovered within 144hrs in the urine (approximately 40% as unchanged drug, with 50% metabolized; M9 and M4 were the major metabolites) and 3.4% in faeces. These results indicate that both renal and hepatic routes are involved in the elimination of palonosetron from the body[69].

In healthy subjects, the total body clearance of palonosetron was 0.160 ± 0.035 L/h/kg and renal clearance was 0.067± 0.018 L/h/kg.

Total body clearance is not significantly affected by age, gender, hepatic or renal impairment.

Contraindications

Palonosteron is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

Precautions and Warnings

- Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other selective 5-HT_3 receptor antagonists
- Serotonin syndrome has been reported, particularly with concomitant use of serotonergic drugs. (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, lithium, and intravenous methylene blue).

Adverse Reactions

The most common adverse reactions are headache and constipation.

Cardiovascular effects (1%): electrocardiogram QTc prolongation, sinus bradycardia, tachycardia, (< 1%) blood pressure decreased, hypotension, hypertension, arrhythmia, ventricular extrasystoles, generalized edema, ECG T wave amplitude decreased, platelet count decreased.

Dermatological (<1%): pruritus, rash, allergic dermatitis.

Gastrointestinal System (1%): flatulence (< 1%), dry mouth, upper abdominal pain, salivary hypersecretion, dyspepsia, diarrhea, intestinal hypomotility, anorexia.

General (< 1%): chills, 1% weakness, <1% fatigue, fever, flu like syndrome.

Liver (<1%): transient increases in AST and/or ALT or other hepatic enzyme increased, occurred predominantly in patients receiving highly emetogenic chemotherapy.

Metabolic (< 1%): hypokalemia, anorexia.

Nervous System (1%): dizziness, <1% somnolence, insomnia, hypersomnia.

Respiratory (< 1%): hypoventilation, laryngospasm.
Urinary System (1%): urinary retention.

Vascular (<1%): vein discoloration, vein distention.

Drug Interactions

The potential for clinically significant drug interactions with palonosetron appears to be low. Co-administration of i.v. palonosetron with dexamethasone or metoclopramide in healthy subjects revealed no pharmacokinetic drug interactions. In controlled clinical trials, it has been safely administered with corticosteroids, analgesics, antiemetics, antispasmodics and anticholinergic agents.

Storage

- Store at controlled temperature of 20–25°C (68°F–77°F).
- Excursions permitted to 15–30°C (59-86°F).
- Protect from freezing.
- Protect from light.

Ramosetron

Composition: Each 2 ml ampule contains: Ramosetron hydrochloride 300 mcg

Description: Ramosetron hydrochloride is a highly selective, long acting 5-HT3 receptor antagonist. It is a chiral compound, chemically described as (-)-(R)-5-[(1-methyl-1H-indol-3yl) carbonyl] 4, 5, 6, 7-tetrahydro-1H-benzimidazole monohydrochloride.
Mol. Formula: $C_{17}H_{17}N_3O.HCl$
Mol. Wt.: 315.8022

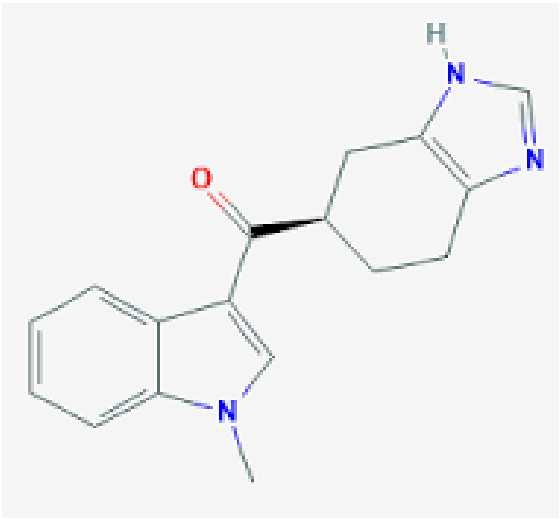

Figure 3: Chemical Structure of Ramosetron

Pharmacokinetics

IV injection of ramosetron HCl into healthy volunteers at doses 0.1-0.8 mg showed that the plasma concentration of the unchanged drug declined biphasically with a half-life of approximately 5 hrs. The AUC (Area under Curve) remained directly proportional to dose.

Distribution: The pharmacokinetics and metabolic disposition revealed Volume Distribution of 2.11 L/Kg and Mean Plasma Half-life of 5.78 hours. Plasma protein Binding Rate of Ramosetron is 91.2%.

Metabolism: Ramosetron is eliminated mainly via two metabolic processes: Demethylation and Hydroxylation. The results of the in vitro metabolism study show that the hepatic drug metabolizing enzymes CYP1A1, CYP1A2, and CYP2D6 are involved in the primary metabolism of Ramosetron hydrochloride in humans.

Elimination: During the first 24 hrs after injection, 16-22% of the dose was excreted as unchanged drug in urine. In addition to the unchanged drug, both the demethylated and hydroxylated metabolites and their conjugates were detected in urine. In healthy volunteers receiving repeated doses, the pharmacokinetic profile remained unaltered and there was no evidence of accumulation.

Total body clearance of ramosetron is 0.27 L/hr/Kg

Indications

- Treatment & prophylaxis of Gastrointestinal symptoms (nausea & vomiting associated with emetogenic cancer chemotherapy
- Prevention of postoperative nausea and vomiting (PONV) for up to 48 hours following surgery.

Contraindications: Ramosetron hydrochloride is contraindicated in patients who have a history of hypersensitivity to any component of the formulation.

Precautions and Warnings: Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other selective 5-HT_3 receptor antagonists

Drug Interactions: Ramosetron hydrochloride injections should not be combined with D-mannitol injections or furosemide Injections as this product has been demonstrated to be incompatible with these injections.

Usage in Pregnancy, Lactation and Elderly

- Since the safety of Ramosetron hydrochloride has not been established in pregnant women, this drug should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.
- Caution should be exercised when ramosetron HCl is administered to nursing mothers. (It has been reported that ramosetron HCl is excreted in the milk of lactating rats.)
- The safety of Ramosetron hydrochloride in children has not been established.

Adverse Reactions: Ramosetron hydrochloride is generally well tolerated. The most commonly reported adverse reactions with the drug include rash, headache, sleepiness, diarrhoea and constipation.

- Hepatic dysfunction: increase in AST, ALT, GGTP, LDH and bilirubin level
- Renal dysfunction: increased blood urea and serum creatinine level
- Epileptiform attacks have been reported with other 5-HT3 receptor antagonist anti-emetics.
- Anaphylactoid symptoms: ill feeling, chest distressed feeling, dyspnea, wheezing, facial hot flushes, redness, itching, cyanosis, and hypotension etc.

Patients therefore should be observed carefully, and if such reactions are observed during treatment, treatment should be discontinued and appropriate medical therapy be instituted.

Adult Dosage: The recommended adult intravenous dosage of Ramosetron hydrochloride injection for the treatment of postoperative nausea and vomiting is 0.3 mg given towards the end of surgery.

If a sufficient response is not achieved, an additional 0.3 mg dose may be given. However, the maximum dosage of the drug is 0.6 mg a day.

Dosage form and strength is 0.3 mg/2 ml ampule. (concentration: 0.15 mg/ml)

Storage Conditions

- Store in a cool, dry place below 25°C (Room temperature).
- Protect from sunlight.
- Shelf-Life: 24 months from the date of manufacturing.

Studies related to 5-HT_3 Receptor Antagonists

In 2008, Kovac et al[68] evaluated the efficacy and safety of three different doses of palonosetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period and concluded that a single 0.075-mg IV dose of palonosetron effectively reduced the severity of nausea and delayed the time to emesis and treatment failure in the inpatient surgical setting. They also found that lower doses were not as effective and also that 1 mcg/kg dose of palonosetron was comparable to the highest dose (0.075 mg) studied for PONV.

Rojas C et al[67] in 2010 studied the association of palonosetron with substance P-mediated responses. They mentioned that accumulating evidence suggests that substance P (SP), the endogenous ligand acting preferentially on neurokinin-1 (NK-1) receptors, not serotonin (5-HT), is the dominant mediator of delayed emesis. Recent data have revealed cross-talk between the NK-1 and $5HT_3$ receptor signalling pathways; they postulated that if palonosetron differentially inhibited NK-1/5-HT_3 cross-talk, it could help explain its efficacy profile in delayed emesis. Consequently, they evaluated the effect of palonosetron, granisetron, and ondansetron on Sustance P-induced responses in vitro and in vivo. Palonosetron, but not ondansetron or granisetron, dose-dependently inhibited the cisplatin-induced Substance P enhancement. These results led to the conclusion that pharmacology of palonosetron differs from older 5-HT_3 receptor antagonists and provided a rationale for the efficacy observed with palonosetron in delayed CINV.

Hahm TS et al[70] in 2010 conducted a randomised controlled trial to compare the anti-emetic efficacy of ramosetron and ondansetron in patients at high risk for postoperative nausea and vomiting (PONV) after total knee replacement and found that more patients in ramosetron group had a complete response (no PONV and no rescue anti-emetic required) between 2 and 48 hours. 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 for prevention of postoperative nausea and vomiting in patients at high risk undergoing unilateral total knee replacement.

Park SK et al[71] in 2011 conducted a randomized controlled, double-blind study to compare palonosetron with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery and found that the incidence of PONV and nausea (not vomiting) was significantly lower in the palonosetron group than in the ondansetron group during the overall 0 – 24 h time interval.

Moon YE et al[72] in 2012 in a prospective, randomized controlled, double-blind study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving IV PCA after thyroidectomy. Palonosetron was found to be more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2–24 h after surgery.

Kim SH et al[73] in 2013 compared palonosetron with ondansetron and ramosetron in high-risk patients undergoing laparoscopic surgery in a prospective, randomized controlled, double-blinded study and found out that the overall incidence of nausea/retching/vomiting was lower in the palonosetron (22.2%/11.1%/5.6%) than in the ondansetron (77.1%/48.6%/28.6%) and ramosetron (60.5%/28.9%/18.4%) groups. The requirement of rescue antiemetic therapy was also less in the palonosetron group than the other groups ($P < 0.001$). It was concluded that palonosetron had the highest anti-emetic efficacy followed by ramosetron and ondansetron.

Kang JW et al[74] in 2014 studied whether continuous infusion of palonosetron using a patient-controlled analgesia device following single injection could reduce PONV to a greater extent than single injection only and found that continuous palonosetron infusion, following single injection, reduces the incidence of PONV compared with single injection only.

Chun HR et al[75] in 2014 evaluated the efficacy of palonosetron, the latest 5-HT_3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) during the first 72 h after operation in a randomized controlled, double-blinded, placebo-controlled study. They reported that the incidence of PONV was lower in the palonosetron group compared with the placebo group during the 0-24 h (33% vs 47%) and 0-72 h period (33% vs 52%) ($P<0.05$), but not during the 24-72 h postoperative period (6% vs 11%). The incidence of nausea was also significantly lower in the palonosetron group than in the placebo group during the 0-24 and 0-72 h period ($P<0.05$), but not during the 24-72 h postoperative period. However, there were no significant differences in the incidence of vomiting, and the use of rescue anti-emetics between the groups.

Moon HY et al[76] 2014 compared palonosetron and aprepitant (a neurokinin-1 receptor antagonist) for PONV prevention in patients indicated for laparoscopic gynaecologic surgery: a double-blind randomised controlled trial. They reported that both the drugs were effective for PONV prevention in the patients indicated for laparoscopic gynaecologic surgery. These drugs can be used in combination for multimodal therapy because they bind to different receptors.

Joo J et al[77] in 2015 compared ramosetron and ondansetron for prevention of PONV in strabismus surgery patients and found out that incidence of nausea was significantly lower at 2 hrs in ramosetron group (9.4%) than ondansetron group (34.7%) ($p<0.05$). incidence was also significantly lower in ramosetron group at 24 hrs than ondansetron group ($p<0.05$). They concluded that ramosetron has superior antiemetic activity to ondansetron in adult strabismus surgery patients.

Kim MS et al[12] in 2017 conducted a meta-analysis of randomised controlled trials that included comparison of palonosetron and ramosetron for postoperative nausea and vomiting (PONV) prophylaxis. It showed that there was no difference in postoperative nausea (PON) or postoperative vomiting (POV) between the two drugs for the total 48 hr period after surgery. However, palonosetron showed better prevention of POV during the delayed period overall [relative risk (RR), 0.59; 95% confidence interval (CI), 0.39 to 0.89; p=0.013], as well as after subgroup analyses for females and laparoscopies (RR, 0.56; 95% CI, 0.36 to 0.86; p=0.009 and RR, 0.46; 95% CI, 0.23 to 0.94; p=0.033). Subgroup analysis for spinal surgery showed that ramosetron was more efficacious in reducing POV during the total 48-hr (RR, 3.34; 95% CI, 1.46 to 7.63; p=0.004) and early periods (RR, 8.47; 95% CI, 1.57 to 45.72; p=0.013). They concluded that there was no definite difference in PONV prevention between the two drugs.

Park EH et al[78] in 2018 evaluated the efficacy of ramosetron for the reduction of PONV in patients with colorectal cancer and found out that 92% of the patients had complete response (no PONV) upto 48 hours after surgery. No serious adverse events were seen. They concluded that postoperative ramosetron injection is effective for the prevention of PONV after a laparoscopic colectomy in colorectal-cancer patients. Reddy GS et al[79] in 2019 compared the efficacy of ramosetron and palonosetron in preventing PONV following laparoscopic cholecystectomy. They found out that the incidence of a complete response (no PONV and no rescue medication) during 0-3 h in the postoperative period was 82.5% with ramosetron and 90% with palonosetron; the incidence during 3-24 h postoperative period was 80% with ramosetron and 87.5% with palonosetron. During 24-48 h postoperative period, the incidence was 65% and 90%, respectively (P < 0.05). The incidences of adverse effects were statistically insignificant between the groups. They concluded that palonosetron is more effective than ramosetron for long-term prevention of PONV following laparoscopic cholecystectomy.

Lacunae in Existing Knowledge

Both palonosetron and ramosetron have been compared with ondansetron and reported to be superior to it for PONV prevention. However, there is paucity in literature about comparison between palonosetron and ramosetron. Therefore, this study is being undertaken to compare the efficacy of palonosetron and ramosetron for the prevention of PONV in middle ear surgeries.

Research Question

Is Ramosetron comparable to Palonosetron for preventing post operative nausea vomiting following middle ear surgeries?

Hypothesis

Ramosetron is comparable to palonosetron for preventing post operative nausea vomiting following middle ear surgeries.

Aim and Objectives

Aim is to evaluate and compare Ramosetron and Palonosetron for prevention of post operative nausea and vomiting in middle ear surgery under general anaesthesia in adult patients.

Primary Outcome Measures

Number of episodes of PONV in 24 hours following conclusion of anaesthesia

Secondary Outcome Measures

1) Rescue antiemetic, if required
2) Overall satisfaction of patient with nausea and vomiting experience
3) Incidence of adverse effects like headache, dizziness, drowsiness, injection site reaction etc

All the above 3 parameters were observed over 24 hours following conclusion of anaesthesia.

3. Material and Methods

The study was conducted in the Department of Anaesthesiology, ABVIMS and Dr. Ram Manohar Lohia Hospital after obtaining approval from the institutional review board and institutional ethics committee.

Sample Size

60 patients of American Society of Anaesthesiologists physical grade I or II, scheduled for middle ear surgeries in the ENT Department of the hospital were selected as cases. All the patients were anaesthetised after thorough clinical examination and proper investigations.

Study Design

Single Blinded Randomised Controlled Study.

60 patients were randomly divided into 2 groups of 30 each. Patients were unaware of allocated groups and groups were allocated by computer generated randomisation list.

Group P: Inj Palonosetron 1 mcg/kg IV upto a maximum dose of 75 mcg single dose given at the time of induction

Group R: Inj Ramosetron 0.3 mg IV single dose given at the end of surgery

Study Duration

1st November 2018 to 1st February 2020

Criteria for Study Population

Inclusion Criteria

- Adult patients of either sex
- ASA grade – I and II
- BMI <30 kg/m^2
- Middle ear surgery

Exclusion Criteria

- Known hypersensitivity to serotonin antagonists
- History of motion sickness, PONV
- Pregnant and Lactating mothers
- Patients with ongoing gastrointestinal disease
- Patients with liver dysfunction
- People who have received chemotherapy in the last few weeks
- Patients who are on antiemetics, psychomimetics or steroids preoperatively

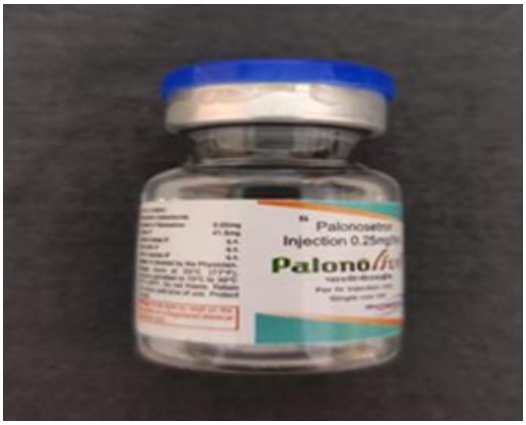

Figure 4: Vial of Palonosetron (0.05 mg/ml)

Figure 5: Ampoule of Ramosetron (0.15 mg/ml)

4. Procedure

Study was conducted after obtaining clearance from the ethical committee. Bilingual written informed consent was taken from all the patients. Patients were explained about the study. Patient Information Sheet was read to the patients and their signature was taken.

Preoperative assessment was done for each patient.

The pre-anaesthetic regimen, anaesthesia procedure and surgical technique was kept standardized and uniform for all subjects.

Patients were kept nil per orally for solids 6hrs and clear fluids 2hrs before surgery.

On the Day of Surgery (In the Operating Room)

20 minutes before the scheduled time of induction of anaesthesia, IV line was secured using 18G intravenous cannula and iv fluids were started.

Patients were premedicated with Inj fentanyl 2mcg/kg and monitored throughout with routine monitoring of baseline heart rate, blood pressure and oxygen saturation.

Anaesthetic Technique

Technique of anaesthesia adopted was general anaesthesia with endotracheal intubation and controlled ventilation.

Based on the random number generated by computerized randomisation, patients were given either Palonosetron or Ramosetron. Palonosetron 1 microgram/kg upto a maximum dose of 75 mcg was given at the time of induction and Ramosetron 0.3 mg iv was given at the end of surgery.

The patients were preoxygenated with 100% oxygen for 3 minutes. Anaesthesia was induced with Inj Propofol(1%) 2 mg/kg slow iv till loss of verbal contact. Then, endotracheal intubation was facilitated by adequate neuromuscular blockade achieved with Inj Vecuronium 0.1 mg/kg iv with appropriate size cuffed endotracheal tube.

Anaesthesia was maintained with intermittent positive pressure ventilation with oxygen and nitrous oxide (50:50) along with sevoflurane 1-2%, maintaining a MAC of 1.0 using a closed circuit with a circle absorber, along with intermittent boluses of Inj Vecuronium 0.02 mg/kg iv for maintenance of muscle relaxation. Ventilation was adjusted to maintain end tidal carbon dioxide between 35-40 mmHg throughout the procedure.

Intraoperative pain relief was achieved with Inj paracetamol infusion 15 mg/kg and Inj diclofenac sodium aqueous 1 mg/kg slow intravenous 20 minutes before completion of surgery.

Residual neuromuscular block was reversed with Inj neostigmine 0.05 mg/kg and Inj Glycopyrrolate 0.01 mg/kg slow iv. Endotracheal tube was removed on return of protective airway reflexes as per standard protocols. 100% oxygen was administered for 5 minutes post extubation to avoid hypoxia as a routine in all patients.

Patient was assessed for PONV at the time of reversal and during the time interval of 0-2 hours, 2-6 hours, 6-12 hours and 12-24 hours after completion of surgery.

PONV Score

0 – No nausea/vomiting/retching/no rescue antiemetic required
1 – Nausea
2 – Retching
3 – Vomiting

Rescue antiemetic required for patients with complaint of nausea, retching or vomiting, not controlled in any group was INJ DEXAMETHASONE 4 mg iv.

Patients was monitored for any adverse effects like headache, dizziness, drowsiness and any adverse reactions to the drugs for 24 hours following surgery.

Overall satisfaction of the patient with nausea and vomiting experience was also assessed.

Patient Satisfaction

- Satisfied- No PONV/Adverse effects
- Neutral- incidence of nausea or adverse effects
- Dissatisfied- incidence of retching/vomiting

For the purpose of the study, an episode of PONV denotes either a distinct spell of nausea, retching (an involuntary attempt to vomit but not actually productive of stomach contents) and/or vomiting (actual expulsion of stomach contents).

Statistical Analysis

Sample Size

A power analysis indicated that 45 subjects were required per group to show that Palonosetron and Ramosetron are comparable for prevention of PONV in middle ear surgery. We chose a 50% baseline ratio of incidence of PONV based on a previous study conducted by Kim et al.[12] comparing the efficacy of palonosetron and ramosetron for prevention of PONV and clinical experience in patients undergoing middle ear surgeries performed under general anaesthesia. Factoring a droupout rate of approximately 10%, we calculated that 50 patients per group would be required.

The formula for calculated sample size is given below

$$n = \frac{[z_{1-\alpha/2}.\sqrt{2P(1-P)} + z_{1-\beta}.\sqrt{\{P_1(1-P_1) + P_2(1-P_2)\}}]^2}{(P1-P2)^2}$$

$$= \frac{[1.645*0.685 + 0.842*0.661]^2}{(0.25*0.25)}$$

$$= 2.833/0.0625$$

$$= 45.32$$

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 one sided and the critical value is 1.645), Z_{β} is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2) and p_1 and p_2 are the expected sample proportions of the two groups.

Since our study was time bound and needed completion within a specified period. Therefore, the proposed study was undertaken with a smaller sample size of 30 cases per group.

Statistical Methods

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean±SD or median if the data was unevenly distributed. Categorical variables were expressed as frequencies and percentages. The comparison of continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups was compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Mann Whitney U test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

5. Results

Group Distribution

Study included 60 patients, randomly divided into two groups of 30 each.

Table 3: Group Distribution

Groups	Frequency	%
Group R	30	50.0%
Group P	30	50.0%
Total	60	100%

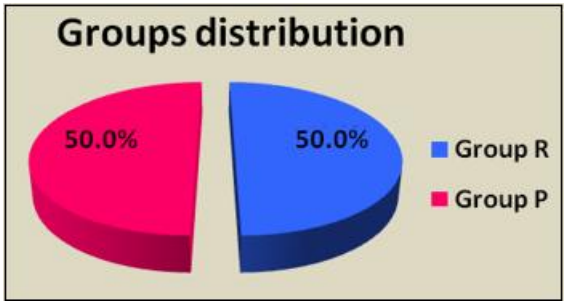

Figure 6: Distribution of Groups

Age and BMI Distribution

All patients were above 18 years of age with BMI between 18.5 kg/m^2 and 24.9 kg/m^2

Table 4: Age and BMI Distribution

	Group R	Group P	P Value
	Mean ± SD	Mean ± SD	
Age	30.00 ± 11.61	37.20 ± 10.35	0.328
BMI	21.44 ± 2.57	21.58 ± 1.89	0.813

p value is not significant (p>0.05)

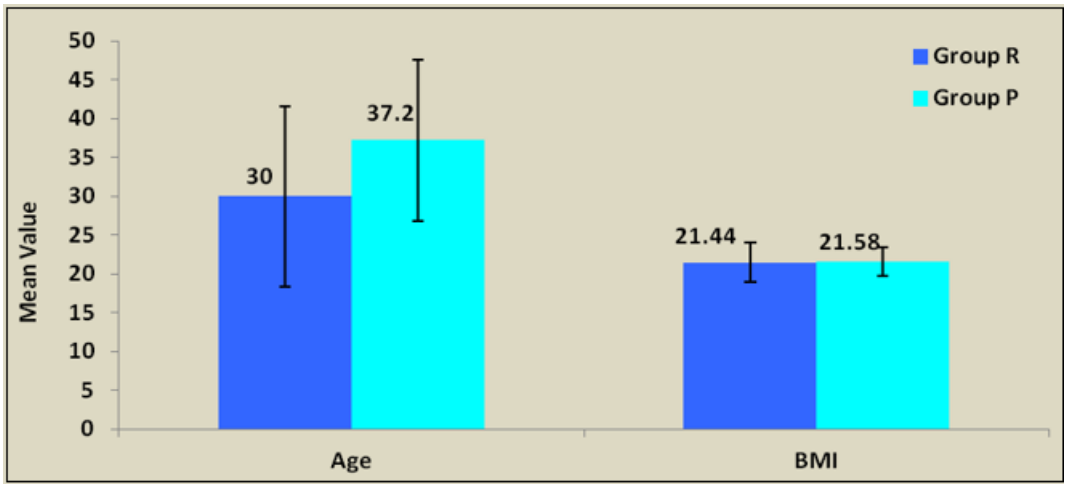

Figure 7: Comparison of Age and BMI

Both groups were comparable with respect to age and BMI

Sex Distribution

Table 5: Sex Distribution

Sex	Group R		Group P		P Value
	Frequency	%	Frequency	%	
F	12	40.0%	19	63.3%	0.071
M	18	60.0%	11	36.7%	
Total	30	100%	30	100%	

p value is not significant (p>0.05)

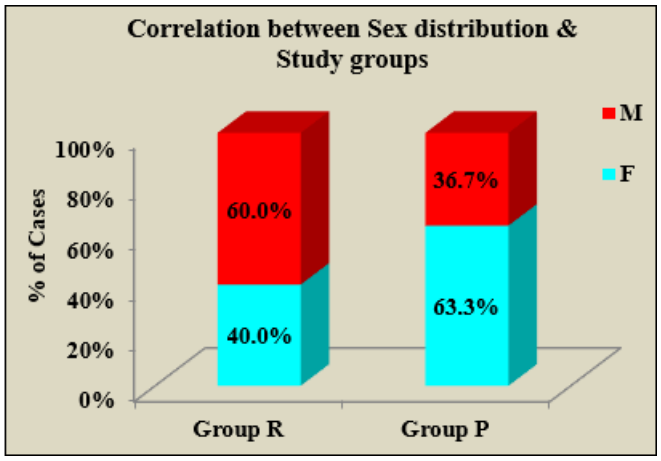

Figure 8: Correlation between Sex Distribution and Study Groups

Both groups were comparable regarding sex distribution.

ASA Grade in Study Groups

No statistically significant difference was noted between the groups with respect to ASA grade

Table 6: ASA Grade in Study Groups

ASA Grade	Group R		Group P		P Value
	Frequency	%	Frequency	%	
I	23	76.7%	25	83.3%	0.519
II	7	23.3%	5	16.7%	
Total	30	100%	30	100%	

p value is not significant (p>0.05)

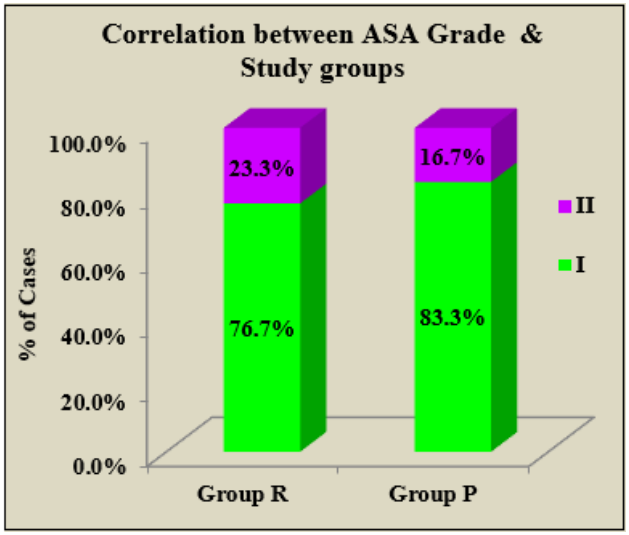

Figure 9: Correlation between ASA Grade and Study Groups

Duration of Anaesthesia

Table 7: Duration of Anaesthesia

	Group R	Group P	P Value
	Mean ± SD	Mean ± SD	
Duration (min)	162.00 ± 34.18	152.00 ± 32.61	0.251

p value is not significant

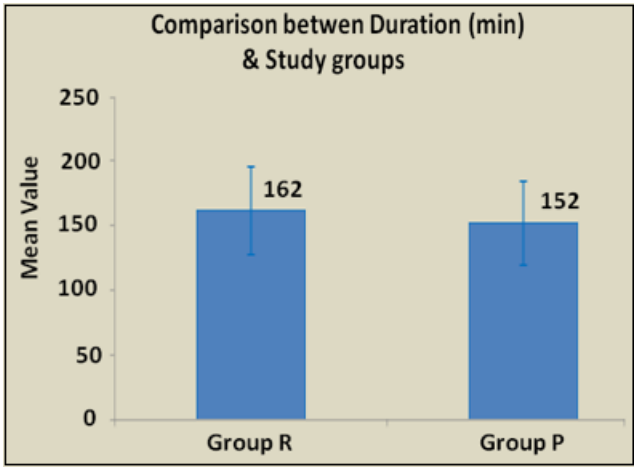

Figure 10: Comparison of Duration of Anaesthesia

Both groups were comparable with respect to duration of anaesthesia

PONV Score

Table 8: PONV Score

PONV Score		Group R		Group P		P Value
		Frequency	%	Frequency	%	
At time of Reversal/ Awakening	0	30	100.0%	30	100.0%	-
0-2 hrs	0	25	83.3%	28	93.3%	0.424
	1	5	16.7%	2	6.7%	
	2	0	0.0%	0	0.0%	
	3	0	0.0%	0	0.0%	
2- 6 hrs	0	24	80.0%	27	90.0%	0.509
	1	4	13.3%	3	10.0%	
	2	1	3.3%	0	0.0%	
	3	1	3.3%	0	0.0%	
6- 12hrs	0	21	70.0%	28	93.3%	0.036
	1	4	13.3%	2	6.7%	
	2	0	0.0%	0	0.0%	
	3	5	16.7%	0	0.0%	
12- 24hrs	0	27	90.0%	30	100.0%	0.237
	1	3	10.0%	0	0.0%	

p value is significant in 6-12 hours time interval ($p<0.05$)

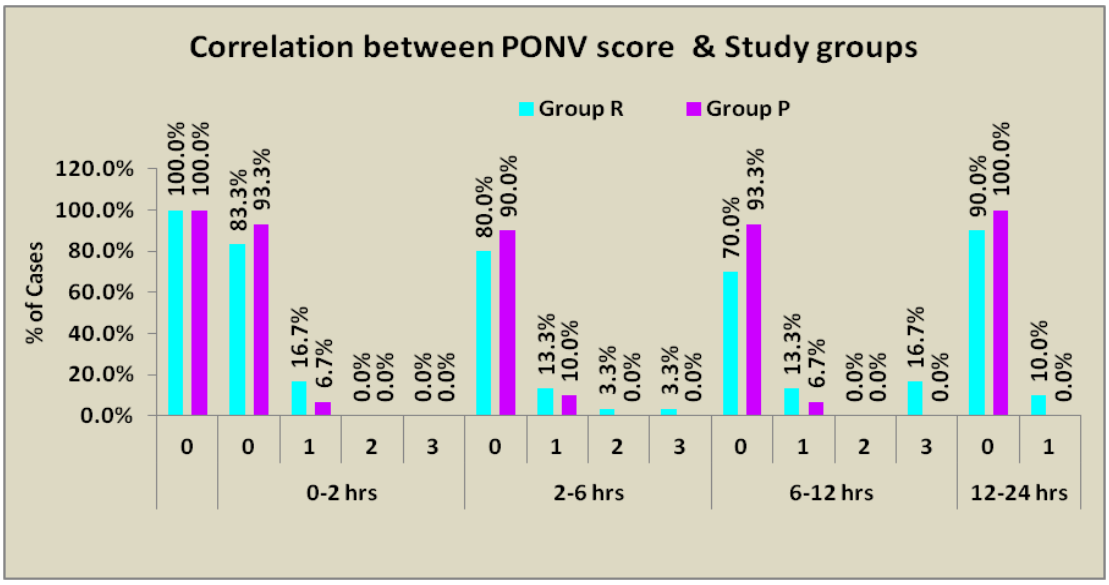

Figure 11: Correlation between PONV Score and Study Groups

PONV Score at the time of reversal, during 0-2 hours, 2-6 hours and 12-24 hours were comparable between the two groups ($p>0.05$). However, PONV Score during 6-12 hours is higher in Group R as compared to Group P ($p=0.036$)

Incidence of PONV Episodes

0 – No PONV Episode

1 – PONV episode seen

Table 9: PONV Episodes

PONV Episodes		Group R		Group P		P Value
		Frequency	%	Frequency	%	
At time of Reversal / Awakening	0	30	100.0%	30	100.0%	-
0-2 hrs	0	25	83.3%	28	93.3%	0.424
	1	5	16.7%	2	6.7%	
2- 6 hrs	0	24	80.0%	27	90.0%	0.472
	1	6	20.0%	3	10.0%	
6- 12hrs	0	21	70.0%	28	93.3%	0.042
	1	9	30.0%	2	6.7%	
12- 24hrs	0	27	90.0%	30	100.0%	0.237
	1	3	10.0%	0	0.0%	

p value is significant in 6-12 hours time interval ($p<0.05$)

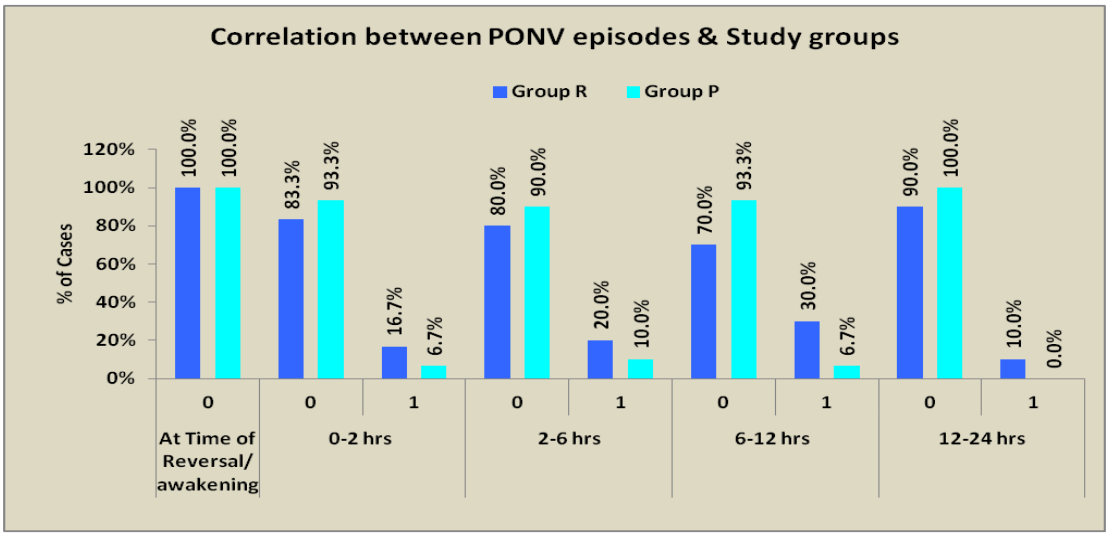

Figure 12: Correlation between PONV Episodes and Study groups

Incidence of PONV episodes seen at the time of reversal, during 0-2 hours, 2-6 hours and 12-24 hours were comparable between the two groups (p>0.05). However, during 6-12 hours, higher incidence of PONV episodes were seen in Group R as compared to Group P (p=0.042)

Rescue Antiemetic Use

Table 10: Rescue Antiemetic Use

Rescue Antiemetic Use	Group R		Group P		P Value
	Frequency	%	Frequency	%	
Y (Yes)	23	76.7%	30	100.0%	0.011
N (No)	7	23.3%	0	0.0%	
Total	30	100%	30	100%	

p value is significant (p<0.05)

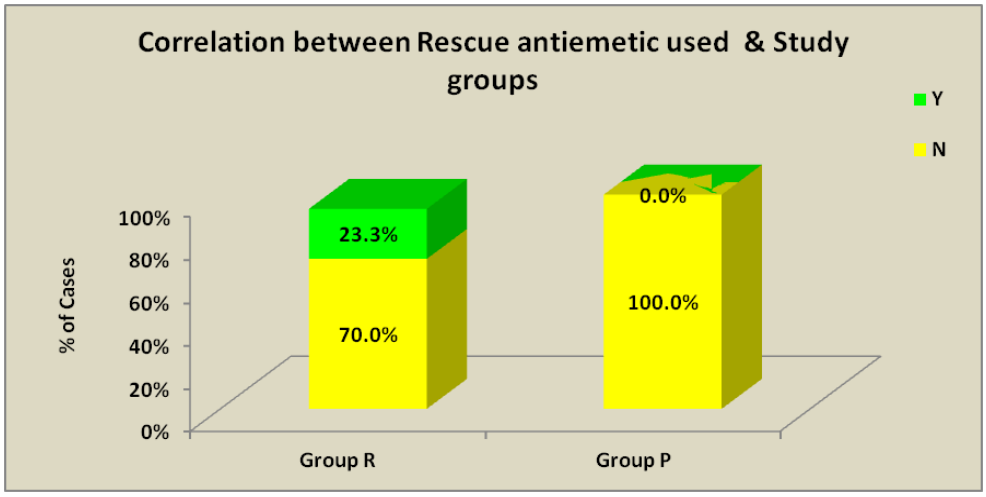

Figure 13: Correlation between Rescue Antiemetic used and Study Groups

Rescue antiemetic (Inj Dexamethasone 4 mg) has been used only in Group R (p=0.011)

Adverse Effects

Table 11: Adverse Effects

Adverse Effects	Group R		Group P		P Value
	Frequency	%	Frequency	%	
None	27	90%	24	80.0%	0.365
1 (Headache)	3	10.0%	3	10.0%	
2 (Dizziness)	0	0.0%	1	3.3%	
3 (Drowsiness)	0	0.0%	2	6.7%	
Total	30	100%	30	100%	

p value is not significant (p>0.05)

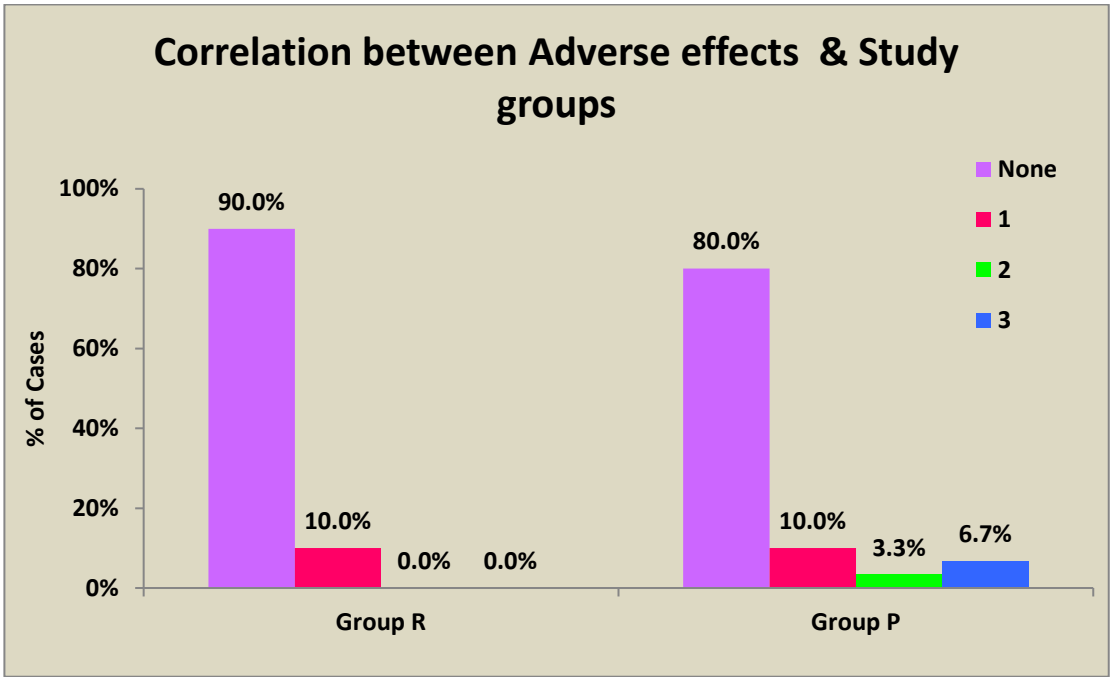

Figure 14: Correlation between Adverse Effects and Study Groups

Frequency of Adverse Effects is comparable in both the groups (p>0.05)

Patient Satisfaction

Table 12: Patient Satisfaction

Patient Satisfaction	Group R		Group P		P Value
	Frequency	%	Frequency	%	
D (Dissatisfied)	7	23.3%	0	0.0%	0.011
N (Neutral)	9	30.0%	10	33.3%	0.781
S (Satisfied)	14	46.7%	20	66.7%	0.118
Total	30	100%	30	100%	

p value is significant in the Dissatisfied group (p<0.05)

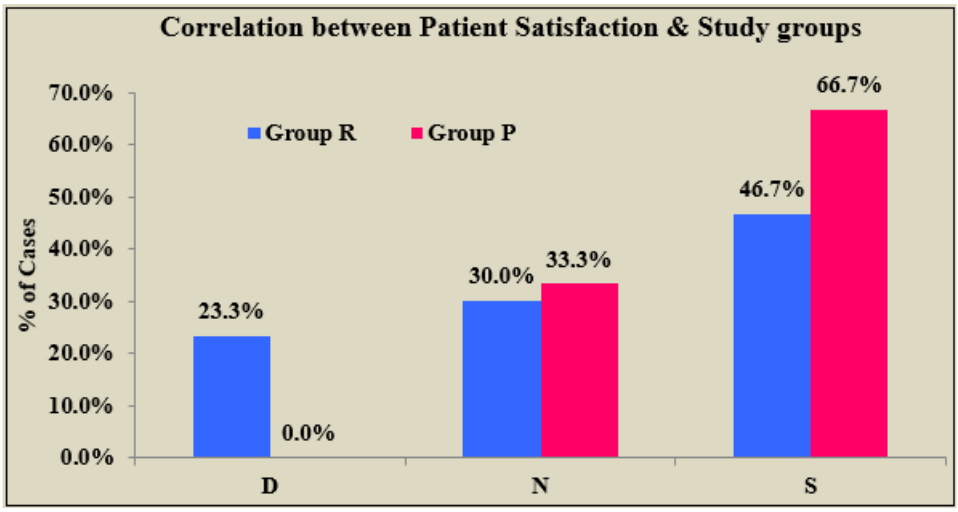

Figure 15: Correlation between Patient Satisfaction and Study Groups

Patient dissatisfaction was lower in Group P as compared to Group R (p=0.011)

6. Discussion

Postoperative Nausea and Vomiting is one of the most common and undesirable side effects following surgery.

5-HT_3 receptor stimulation is the primary event in initiation of vomiting reflex. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT_3 receptors on the CTZ and also by releasing serotonin from the enterochromaffin cells of the small intestine and subsequent stimulation of 5-HT_3 receptors on vagus nerve afferent fibres 5-HT_3 receptor antagonists are commonly used as they are more effective in PONV prevention and treatment and have fewer side effects.[80]

Palonosetron is a potent 5-HT_3 receptor antagonist. It has a greater binding affinity and longer half life than older 5-HT_3 receptor antagonists like ondansetron. Recent receptor binding studies suggest that palonosetron interacts with 5-HT_3 receptors in an allosteric, positively cooperative manner at sites different from those that bind with ondansetron and granisetron.[65]

Ramosetron is a highly selective, long acting 5-HT_3 receptor antagonist. It has prolonged activity and greater affinity to 5-HT_3 receptors than older 5-HT_3 receptor antagonists like ondansetron and granisetron

There have been previous studies comparing either ramosetron[12] or palonosetron[11] with ondansetron, but a direct comparison between the two in middle ear surgery has not yet been done.

A randomised controlled trial conducted by Xiong, et al.[11] concluded that palonosetron provides better prophylaxis against early PON (0–6 hr), late PON (6–24 hr), and late POV (6–24 hr), compared to ondansetron. However, this analysis was conducted for any elective surgery and not specifically middle ear surgeries.

Gao, et al.[81] found ramosetron to be more effective than ondansetron for prophylaxis of Postoperative vomiting at 0–24 hrs with fewer side effects.

In terms of adverse events related to the administration palonosetron or ramosetron, two studies were found. Kim, et al.[82] and Lee, et al.[83] compared the efficacy of palonosetron and ramosetron for prevention of PONV after gynaecological laparoscopic surgery. Both the studies commented that there were no differences between groups with regards to headache and dizziness. While there was a considerable difference in the adverse events that were evaluated in each study, the most commonly noted complications were headache, dizziness, and constipation.

In our study, the demographic data like age, sex and BMI were comparable in both the groups. Patients in the study were either ASA grade 1 or 2 and were equally distributed between the two groups. Duration of anaesthesia was comparable between the groups. (Anaesthesia time was defined as the time from anaesthetic induction till the patient was shifted to post anaesthesia care unit).

PONV score at the time of reversal, 0-2 hours, 2-6 hours and 12-24 hours were comparable between the two groups. However, PONV score during 6-12 hours was higher in ramosetron group compared to palonosetron group. 4 patients (13.3%) had nausea and 5 patients (16.7) had vomiting in the ramosetron group as compared to 2 patients (6.7%) having nausea in the palonosetron group. No patient had vomiting in the palonosetron group. This difference of PONV Score was found to be statistically significant with a p value of less than 0.05

Incidence of PONV episodes was comparable at time of reversal, during 0-2 hours, 2-6 hours and 12-24 hours between the two groups. However, higher incidence of PONV episodes was seen during 6-12 hours in ramosetron group compared to palonosetron group. 9 patients (30%) exhibited PONV episodes in ramosetron group as compared to 2 patients (6.7%) in the palonosetron group. This difference of PONV episodes during 6-12 hours was found to be statistically significant ($p<0.05$).

The comparable PONV score and PONV episodes during 12-24 hours may be attributed to reduced exposure to risk factors for PONV during this time period, such as washout of anaesthetic agents, absence of surgical stimuli and use of non emetogenic drugs like paracetamol and diclofenac for pain relief. It may also be attributed to use of rescue antiemetic before this time period.

Overall, Rescue antiemetic (Inj Dexamethasone 4 mg) was used in 7 patients (23.3%) belonging to ramosetron group. No rescue antiemetic was used in palonosetron group. This difference was statistically significant ($p<0.05$).

The frequency of adverse effects such as headache, dizziness, drowsiness and injection site reaction was not statistically significant between the two groups ($p>0.05$)

Patient satisfaction was labelled as satisfied, neutral or dissatisfied. Number of satisfied and neutral patients were comparable between the two groups. However, no Dissatisfied patient was seen in Group P while 7 patients (23.3%) were dissatisfied in Group R. This difference was statistically significant ($p<0.05$)

Study Limitations

This study was performed in a single centre with a small sample size of 60 patients. Further multicentre studies need to be conducted with a large sample size on a large scale of population.

7. Summary and Conclusion

1) The study was done to compare intravenous palonosetron 1mcg/kg and ramosetron 0.3mg in prevention of PONV in 60 adult patients undergoing middle ear surgery under general anaesthesia and also to compare secondary variables like requirement of rescue anti-emetic (inj dexamethasone 4 mg iv), adverse effects and patient satisfaction.
2) The demographic study of both the groups showed that demographic data like age and weight were comparable in both the groups, the patients in the study were either ASA grade 1 or 2 and were equally distributed between the two groups and the duration of anaesthesia was comparable.
3) Palonosetron has a longer half life that is why it was administered at the time of induction while ramosetron, with a shorter half life was administered at the end of surgery.
4) It was observed that the PONV score and Incidence of PONV episodes were significantly lower in the palonosetron group than in the ramosetron group in 6 to12 hours post operative period. In our study palonosetron was superior to ramosetron for prophylaxis of PONV during 6-12 hr period while at the time of

reversal, 0-2 hrs, 2-6 hrs and 12-24 hrs, palonosetron was as effective as ramosetron in controlling PONV.

5) The comparable PONV score between 12-24hrs hours may be explained by decrease in the number of risk factors for PONV that the patient was exposed to during that period such as washout of anaesthetic agents and metabolism of opioids used in PACU/recovery room, absence of surgical stimuli and use of non emetogenic drugs like Paracetamol and Diclofenac for pain relief. It may also be attributed to use of rescue antiemetic before this time period.
6) Another parameter used by us to compare the two drugs was the requirement of rescue anti-emetic (inj dexamethasone 4 mg) in postoperative period. We observed that rescue anti-emetic was required only in the ramosetron group. This difference was statistically significant.
7) The frequency of adverse effects reported by the patients in both the groups was comparable. Most adverse effects were mild and transient thus reflecting the similar safety profile of both the drugs.
8) Number of satisfied and neutral patients was comparable between the two groups. However, higher incidence of dissatisfied patients was seen in the ramosetron group. This difference was statistically significant.
9) We recommend the use of palonosetron over ramosetron for prophylaxis of PONV considering better control of PONV score, lesser incidence of PONV, similar safety profile with longer duration of action which can make recovery smoother for patients and decrease healthcare costs.

7.1 Conclusion

PONV (postoperative nausea and vomiting) is one of the most common complications for patients undergoing middle ear surgery under general anaesthesia. The consequences of PONV are physical, surgical and anaesthetic complications for patients as well as financial implications for the hospitals or institutions. Hence, prophylactic antiemetic therapy is needed for all these patients.

There are multiple risk factors associated with the occurrence of PONV and several risk factor scoring systems have been described in literature of which the simplified risk scoring by Apfel et al was followed by us. This can have implication in risk factor reduction for better control of PONV in high risk patient group.

In our study palonosetron has been found to be superior to ramosetron for PONV prophylaxis. It has similar safety profile as ramosetron but longer duration of action which can have implications in providing a better and longer duration of prophylaxis.

Depending on the level of risk, prophylaxis should be initiated with monotherapy or combination therapy using interventions that reduce baseline risk, and antiemetics combined with antiemetic of a different class based on modern multimodal approach especially in a busy clinical environment such that it becomes an integral part of anaesthesia practice.

8. Recommendations

- Ours was a single centre study which included only 60 patients. A multicentre study with a large sample size is required to lend further credence to the present study.
- Further trials are required to conclusively prove the superiority of Palonosetron over Ramosetron for PONV prophylaxis.

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APPENDICES

STUDY PROFORMA
Demographic Characteristics
NAME: DATE OF SURGERY:
AGE: OT:
SEX: SURGEON:
SERIAL NUMBER:
WARD/BED NUMBER:
START TIME OF SURGERY:
BMI: END TIME OF SURGERY:
DURATION OF SURGERY:
(in minutes)
DIAGNOSIS:

PROCEDURE:
ASA PS –
I ( )
II ( )
GROUP ALLOCATED:
DRUG AND DOSE:

Pre Anaesthetic Evaluation
Previous anaesthesia/PONV:
Associated medical problems:
Cardiovascular system:
Respiratory system:
GIT system:
CNS:
Nil by mouth status:

Observations to be recorded
PONV Score
0 – no nausea/vomiting/retching/no rescue antiemetic given
1 – nausea
2 – retching
3 – vomiting

All the patients to be asked for nausea and to be observed for vomiting and retching

TIME DRUG (GROUP A/B)
At the time of reversal/awakening
Nausea, Vomiting, Retching YES/NO

0-2 hours
PONV Score
Number of PONV episodes
Rescue anti-emetic used

2-6 hours
PONV Score
Number of PONV episodes
Rescue anti-emetic used

6-12 hours
PONV Score
Number of PONV episodes
Rescue anti-emetic used

12-24 hours
PONV Score
Number of PONV episodes
Rescue anti-emetic used

ADVERSE EFFECTS MONITORING
Adverse Effect Drug (Group A/B)
Headache
Dizziness
Drowsiness
Injection site reaction

PATIENT SATISFACTION
Drug (Group A/B)
Satisfied
Neutral
Dissatisfied

CLASSIFICATIONS/SCORES

1. American Society of Anaesthesiologists Physical Status Classification

ASA 1	Healthy patient without organic, biochemical, or psychiatric disease.
ASA 2	A patient with mild systemic disease, e.g., mild asthma or well-controlled hypertension. No significant impact on daily activity. Unlikely impact on anesthesia and surgery.
ASA 3	Significant or severe systemic disease that limits normal activity, e.g., renal failure on dialysis or class 2 congestive heart failure. Significant impact on daily activity. Likely impact on anesthesia and surgery.
ASA 4	Severe disease that is a constant threat to life or requires intensive therapy, e.g., acute myocardial infarction, respiratory failure requiring mechanical ventilation. Serious limitation of daily activity. Major impact on anesthesia and surgery
ASA 5	Moribund patient who is likely to die in the next 24 hours with or without surgery
ASA 6	Brain-dead organ donor

2. Post-Operative Nausea and Vomiting (PONV) Score
0 No nausea/ vomiting/ retching/no rescue antiemetic required
1 Nausea
2 Retching
3 Vomiting

MASTER CHART

S.No	CR. No	Group	Age (Years)	Sex	BMI (kg/m2)	ASA Grade	Duration (min)	PONV Score					PONV Episodes					Rescue antiemetic used	Adverse effects	Patient Satisfaction
								At Time of Reversal/ awakening	0-2 hrs	2-6 hrs	6-12 hrs	12-24 hrs	At Time of Reversal/ awakening	0-2 hrs	2-6 hrs	6-12 hrs	12-24 hrs			
1	201931753	R	42	M	29.3	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
2	201933819	R	18	M	26.02	1	240	0	0	0	0	0	-	-	-	-	-	N	-	S
3	201931718	R	19	M	22.03	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
4	201933501	R	20	M	19.9	1	120	0	0	1	0	0	-	-	-	-	-	N	-	N
5	20193313	R	35	M	18.8	2	240	0	0	1	3	0	-	-	-	1	-	Y	-	D
6	201937064	R	49	F	22.6	1	180	0	0	0	1	1	-	-	-	-	-	N	1	N
7	201937298	R	23	F	20.8	2	180	0	1	0	0	0	-	1	-	-	-	N	-	N
8	201938457	R	51	F	20.8	2	180	0	0	0	0	0	-	-	-	-	-	N	-	S
9	201940747	R	35	F	22.2	1	180	0	1	0	0	0	-	1	-	-	-	N	-	N
10	201942361	R	42	M	24.6	2	180	0	0	0	0	0	-	-	-	-	-	N	-	S
11	201944825	R	55	M	24.2	1	180	0	0	0	3	0	-	-	-	1	-	Y	-	D
12	201947759	R	18	M	18.5	1	120	0	1	2	0	0	-	-	1	-	-	Y	-	D
13	201943169	R	19	M	18.6	1	120	0	0	0	0	0	-	-	-	-	-	N	-	S
14	201949657	R	29	M	22.1	1	120	0	0	1	3	0	-	-	-	1	-	Y	-	D
15	201946384	R	31	M	19.5	1	120	0	0	0	3	0	-	-	-	1	-	Y	-	D
16	201962536	R	19	M	19.5	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
17	201952419	R	45	F	22.1	2	150	0	0	0	1	0	-	-	-	-	-	N	-	N
18	201957267	R	29	F	20.8	1	195	0	0	0	0	0	-	-	-	-	-	N	-	S
19	201960668	R	19	M	18.6	1	135	0	0	0	0	0	-	-	-	-	-	N	-	S
20	201966210	R	30	F	21.2	1	180	0	0	0	1	1	-	-	-	-	-	N	-	N
21	201966208	R	48	M	24.2	2	180	0	0	1	3	0	-	-	-	1	-	Y	-	D
22	201966769	R	23	M	19.7	1	170	0	0	0	0	0	-	-	-	-	-	N	1	N
23	201970514	R	21	M	18.9	1	130	0	1	0	0	0	-	-	-	-	-	N	-	N
24	201970515	R	19	F	19.1	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
25	201972897	R	35	F	21.2	1	120	0	0	0	0	0	-	-	-	-	-	N	-	S
26	201973896	R	20	F	19.2	1	140	0	0	0	0	0	-	-	-	-	-	N	-	S
27	201978952	R	40	F	24.6	2	165	0	1	3	0	0	-	-	1	-	-	Y	-	D
28	201979061	R	22	M	21.2	1	120	0	0	0	1	1	-	-	-	-	-	N	1	N
29	201983497	R	22	M	23.3	1	175	0	0	0	0	0	-	-	-	-	-	N	-	S
30	201983835	R	22	F	19.6	1	120	0	0	0	0	0	-	-	-	-	-	N	-	S
31	201953438	P	27	M	24.7	1	90	0	0	0	0	0	-	-	-	-	-	N	-	S
32	201957951	P	29	M	20.1	2	150	0	0	0	0	0	-	-	-	-	-	N	-	S
33	201959600	P	53	F	24.1	2	120	0	0	0	0	0	-	-	-	-	-	N	-	S
34	201948620	P	20	F	24.4	1	120	0	0	0	0	0	-	-	-	-	-	N	-	S
35	201960959	P	19	M	22.0	1	150	0	0	0	0	0	-	-	-	-	-	N	-	S
36	201935342	P	20	M	21.5	1	120	0	0	0	0	0	-	-	-	-	-	N	-	S
37	201942385	P	19	F	18.7	1	120	0	0	0	0	0	-	-	-	-	-	N	1	N
38	201947761	P	23	F	18.5	1	120	0	0	0	0	0	-	-	-	-	-	N	-	S
39	201950534	P	25	M	22.2	1	180	0	0	0	1	0	-	-	-	-	-	N	-	N
40	201962521	P	35	M	24.7	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
41	201928037	P	24	F	19.0	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
42	201928014	P	27	F	22.5	1	180	0	0	1	0	0	-	-	-	-	-	N	-	N
43	201950740	P	27	F	22.6	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
44	201951567	P	21	F	23.5	1	170	0	0	0	0	0	-	-	-	-	-	N	-	S
45	201951826	P	19	F	19.6	1	180	0	0	1	0	0	-	-	-	-	-	N	1	N
46	201958892	P	21	F	19.8	1	120	0	0	0	0	0	-	-	-	-	-	N	-	S
47	201959603	P	40	F	23.4	2	240	0	0	0	1	0	-	-	-	-	-	N	2	N
48	201962822	P	19	M	20.8	1	140	0	0	0	0	0	-	-	-	-	-	N	3	N
49	201967391	P	20	F	19.6	1	105	0	0	0	0	0	-	-	-	-	-	N	-	S
50	201968487	P	65	F	20.8	2	155	0	1	0	0	0	-	-	-	-	-	N	3	N
51	201968482	P	21	F	18.6	1	105	0	0	0	0	0	-	-	-	-	-	N	-	S
52	201970663	P	20	M	21.6	1	150	0	0	0	0	0	-	-	-	-	-	N	1	N
53	201973222	P	34	F	23.8	1	150	0	0	1	0	0	-	-	-	-	-	N	-	N

S.No	CR. No	Group	Age (Years)	Sex	BMI (kg/m2)	ASA Grade	Duration (min)	PONV Score					PONV Episodes					Rescue antiemetic used	Adverse effects	Patient Satisfaction
								At Time of Reversal/ awakening	0-2 hrs	2-6 hrs	6-12 hrs	12-24 hrs	At Time of Reversal/ awakening	0-2 hrs	2-6 hrs	6-12 hrs	12-24 hrs			
54	201976149	P	23	M	22.3	1	190	0	0	0	0	0	-	-	-	-	-	N	-	S
55	201978956	P	25	F	20.8	1	180	0	0	0	0	0	-	-	-	-	-	N	-	S
56	201980146	P	22	F	20.6	1	165	0	1	0	0	0	-	-	-	-	-	N	-	N
57	201981819	P	32	F	20.7	1	150	0	0	0	0	0	-	-	-	-	-	N	-	S
58	201982766	P	32	M	23.1	2	180	0	0	0	0	0	-	-	-	-	-	N	-	S
59	201984628	P	30	F	20.5	1	135	0	0	0	0	0	-	-	-	-	-	N	-	S
60	201985616	P	24	M	22.8	1	155	0	0	0	0	0	-	-	-	-	-	N	-	S

Key To Master Chart

- **GROUP**
  - R- Inj Ramosetron 0.3 mg iv
  - P- Inj Palonosetron 1 mcg/kg iv

- **PONV SCORE**
  - 0- No nausea/ vomiting/retching/no rescue antiemetic given
  - 1- nausea
  - 2-retching
  - 3- vomiting

- **RESCUE ANTIEMETIC USED (INJ DEXAMETHASONE 4 MG)**
  - Y- YES
  - N- NO

- **ADVERSE EFFECTS**
  - 1- HEADACHE
  - 2- DIZZINESS
  - 3- DROWSINESS
  - 4- INJECTION SITE REACTION

- **PATIENT SATISFACTION**
  - 1- Satisfied
  - 2- Neutral
  - 3- Dissatisfied