"TO COMPARE THE EFFICACY OF RAMOSETRON AND GRANISETRON IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"

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ENDORSEMENT

This is to certify that the dissertation titled **"TO COMPARE THE EFFICACY OF RAMOSETRON AND GRANISETRON IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"** is a bonafide research work done by **REG NO.BA0113001.**

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LIST OF ABBREVIATIONS USED

ASA	–	American society of Anaesthesiologists
cm	–	Centimetre
CNS	–	Central nervous system
CO_2	–	Carbon dioxide
CVS	–	Cardiovascular system
ECG	–	Electrocardiogram
$ETCO_2$	–	End tidal carbon dioxide
GIT	–	Gastro-intestinal tract
Hb	–	Haemoglobin
Inj.	–	Injection
IV	–	Intravenous
Kg	–	Kilogram
MAO	–	Mono Amine Oxidase
N_2O	–	Nitrous oxide
µg	–	Microgram
mg	–	Milligram
Min	–	Minute
ml	–	Millilitre
PACU	–	Post Anaesthesia Care Unit
PONV	–	Post-operative nausea and vomiting
SPO_2	–	Saturation percentage of oxygen
α	–	Alpha
β	–	Beta

ABSTRACT

Background and objectives

Postoperative nausea and vomiting (PONV) is one of the common side effects faced by anaesthesiologists in day to day practice. It is physiologically and emotionally an unpleasant experience for the patient in the early postoperative period. The incidence of PONV is between 20 to 30% in patients recovering from anaesthesia. The main objective of this study was to compare the efficacy of ramosetron and granisetron in preventing PONV in patients undergoing laparoscopic appendicectomy under general anaesthesia.

Methodology:

The study was conducted in the Department of Anaesthesiology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi in patients undergoing laparoscopic appendicectomy between January 2014 to December 2014. Approval from the ethical committee was obtained. Written informed consent was taken from the patients who were to be included in this study. ASA I and II patients in the age group of 18 to 60 years who underwent laparoscopic appendicectomy were included in the study. They were then randomly divided into two groups: Group R (Ramosetron) and Group G (Granisetron) using a computer generated table. After extubation the incidence of PONV was recorded every six hours using the PONV scoring system.

0 – No nausea

1 – Nausea

2 – Retching

3 – Vomiting

Patients with PONV score ≥2 received injection dexamethasone 0.1mg/kg IV as rescue anti-emetic.

Results

PONV scores were lower in the ramosetron group and the difference was significant in the first 18 hours. PONV incidence (PONV score≥1) was 1.5%, 3.6% and 9.1% in Group R compared to 61.9%, 61.9%and 34.5% in Group G during the first, second and third six hours post-operatively (p-value<0.001). Incidence of emetic episodes (PONV score≥2) was similar in both the groups (p-value>0.05).

Conclusions

From our study we conclude that ramosetron is better than granisetron at preventing PONV after laparoscopic appendicectomy under general anaesthesia. We also found that both are equally effective at preventing emetic episodes.

Keywords: Ramosetron, Granisetron, PONV, laparoscopic appendicectomy

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INTRODUCTION

Postoperative nausea and vomiting (PONV) remains a common problem after general anesthesia and can delay the patient's discharge or result in unexpected hospital admission[1]. It occurs in 20 to 30% of patients and is the second most common complaint after pain. PONV can be such an unpleasant experience that patients often rate it worse than postoperative pain[2].

PONV in addition to being extremely unpleasant to the patients can also cause post-surgical morbidities like wound dehiscence and surgical site bleeding.

Modern anesthesia focuses on ensuring a smooth and uneventful recovery from anesthetics. Hence techniques and drugs have been modified to reduce the incidence of PONV. However, PONV still occurs after surgery and anesthesia and its description as "the big little problem" encapsulates the general perception[3].

Patient factors which increase PONV include the female gender, obesity and history of gastro oesophageal reflux disease. Anaesthesia factors include use of volatile inhalational agents and opioids. Surgical risk factors include ocular surgery to correct strabismus, middle ear surgery, oropharyngeal surgery like tonsillectomy etc.

Many drugs have been used to prevent and treat PONV eg. dopamine antagonists, antihistamines, anticholinergics and phenothiazine derivatives. But they are associated with side effects like sedation, dysphoria, extra pyramidal symptoms, dry mouth, urinary retention, tachycardia and prolonged QT interval[4].

5-hydroxytryptamine type 3 ($5HT_3$) receptor antagonists have revolutionized the management of PONV. Granisetron has been used effectively for the treatment of PONV and chemotherapy induced nausea and vomiting(CINV) since the early 90s[5].

Ramosetron has been more recently introduced and is claimed to be more potent and longer acting than granisetron[6].

Laparoscopy, general anaesthesia and surgeries involving bowel manipulation like appendicectomy increase the chances of PONV[2].

Hence the present study has been undertaken to compare the efficacy of granisetron and ramosetron in preventing PONV in patients undergoing laparoscopic appendectomy under general anaesthesia.

AIMS AND OBJECTIVES

To compare the efficacy of ramosetron and granisetron in preventing post-operative nausea and vomiting in patients undergoing laparoscopic appendicectomy under general anaesthesia.

REVIEW OF LITERATURE

Post-operative nausea and vomiting (PONV) is a common complication of anaesthesia and surgery causing both dissatisfaction and discomfort to the patient. PONV can have medical and economic consequences. PONV can vary from a mild nausea causing a minor annoyance to the patient to repeated and continuous retching and vomiting which can cause aspiration, suture dehiscence or bleeding from the surgical site.

Many types of drugs have been used to prevent and treat PONV. These include antihistamines, phenothiazines, dopamine antagonists, anti-cholinergics etc. Most have side effects like sedation, tachycardia, dry mouth, urinary retention etc. $5HT_3$ antagonists are newer class of drugs which have proved to be efficacious and safe in preventing and treating PONV.

PONV has been a part of anaesthesia and surgery since the very beginning of these specialities. The incidence of PONV varies between 20% and 30% depending on surgical and patient factors[2]. Several studies have been made to find out the most economical and most preferred drug to prevent PONV.

5-HT_3 receptor antagonists like ondansetron, tropisetron, granisetron and ramosetron have revolutionized the treatment of PONV due to their effectiveness and favourable safety profiles. They are chemically different compounds but have a very specific antagonistic activity at the 5-HT_3 receptor.

Fuji Y et al.[7] in 1999 compared ramosetron versus granisetron for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. 80 patients split equally into groups of 40 each received either 3mg granisetron or

0.3mg ramosetron IV at the end of surgery. It was found that ramosetron was more effective than granisetron for prevention of PONV during the initial 48 hours after anaesthesia for laparoscopic cholecystectomy.

Kranke P et al.[8] in 2000 performed a prospective, randomized, double-blinded study in which they evaluated the efficacy of granisetron and ramosetron for preventing postoperative nausea and vomiting (PONV) in major gynaecological surgery. They concluded that prophylactic therapy with ramosetron is more effective than granisetron for the long-term prevention of PONV after major gynaecological surgery.

Fuji Y et al.[9] in 2000 did a prospective, randomized, double-blinded, placebo-controlled trial for ramosetron in preventing PONV in women undergoing gynaecological surgery. The report shows that ramosetron 0.3 mg IV is an effective antiemetic for preventing PONV during 0-48 h after anaesthesia in female patients undergoing gynaecological surgery. Increasing the dose to 0.6 mg provided no further benefit.

But a study done by S.Y. Lee et al[10] in 2002 to compare the antiemetic effects and safety of granisetron and ramosetron in patients undergoing thyroidectomy came to a different conclusion. Two groups of 36 patients each received either granisetron 20mcg/kg IV or ramosetron 4µg/kg IV over 2-5 minutes before induction of anaesthesia. Another group of 41 patients received placebo with normal saline. Incidence of PONV was similar in the placebo and ramosetron group. They found that only granisetron and not ramosetron was superior to placebo in the prevention of PONV after thyroidectomy.

A meta-analysis of ramosetron for the prevention of postoperative nausea and vomiting done by Kim W et al.[11] in 2011 found that ramosetron is effective and safe in children and adults without serious adverse effects compared to other drugs or placebo.

I Bhat et al.[12] in 2013 compared the efficacy of ramosetron in prevention of PONV in females after laparoscopic cholecystectomy and compare it with granisetron. Patients were allocated into two groups of 50 each and given either granisetron 2mg or ramosetron 0.3mg IV. They found that ramosetron is a better antiemetic and is superior to granisetron in providing prolonged relief from PONV in these surgeries. They found that ramosetron has a longer antiemetic duration and was associated with longer emesis free periods.

Maulana M et al.[13] in 2013 compared ramosetron and ondansetron for control of PONV following laparoscopic cholecystectomy. Two groups of 65 patients each received either ramosetron 0.3mg or ondansetron 4mg IV. They concluded that ramosetron was a more effective antiemetic in patients undergoing laparoscopic cholecystectomy.

Kuldip G et al.[14] in 2014 compared the efficacy of ondansetron, granisetron and ramosetron in preventing PONV in patients undergoing surgeries under general anaesthesia. Patients were divided into groups of 30 each and administered either injection ondansetron 0.1mg/kg or injection granisetron 40mcg/kg IV or injection ramosetron 0.3mg IV. Postoperative nausea, retching, vomiting and the need of a rescue antiemetic were scored. It was concluded that up to 3 hours postoperative period all the three study drugs were comparable to each other. But both granisetron

and ramosetron were better than ondansetron from 3 hours up to 24 hours postoperative period.

Waqar-ul-Nisa et al.[15] in 2014 compared ramosetron and granisetron in preventing postoperative nausea and vomiting in patients following thyroidectomy. Two groups of 50 patients each were administered either granisetron 2mg IV or ramosetron 0.3mg IV. There was no significant difference in PONV scores between the two groups immediately after extubation and up to 12 hours postoperatively, however a statistically significant difference was observed in PONV scores 12-18 hours and 18-24 hours postoperatively between the two groups. They came to the conclusion that ramosetron is a better antiemetic and is superior to granisetron in providing prolonged relief from postoperative nausea and vomiting following thyroidectomy in females[15].

Kailash Chandra et al.[16] did study on attenuation of PONV with granisetron and ramosetron after general anaesthesia was published in 2015. 90 patients were divided into three groups and received either granisetron 10mcg/kg IV or ramosetron 0.3mg IV or normal saline 2ml IV. They found that both the drugs prevent postoperative nausea and vomiting but granisetron was more effective than ramosetron.

Another study was done by Thakur R and Naik R[17] in 2015 compared ramosetron, granisetron and ondansetron for prevention of PONV in patients undergoing caesarean section under spinal anaesthesia. 150 patients were divided into three groups and received either ondansetron 4 mg IV, granisetron 3 mg IV or ramosetron 0.3 mg IV. They concluded that ramosetron followed by granisetron was

better than ondansetron for prophylaxis against PONV after caesarean section under spinal anaesthesia

Even though many studies have been done comparing ramosetron and granisetron, none have been done comparing them in the context of laparoscopic appendicectomy. Hence we have done this study to compare the two drugs in patients undergoing laparoscopic appendicectomy under general anaesthesia.

BASIC SCIENCES

The term nausea is derived from Greek word "*nautia*" meaning seasickness[18].Nausea is defined as a subjective sensation of unease and discomfort in the stomach with an urge to vomit which is referred to the pharynx and upper abdomen, and is accompanied by loss of gastric tone, duodenal contractions and reflux of intestinal contents into the stomach. Retching is defined as laboured, spasmodic, rhythmic contractions of the respiratory muscles including diaphragm, chest wall and abdominal wall muscles *without* the expulsion of gastric contents. Vomiting or emesis is the forceful expulsion of gastric contents from the mouth and is brought about by the powerful sustained contractions of the abdominal muscles, descent of diaphragm and opening of the gastric cardia.

Mechanism of emesis

Like any other reflex, the vomiting reflex has three major components, these are:

- Emetic detectors
- Integrative mechanism
- Motor components

Emetic detectors

There are various detectors which form the sensory component of the vomiting reflex. They include:

1. Abdominal visceral afferents

The gut wall mucosa is capable of detecting the accidental ingestion of toxins and is capable of activating the vomiting reflex. Ingested toxins and those produced by a pathogen can stimulate this reflex. Vagal afferent fibres carry the signals from

the intestinal mucosa. Electrical stimulation of these vagal afferents from the intestinal mucosa induces vomiting within 20 seconds[19].

These vagal afferents carry signal from two types of receptors.

a. Mechanoreceptors: These are stimulated by mechanical stretching/distension of the intestine. Examples include distension produced by intestinal obstruction and due to overeating. They are located in the muscular layer of the gut.
b. Chemoreceptors: These are located in the mucosa of the foregut mainly. They respond to hypertonic contents, strong alkalis, acids, temperature and toxins.

2. Area Postrema

This is medullary structure which plays a vital role in the vomiting reflex. It is small protuberance found at the inferoposterior limit of the fourth ventricle[20]. It is considered to be a circumventricular organ because its endothelial cells do not allow tight junctions and hence there is no definitive blood brain barrier here. This allows for free exchange of molecules between blood and brain tissue. This part is known as the chemoreceptor trigger zone(CTZ). This organ is able to detect toxins and other emetogenic substances in the blood stream. Dopamine receptors of the subtype D-2 modulate the reflex at this level.

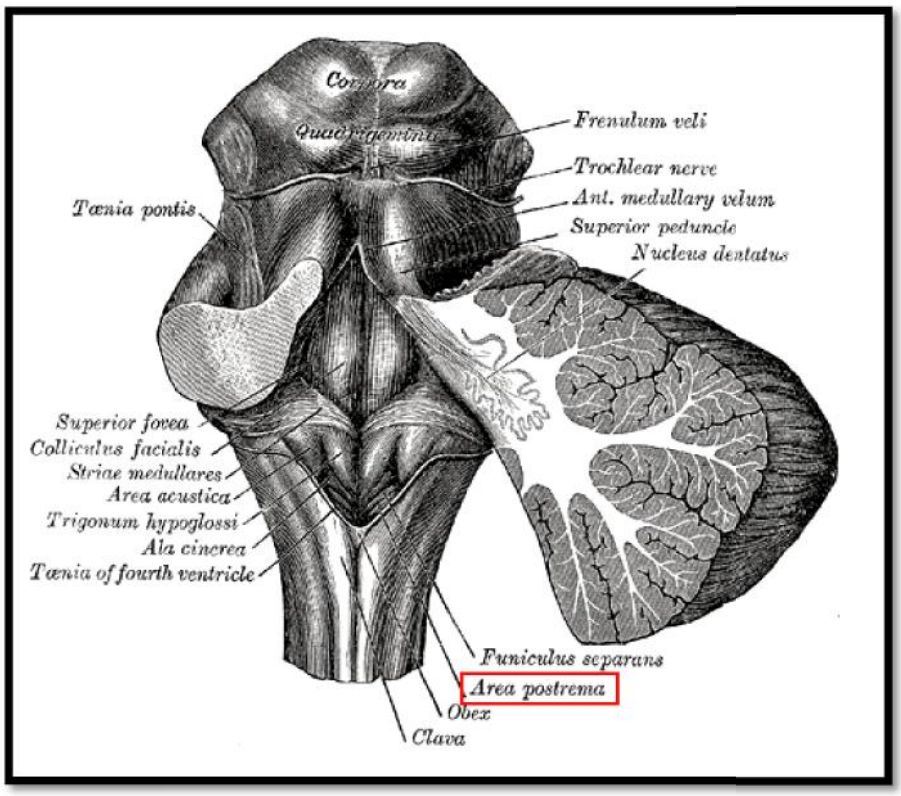


Figure 1: Medulla showing area postrema at the floor of the fourth ventricle

3. Vestibular system

Vestibular nucleus is the relay station for spatial and motion input, and through its action on the CTZ it can mediate the nausea and vomiting of "motion sickness" or "sea sickness". Position of the head can stimulate the vomiting centre and influenceemetic response to drugs. Motion stimulates the receptors of the labyrinth and the impulses are transmitted by the vestibular nuclei into the cerebellum. After passing through the uvula and nodule of the cerebellum, the signals are transmitted to CTZ and then to the emetic centre to cause vomiting. Muscarinic and histaminic receptors modulate the vomiting reflex at this site.

4. Higher centres

Input from higher centres like the limbic centre can induce nausea and vomiting. They modulate the sensitivity of the brain stem emetic system. They are also involved in emesis induced due to strong emotional responses like disgust.

5. Miscellaneous

Nausea and vomiting are seen whenever there is increase or decrease in intracranial tension. Unpleasant taste or smell can evoke vomiting. Mechanical stimulation of the pharyngeal afferents projecting to the brain stem in the glossopharyngeal nerve and stimulation of Arnold's nerve can cause nausea and vomiting. Nausea and vomiting occurring in association with myocardial infarction (MI) is mainly because of stimulation of ventricular cardiac afferents[21].

Integrative Mechanism: The Vomiting Centre

Vomiting is a complex stereotyped response involving coordination between the sensory and motor components of the nervous system. It involves detection of the emetic stimulus and then have the body respond to it via the act of emesis which is a coordinated effort of the diaphragm, chest wall and gastro intestinal musculature. Studies have shown that the parvicellular reticular formation has access to the motor pathways responsible for the visceral and somatic output involved with vomiting[22]. This is situated in the brainstem in the lateral reticular formation which is very close to the nucleus tractus soliatarius. The chemoreceptor trigger zone(CTZ) can also be considered to be an extension of the

vomiting centre as it has integrative functions in additions to its sensory role in the vomiting reflex.

Motor Components of the Vomiting Reflex:

The reflex is divided into three phases:

Pre-ejection Phase(Prodromal Phase):

This phase is dominated by the subjective feeling of nausea and is associated with autonomic responses. These responses include heavy salivation, swallowing, cold sweating, tachycardia and pupillary dilation. A sub-emetic stimulus may elicit this response without any actual vomiting or retching. This phase may last minutes, hours or even days as seen in the first trimester of pregnancy, during chemotherapy and sea sickness. This autonomic response can be explained by the proximity of the vomiting centre to the vagal and other autonomic nuclei in the brainstem.

This phase is also associated with a set of gastrointestinal changes including profound relaxation of the proximal stomach. This is mediated by the vagus nerve. Along with this a retrograde contraction starts in the mid small intestine and travels towards the stomach. This anti-peristaltic wave travels at the rate of 2 to 3 cm/sec. As a result of this the duodenum becomes over distended. This distension is what causes the progress of the rest of the vomiting reflex. Strong contractions occur both in the duodenum and stomach and there is a lowering of the lower oesophageal sphincter tone. This allows the vomitus to move into the oesophagus from where it can be expelled during the ejection phase.

Ejection Phase:

Impulses are transmitted by both vagal and sympathetic afferents to the bilateral vomiting centres of the medulla. Appropriate motor reactions begin. The motor impulses transmitted from vomiting centre courses to upper gastro intestinal tract through fifth, seventh, ninth, tenth and twelfth cranial nerves and through spinal nerves to the diaphragm and abdominal muscles. In this phase oesophagus and stomach play a passive role and the emesis is achieved by the active contraction of diaphragmatic, thoracic and abdominal muscles.

The vomiting reflex:

It is a complex act involving both the striated and visceral muscles. When the vomiting centre is stimulated, there occurs deep inspiration, rising of the hyoid bone and larynx to pull the crico-oesophageal sphincter open, elevation of the soft palate to close nasopharynx and glottis. Proximal stomach relaxes and a giant contraction in mid intestine propels the ingested contents into the relaxed stomach there by diluting and buffering the gastric acid.

In the final part of the vomiting act the contraction of oesophageal muscle pulls the stomach into thorax, forming an oesophageal funnel and forcing the food out of stomach by contraction of abdominal muscles against the lowered diaphragm. If the glottis is closed, only retching results; if pharynx is relaxed then the contents exit through mouth. During retching and vomiting, all animals adopt a characteristic posture that permits maximal compression of the stomach by abdominal musculature. Characteristically a wide open mouth, spine held in flexion and forceful expulsion of upper GI contents are observed[23].

Post Ejection Phase:

This phase is characterised by recovery from emesis and sequelae of vomiting. It consists of autonomic and visceral responses that return the body to a quiescent phase with or without residual nausea[24].

Cause for post-operative nausea and vomiting (PONV)

Factors influencing PONV are many; they can be classified as follows.

- Pre-operative factors
- Intra-operative factors
- Post-operative factors

Preoperative factors:

a. Food

A patient who has not been fasted prior to anaesthesia is at a higher risk of emesis[25]. Food sensitises the vagal afferents due to its volume and chemical composition. In addition to this many hormones like gastrin and motilin released by the gut in response to food in the gut sensitises the area postrema to the effects of other stimuli. This when combined with other causes of emesis like anaesthetic drugs is sufficient to induce the vomiting reflex.

b. Pre-existing comorbidities

Pre-existing conditions like poorly controlled diabetes mellitus, uremia, raised intra cranial tension, gastro oesophageal reflux disease (GERD), motion sickness etc. increase the risk of post-operative nausea and vomiting. Other factors include pregnancy, female patient, obesity and history of PONV during previous anaesthetics.

c. Anxiety and stress

These increase the risk of emesis due to increased release of catecholamines. Another consequence is excessive air swallowing or aerophagia which happens when a patient is extremely anxious and is hyperventilating. This leads to gastric distension which stimulates the vagal afferents.

d. Pre-medication

Opioid drugs decrease gastric emptying by increasing the duodenal tone. They act on the vestibular nucleus by promoting the release of leukoencephalin thereby sensitising the vestibular system. They also increase the release of 5-HT_3 by the enterochromaffin cells of the small intestine by inhibiting the tonically inhibiting neural pathways. They also act directly on the area postrema and CTZ through mu opioid receptors[26].

Intra -operative factors:

a. Intubation

Laryngoscopy and intubation when done in an insufficiently deep anaesthetic plane will stimulate the pharyngeal mechanoreceptors which evokes the gag reflex through the glossopharyngeal nerve. This can proceed to nausea and vomiting.

b. Pharmacological effects of anaesthetic agents

Interaction of anaesthetic agents with adrenergic receptors and their adreno-mimetic effect is responsible for PONV. According to recent studies, both alpha-1 and alpha- 2 receptors present in area postrema are implicated in emesis. Antiemetic centre, present in the brain stem when

active will inhibit the vomiting centre. It is very sensitive to the depressant effect of anaesthetics and recovery of the tonic activity is also slow. Thus post-operative nausea

and vomiting results from both direct effects of anaesthetic and surgery and is also facilitated by the indirect effects of prolonged inhibition of antiemetic centre.

c. Physical effects of anaesthesia

Mask ventilation produces gastric distension which stimulates vagal afferents. Intestinal distension can also occur with agents like nitrous oxide. General anaesthesia also causes reduction in gut motility and suppression of belching reflex[21]. Some agents like ether directly irritate the gastric mucosa.

d. Physiological effects of anaesthesia

Peptide hormones like angiotensin, AVP, bombesin, gastrin, somatostatin, insulin, neuropeptide Y, TRH, neurotensin and VIP released during anaesthesia and surgery activates area postrema and cause PONV.

e. Surgery

Certain surgical procedures increase the risk of PONV. Ocular surgery specially surgery to correct squint is correlated with a high incidence of PONV. Traction on the ocular muscles during this procedure stimulates afferent neural pathways to the vomiting centre via the ciliary ganglion or labyrinthine pathway. This leads to the oculo-emetic/oculo-gastric reflex.

Middle ear surgery is associated with higher incidence of PONV due to stimulation of the vestibular apparatus and Arnold's nerve. Oropharyngeal and nasopharyngeal surgery invokes emesis due to swallowed blood which stimulates enterochromaffin cells in the gut mucosa to release 5-HT_3. Pharyngeal stimulation also activates the gag reflex though the glossopharyngeal nerve which leads to emesis.

Intra-abdominal organs like the intestines, mesentery, uterus, bladder etc. are innervated by vagal and splanchnic afferents; surgery on any of these organs can stimulate the vomiting centre due to direct mechanical manipulation.

Direct manipulation of the intestine and stomach stimulates the enterochromaffin cells to release 5-HT_3 which leads to emesis.

Gynaecological surgeries especially laparoscopic surgery has a high incidence of PONV. Women are more sensitive to emetic stimuli than men. Their response also depends on the prevailing hormonal status with a four-fold increase in incidence during menstruation and a lower incidence after menopause[27].

Pregnancy sensitises the emetic mechanism. Incidence is also high after dilation and curettage. Afferents supplying the uterus, broad ligament, vagina and cervix are sensitive to mechanical stimuli like gentle probing and rubbing.

Post-operative factors

a. Residual effects of drugs

Opioids especially the long acting ones like buprenorphine present in the bloodstream stimulate the CTZ[26]. They also delay gastric emptying. Neostigmine used in reversal is also associated with vomiting. This can be explained by marked stimulation of gastric motility which stimulates the vagal afferents.

b. Postoperative pain

Pain is associated with nausea rather than vomiting[28]. The exact mechanism involved in nociceptor induced nausea is not known but two probable explanations are

- Pain raises the general alertness of the central nervous system thus making it susceptible to other emetic stimuli
- Peripheral emetic receptors are activated mainly by the release of serotonin, histamine and cytokinin.

Complications of PONV

a. Delayed recovery

PONV prolongs the stay in PACU and raises hospital costs.

b. Unexpected hospital stays for ambulatory or day care surgery patients

Delayed return to work can increase economic woes.

c. Wound dehiscence

This can necessitate re-suturing or re-exploration. It also raises the risk of wound infection.

d. Risk of aspiration

e. Surgical site bleeding

f. Dehydration

g. Electrolyte imbalances

h. Pain

This can end up as a vicious cycle with pain worsening the nausea.

i. Raised intracranial pressure

j. Raised intraocular pressure

k. Tachycardia and stress response

This can be detrimental in patients with fixed output states like mitral stenosis and in ischaemic heart disease.

l. Distress to the patient

The unpleasantness of nausea and vomiting can often define the hospital stay for the patient.

Antiemetic Drugs: Mechanism of action

Receptors involved in mediating nausea and vomiting include:

Histaminic (H_1)

Dopaminergic (D_2)

Muscarinic (M_1, M_2)

Serotonergic (5-HT_3)

Area postrema is rich in dopamine, opioid and serotonin receptors. Nucleus tractussolitarius is rich in encephalin, histamine and cholinergic muscarinic receptors. Vomiting centre receives separate input from different types of receptors. Antagonism of any one signal by an antiemetic drug will alleviate

emesis associated with stimulation of that receptor. Currently there is no drug which can block all the receptors involved in the emetic response. Each anti emetic agent has prominent action at one or two receptors only. So combination of drugs will be required to havegreater antiemetic action than a single drug. Drugs acting on dopaminergic, histaminergic and cholinergic muscarinic receptors caused sedation, dizziness, drymouth and muscular dystonia as side effects. Drugs acting on 5-HT_3 receptors have a favourable side effect profile; this made them a popular choice in both adult and paediatric surgical population[29].

Physiology and pharmacology of 5-hydroxytryptamine

Serotonin or 5-hydroxytryptamine(5-HT) is a mono amine neurotransmitter biochemically derived from the amino acid tryptophan. About 90% of the body's content of 5-HT is located in the enterochromaffin or Kulchitsky cells of the intestine. The remaining 10% is located mainly in platelets and the brain[30].

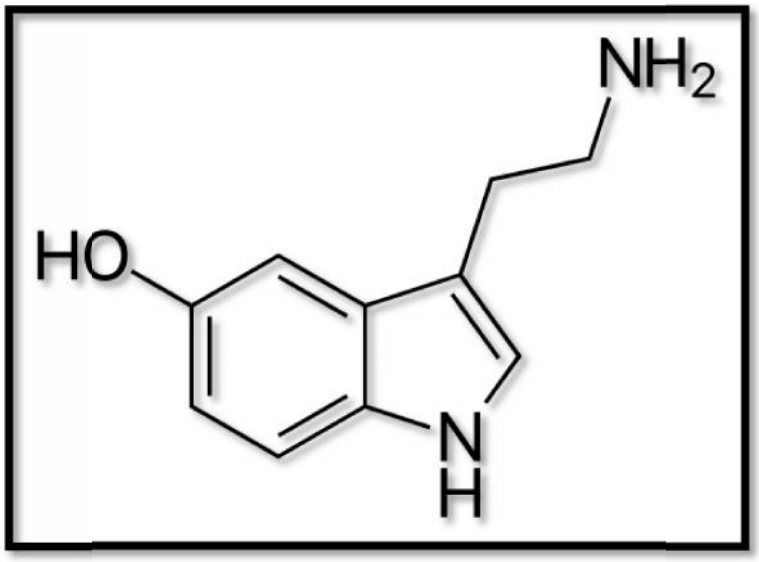


Figure 2: Chemical structure of serotonin/5-hydroxytryptamine

Synthesis, uptake and storage:

5-HT is β-aminoethyl-5-hydroxyindole and is synthesised in situ from the amino acid tryptophan, which is derived from dietary sources. Platelets do not synthesize but acquire 5-HT by active uptake during passage through intestinal blood vessels and is stored within storage granules. 5-HT is degraded primarily by MAO-A enzyme and to a smaller extent by dehydrogenase. Amount of 5-HT roughly equal to that present in the body is synthesised each day. Turnover times of 5-HT in brain and GIT have been estimated at about 1 and 17 hours respectively[31].

Serotonergic action is terminated primarily via uptake of 5-HT from the synapse. This is accomplished through the specific monoamine transporter for 5-HT, SERT, on the presynaptic neuron. Various agents can inhibit 5-HT reuptake, including cocaine, dextromethorphan (an antitussive), tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs).

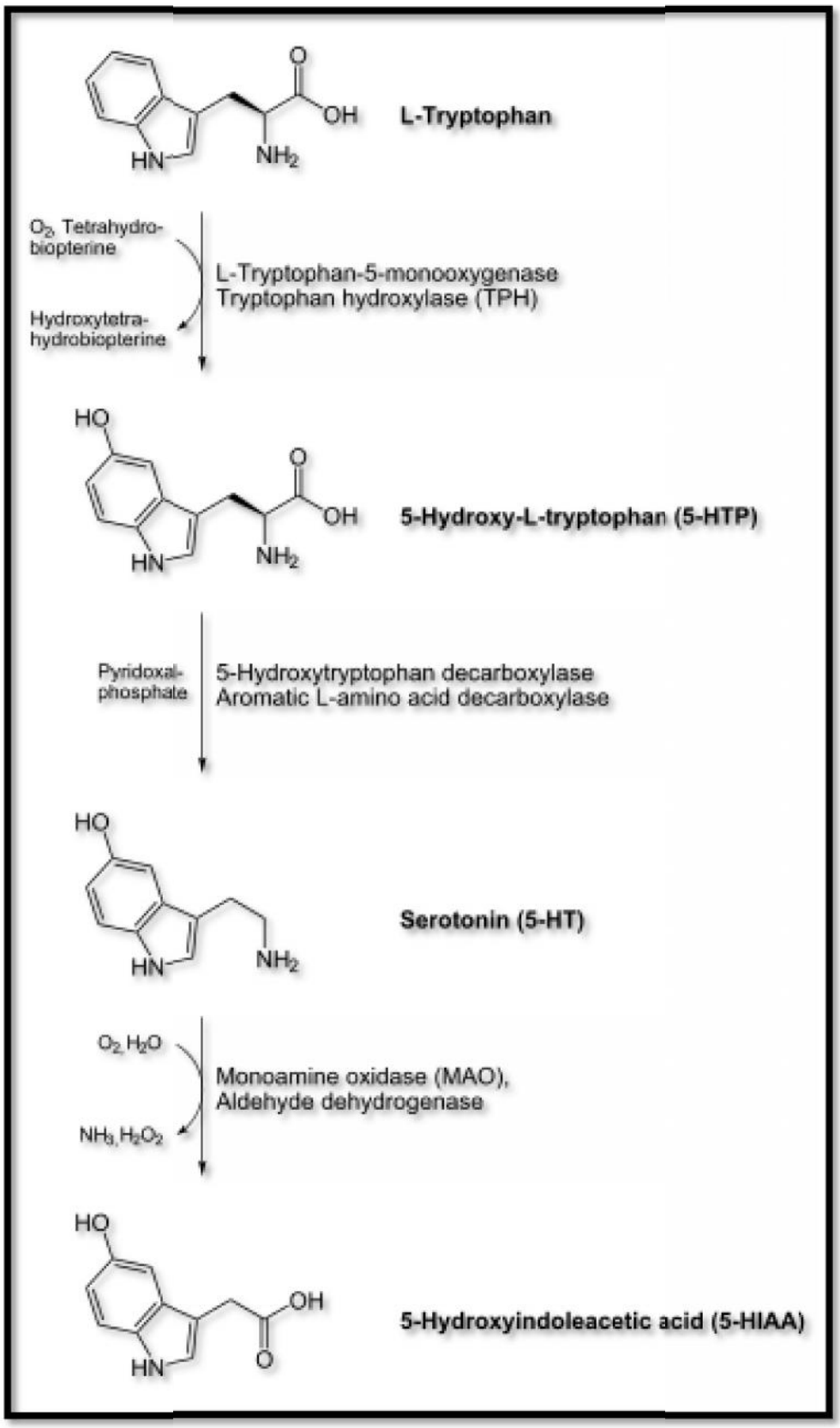


Figure 3: Synthesis of serotonin from tryptophan

Mechanism of action of 5-HT:

All 5-HT receptors except 5-HT_3 are G protein coupled receptors[32,33].

Family	Type	Mechanism	Potential
$5HT_1$	Gi/Go-protein coupled.	Decreasing cellular levels of cAMP	Inhibitory
$5HT_2$	Gq/G11-protein coupled.	Increasing cellular levels of IP3 and DAG.	Excitatory
$5HT_3$	Ligand-gated Na^+ and K^+ cation channel.	Depolarizing plasma membrane	Excitatory
$5HT_4$	Gs-protein coupled.	Increasing cellular levels of cAMP	Excitatory
$5HT_5$	Gi/Go-protein coupled	Decreasing cellular levels of cAMP	Inhibitory
$5HT_6$	Gs-protein coupled	Increasing cellular levels of cAMP	Excitatory
$5HT_7$	Gs-protein coupled	Increasing cellular levels of cAMP	Excitatory

5-HT_3 receptors are *ligand gated cation selective* channels. It mediates membrane depolarization by increasing Na and K conductance.

A functional channel may be composed of five identical 5-HT_{3A} subunits (homopentameric) or a mixture of 5-HT_{3A} and one of the other four 5-HT_{3B},5-HT_{3C}, 5-HT_{3D}, or 5-HT_{3E} subunits (heteropentameric)[33].

The subunits surround a central ion channel in a pseudo-symmetric manner. Each subunit comprises an extracellular N-terminal domain which comprises the orthosteric ligand-binding site; a transmembrane domain consisting of four interconnected alpha helices (M1-M4), with the extracellular M2-M3 loop

involved in the gating mechanism; a large cytoplasmic domain between M3 and M4 involved in receptor trafficking and regulation; and a short extracellular C-terminus.

Whereas extracellular domain is the site of action of agonists and competitive antagonists, the transmembrane domain contains the central ion pore, receptor gate, and principle selectivity filter that allows ions to cross the cell membrane.

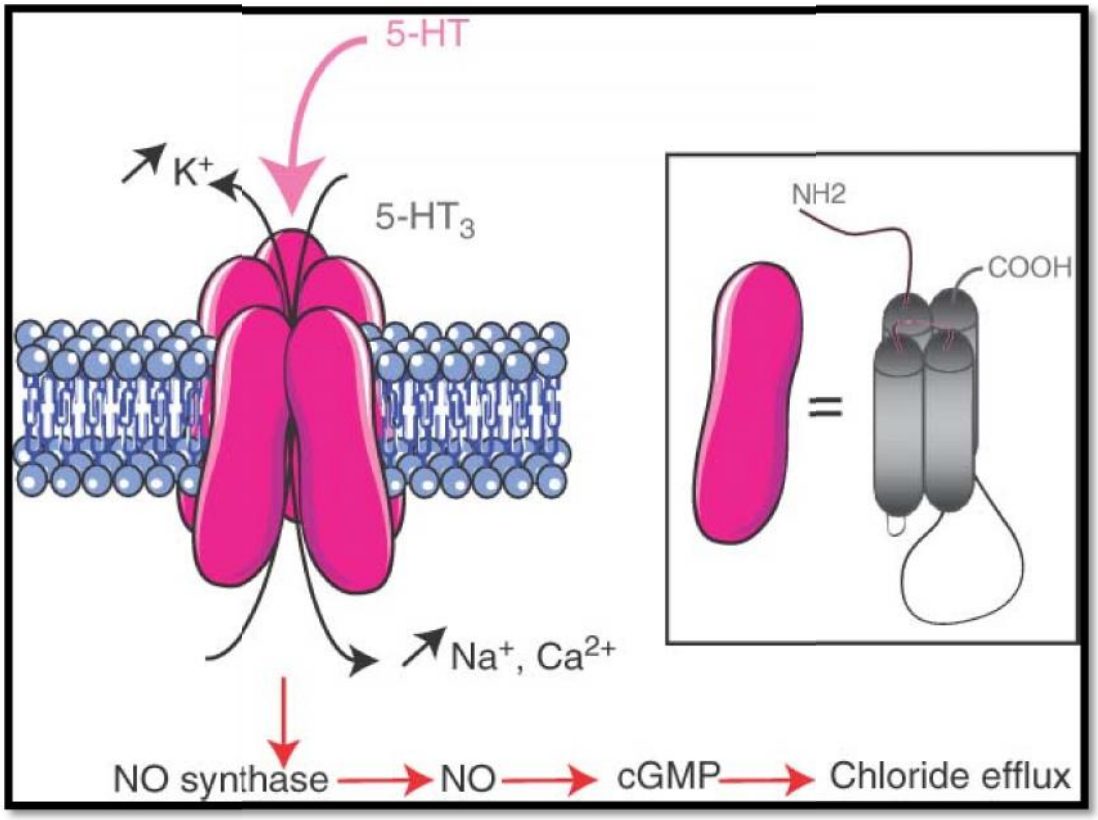


Figure 4: The 5-HT_3 receptor; on the right is the subunit with four transmembrane domains

Absorption, metabolism and excretion of 5-HT:

Most of the 5- HT, either endogenous or ingested undergoes oxidative deamination by monoamine oxidase (MAO) to form 5-hydroxyindole acetaldehyde. This in turn is degraded by oxidation to 5-hydroxyindole acetic acid

(5-HIAA) byacetaldehyde dehydrogenase. Again by aldehyde dehydrogenase 5-HIAA is reduced to5- hydroxyl tryptophol (5-HTOL). The principal metabolite is 5-HIAA and is excreted in the urine (2 to 10 mg/24 hrs).

Antagonists of 5-HT:

5-HT_1 Antagonists: Cyanopinol, Spiperone, Propranolol, Metitipin, Ritanserin

5-HT_2 Antagonists: Ketanserin, Ritanserin, Mianserin

5-HT_3 Antagonists: Ondansetron, granisetron, tropisetron, pancopride, zacopride palonosetron, ramosetron

5-HT_4 Antagonists: Renzapride.

Functions of Endogenous 5-HT:

Major function of 5-HT is to serve as neurotransmitter in the brain and the enteric nervous system of the intestines[35]. It is involved in sleep, temperature regulation, cognitive functions, behaviour and mood. Enterochromaffin or Kulchitsky cells and 5-HT containing neurons regulate peristalsis and local reflexes in the gut[36]. Platelets release 5-HT at the site of injury which accelerates platelet aggregation and clot formation promoting haemostasis. Nausea and vomiting evoked by cytotoxic drugs and radiotherapy is mediated by release of 5-HT[37] and its action on 5-HT_3 receptors in the gut, area postrema and nucleus tractus solitarius.

5-HT and emesis:

Of all the 5-HT_3 receptor antagonists, ondansetron is the first drug of the new class of antiemetic drugs developed to control cancer chemotherapy / radiotherapy induced vomiting and later the drug was found to be highly effective in prevention of postoperative nausea and vomiting. These drugs block the depolarising action of 5- HT through 5-HT_3 receptors on vagal afferents in the GIT as well as in NTS

and CTZ. Cytotoxic drugs /radiation produce nausea and vomiting by causing cellular damage, release of mediators including 5-HT from the intestinal mucosa, activation of vagal afferents in the gut, emetogenic impulses to the NTS and CTZ. 5-HT_3 receptor antagonists block emetogenic impulses both at their peripheral and central relay.

Pharmacology of Ramosetron

Ramosetron is a potent and highly selective 5-HT_3 receptor antagonist. It is a benzimidazole derivative. It was developed in Japan and is now approved for preventing PONV, CINV and in treating Irritable Bowel Syndrome – diarrhoea predominant type, in several South Asian countries[38, 39].

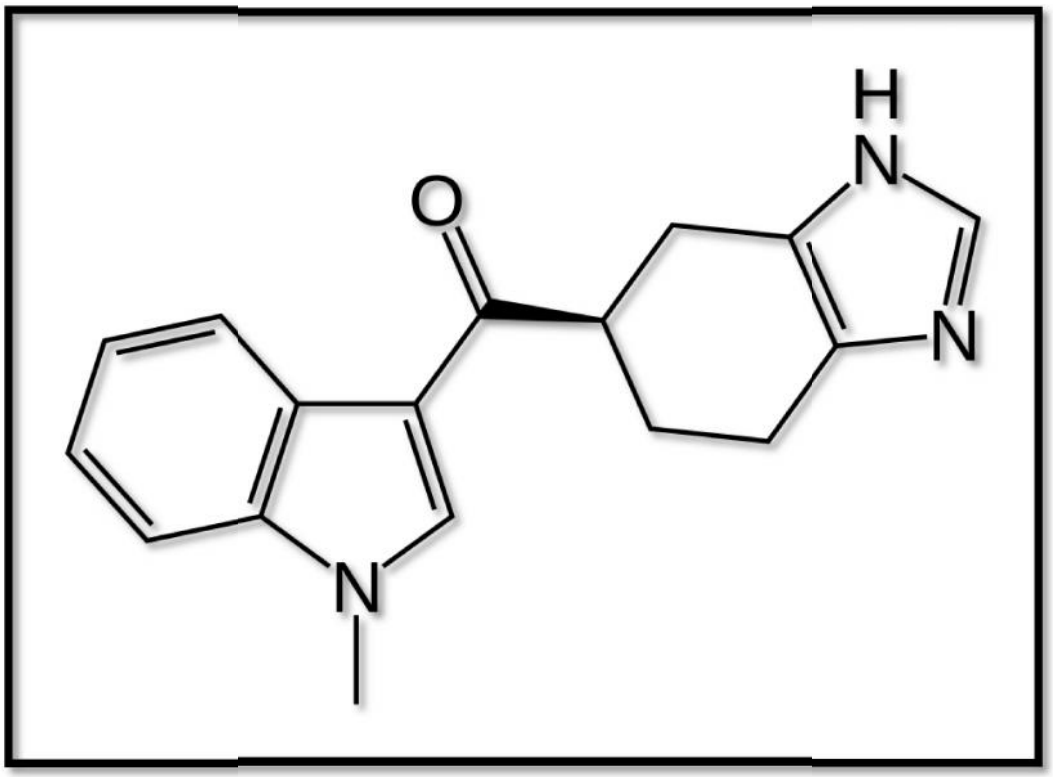


Figure 5: Molecular Structure of Ramosetron

Its chemical formula is: (1-Methylindol-3-yl)-[(5*R*)-4,5,6,7-tetrahydro-3*H*-benzimidazol-5-yl]methanone[40]. Its molecular weight is 279.34.

Pharmacokinetics

After oral or intravenous administration, ramosetron hydrochloride achieves its maximum serum concentration (C_{max}) after 2 hours with a plasma half-life of 5 hours. The C_{max} and area under the curve are linear in nature and dose-dependent.

The oral bioavailability of Ramosetron hydrochloride is about 50%. The drug is widely distributed in the body fluids including breast milk.

It is metabolized in the liver mainly via the CYP1A2 and CYP2D6 enzymes.

Ramosetron hydrochloride is excreted as unchanged drug via the urine as drug metabolites(demethylated and hydroxylated conjugates) and as unaltered drug.

Pharmacodynamics

Ramosetron hydrochloride selectively blocks serotonin receptors ($5\text{-}HT_3$). Serotonin plays a vital role in vomiting, serotonin-induced bradycardic reflex and peristalsis. The pharmacological action of ramosetron hydrochloride is sustained and potent.

Adverse effects

Headache and constipation are commonly reported. QT prolongation like other 5-HT_3 receptor antagonists is not clinically significant[37].

Availability

Ramosetron is available as 1ml ampoules with a concentration of 0.3mg/ml.

Pharmacology of Granisetron

Granisetron was developed by the British drug company Beecham in 1988 and is now available generically. It has found its place in treating CINV and subsequently PONV. It is available as oral tablets and intravenous solutions. In 2008 a transdermal patch was introduced in to the market by 3M Drug Delivery Systems.

Granisetron is a selective 5-hydroxytryptamine3 (5-HT_3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT_1; 5-HT_{1A}; 5-$HT_{1B/C}$; 5-HT_2; for alpha1-, alpha2-, or beta-adrenoreceptors; for dopamine-D2; or for histamine-H1; benzodiazepine; picrotoxin or opioid receptors.

It is a monocarboxylic acid amide resulting from the formal condensation of the carboxy group of 1-methyl-1*H*-indazole-3-carboxylic acid with the primary amino group of (3-*endo*)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine[41].

Its chemical name is: 1-Methyl-*N*-((1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)-1*H*-indazole-3-carboxamide

Its molecular mass 312.195

APF530 is a sustained delivery formulation of granisetron which is currently undergoing clinical trials.

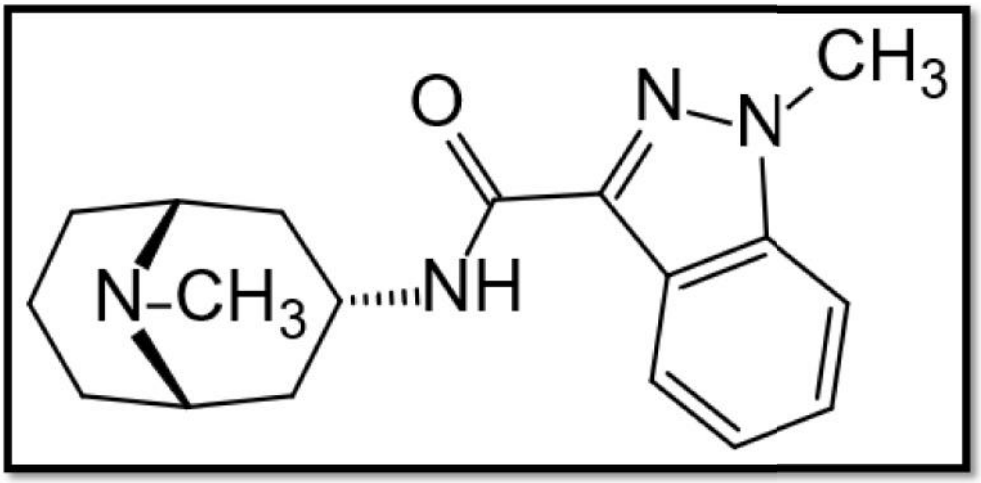


Figure 6: Molecular structure of Granisetron

Pharmacokinetics

Plasma protein binding is approximately 65% and Granisetron distributes freely between plasma and red blood cells. Plasma half-life is around 5-6 hours.

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation[41].

Clearance is predominantly by hepatic metabolism. Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation. In normal volunteers, approximately 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in faeces.

Pharmacodynamics

In healthy subjects, granisetron hydrochloride produced no consistent or clinically significant changes in pulse rate, blood pressure or ECG. There was no evidence of an effect on psychomotor performance at intravenous doses of up to 200 mcg/kg IV granisetron hydrochloride did not affect the plasma levels of prolactin or aldosterone at single intravenous doses of up to 300 mcg/kg or after repeat intravenous doses of 40 mcg/kg for 5.5 days.

Drug Interactions

Granisetron does not have any clinically significant drug interactions.

Adverse effects

The most commonly reported adverse effects are constipation and headache. Other less common adverse effects include skin rashes, pruritus, abdominal pain and rarely anaphylaxis.

Prolongation of QT interval has been noted in post marketing reports but they were clinically insignificant and never induced any arrhythmias.

Geriatric population

The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 mcg/kg intravenous dose of granisetron injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly patients[42].

Renal Failure Patients

Total clearance was not affected in renal failure patients.

Hepatic Impairment

A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients, dosage adjustment in patients with hepatic functional impairment is not necessary.

Availability

IV preparations are available in 1mg/ml concentration as 1ml, 2ml and 3ml ampoules and vials. Oral preparations are available as 1mg, 2mg and 3 mg tablets.

METHODOLOGY

The present study titled **"TO COMPARE THE EFFICACY OF RAMOSETRON AND GRANISETRON IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"** was conducted in patients between the age group of 18-50 years of either gender, belonging to ASA physical status grade I and II who underwent laparoscopic appendicectomy at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru Nagar, Belagavi between January 2014 to December 2014.

Study design:

The study was a randomized controlled trial.

Sample size calculation:

The sample size was calculated by considering the incidence of vomiting as 18%(p1)[43] with granisetron and 2%(p0)[44] with ramosetron.

With type I error rate $\alpha = 0.05$,

type II error rate $\beta = 0.02$

and with a power of 80% and using the formula-

$$n = \frac{2\,(Z\alpha + Z\beta)^2\, pq}{(p0 - p1)^2}$$

Taking the level of significance at 5%(α=0.05) and power of the test as 80%(β=0.2), we get Zα=1.96 and Zβ=0.84. Hence,

$$n=\frac{2\ (1.96+0.84)^2\ 10*90}{(16)^2}$$

n=55.125

Hence two groups containing 55 patients each were created.

Inclusion Criteria:

1. Patients aged 18 – 50 years of either sex
2. ASA physical status grade I & II
3. Patients posted for elective laparoscopic appendicectomy

Exclusion Criteria:

1. Patients with previous history of post-operative nausea and vomiting
2. History of motion sickness
3. History of gastroesophageal reflux disease
4. Patients who have taken any antiemetic 24 hours prior to the surgery
5. Obese patients

After obtaining written informed consent and confirming inclusion and exclusion criteria, patients were randomly divided into 2 groups according to a computer generated randomisation chart.

Group R – received Injection Ramosetron 0.3mg IV n=55

Group G –received Injection Granisetron 1mg IV n=55

On the day of surgery IV access was secured half an hour before surgery. In the operation theatre routine monitors such as ECG, NIBP and pulse oximeter was attached and base line readings were recorded.

Patients in Group I received 0.3mg of injection ramosetron IV and those in group II received 1mg of injection granisetron IV 5 min before induction of general anaesthesia. Patients were pre-medicated with injection glycopyrrolate 0.005mg/kg IV, injection midazolam 0.05mg/kg IV and injection fentanyl 2µg/kg body weight IV. Following pre oxygenation anaesthesia was induced with injection thiopentone sodium 5-7mg/kg and intubation was facilitated with injection succinylcholine 2mg/kg IV. Endotracheal intubation was done with an appropriate size endotracheal tube.

Anaesthesia was maintained with oxygen and nitrous oxide (50/50), halothane (0.4-0.6%) and injection vecuronium 0.1 mg/kg IV. Pulse rate, blood pressure, SPO_2 and $ETCO_2$ were monitored throughout the perioperative period. On completion of the surgery neuromuscular blockade was reversed with injection glycopyrrolate 0.01mg/kg IV and injection neostigmine 0.05mg/kg IV and the patient extubated. Post-op analgesia was provided with diclofenac sodium 75 mg in 100ml normal saline IV infusion up to four times a day depending on the patient requirement.

Post operatively patients were assessed for nausea and vomiting every 6 hours for the first 24 hours. Incidence of the PONV was noted in the two groups according to the post-operative nausea and vomiting score.

0 = No nausea or emetic symptoms

1 = Nausea

2 = Retching

3 = Vomiting

Patients received intravenous dexamethasone 0.1mg/kg IV as rescue antiemetic[45] when PONV score was ≥ 2.

Statistical analysis:

Values were compared statistically using statistical software SPSS 11.5 version; Patient demographics were compared using Student's t-test. Categorical variables and PONV scores were compared using Chi-square test. P value was considered significant when it was < 0.05.

RESULTS

This study was done on 110 patients who underwent laparoscopic appendicectomy under general anaesthesia in KLES Dr. Prabhakar Kore's Hospital and Medical Research Centre, Belagavi. The patients were grouped into group R (ramosetron) and group G (granisetron) according to computer generated randomization.

All data is expressed as +/- standard deviation. Demographic data was analysed using Student's unpaired t test. Categorical variables and PONV scores are compared using chi square test. P value<0.05 is considered significant.

Demographics

Graph 1: Number of patients in each group

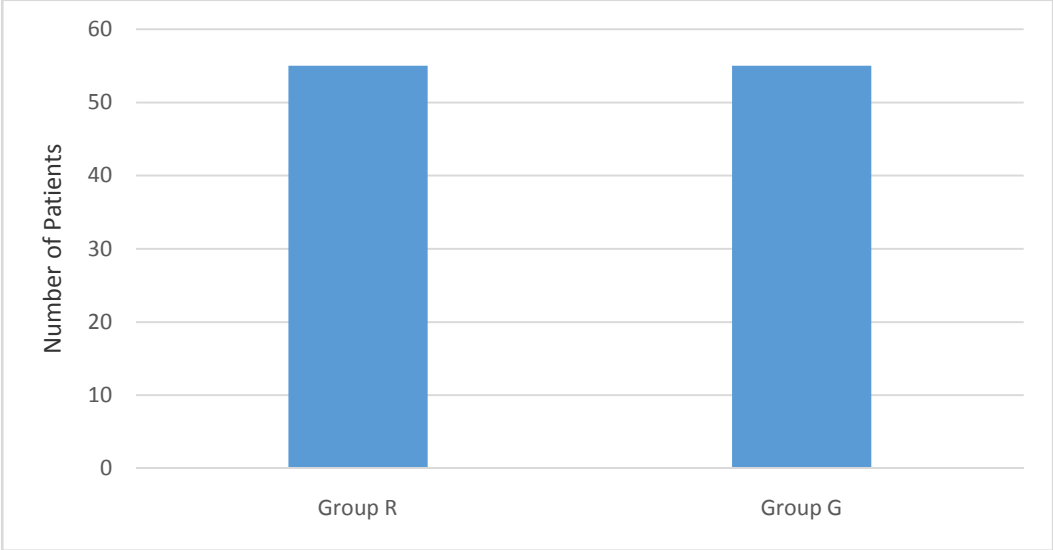


Table 1: Number of patients in each group

Group	Group R	Group G
Number of Patients	55	55

Group R and group G had 55 patients each as shown adding to a total of 110 patients. Patients in group R received injection ramosetron 0.3mg IV and those in group G received injection granisetron 1mg IV.

Graph 2: Age of patients in each group

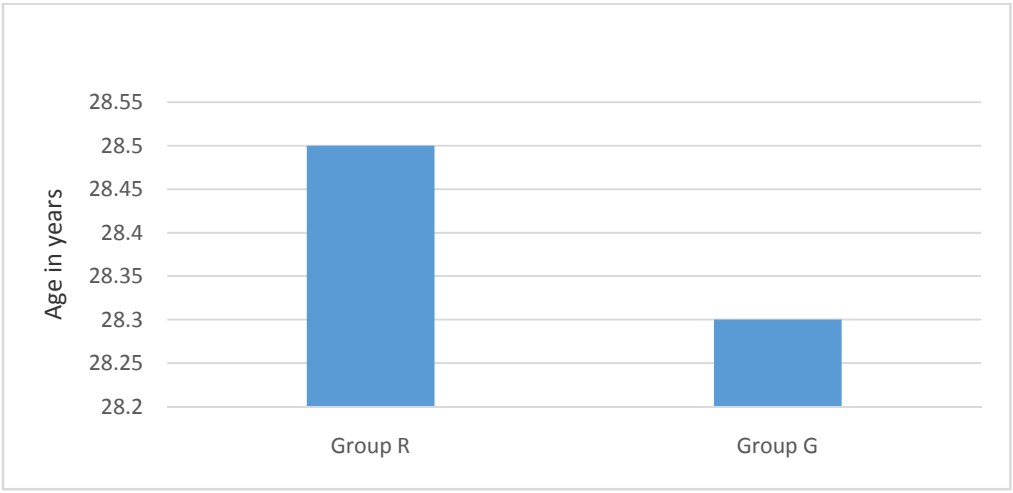
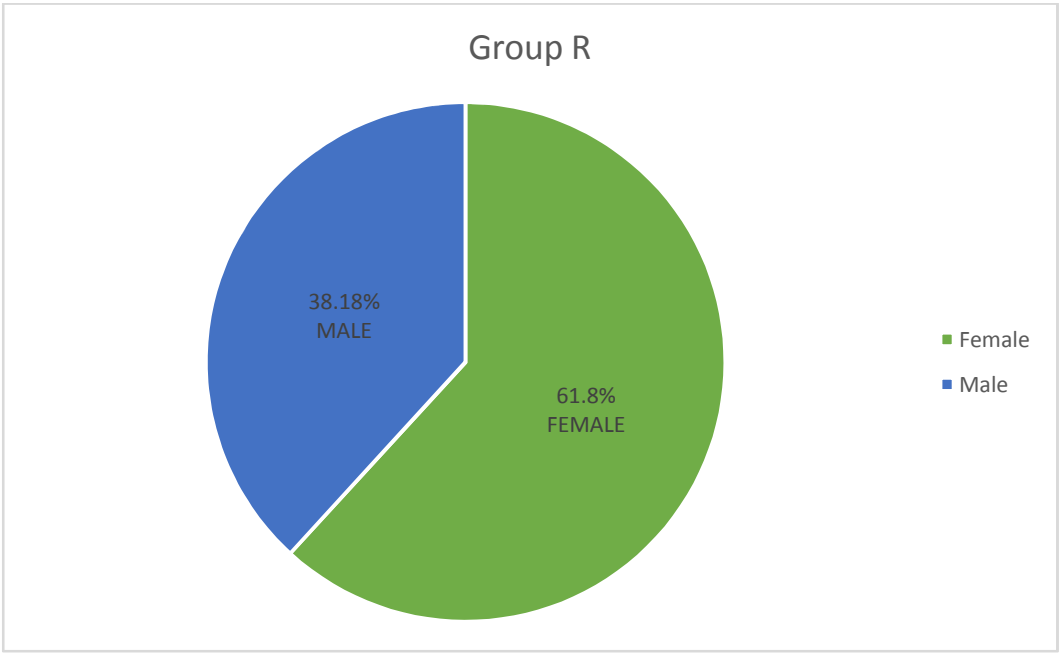


Table 2: Age of patients in each group

	Group R	Group G
Average age in years	28.5±6.52	28.3±6.66

The average age of patients in group R was 28.5±6.52 years and in group G was 28.3±6.66 years. There was no significant difference in the mean age of both groups(p-value=0.908).

Graph 3: Pie charts showing sex distribution in each group



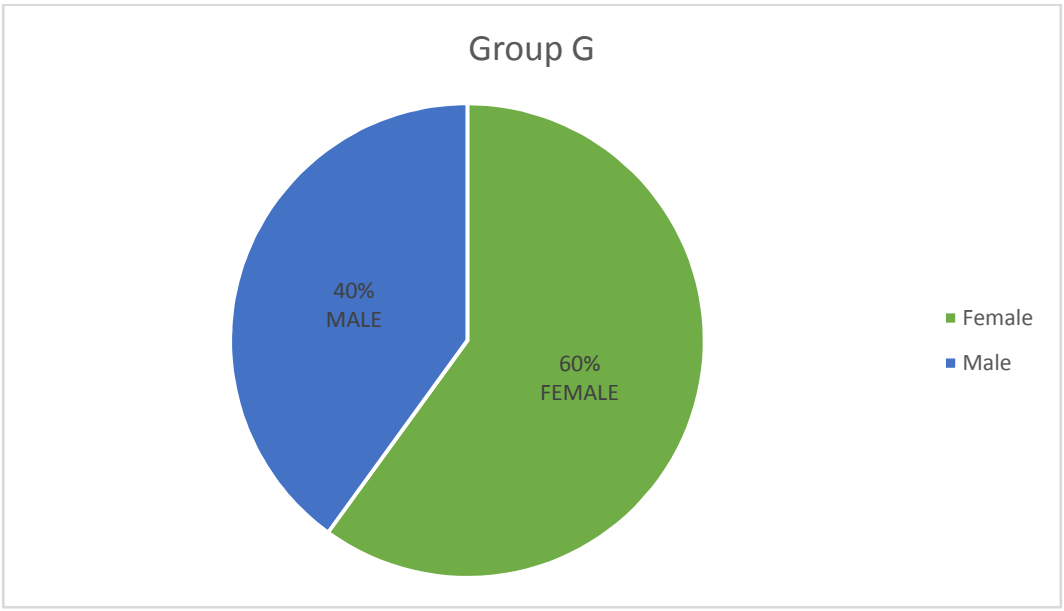


Table 3: Sex distribution in each group

	Group R	Group G	p-value
Males	21/55	22/55	0.845
Females	34/55	33/55	

Ofthe 55 patients in group R, 34(61.8%) were female and 21(38.18%) were male. Of the 55 patients in group G, 33(60%) were female and 22(40%) were male. There was no significant difference in the sex ratio of either groups (p-value=0.845).

Graph 4: ASA class distribution in each group

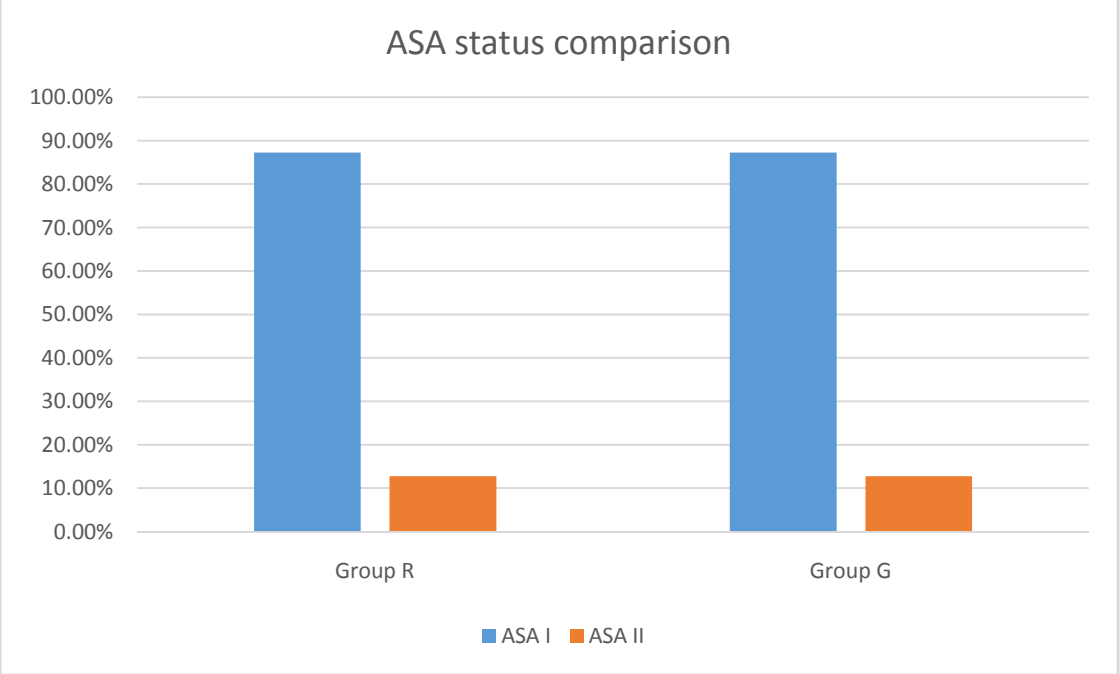


Table 4: ASA class distribution in each group

	Group R	Group G
ASA I	48	48
ASA II	7	7

Of the 55 patients in group R, 48 were ASA I (87.27%) and 7 were ASA II (12.75%).

Of the 55 patients in group G, 48 were ASA I (87.27%) and 7 were ASA II (12.75%).

This was found to be comparable(p=1).

Graph 5: Height of the patients in each group

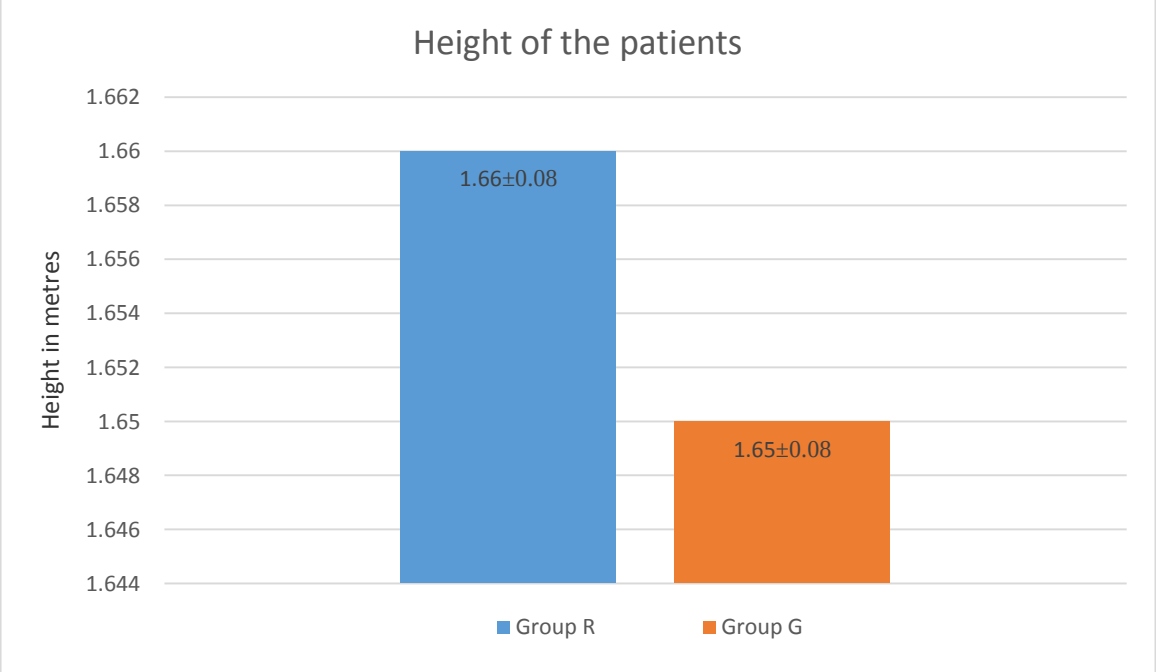


Table 5: Height of the patients in each group

	Group R	Group G	p-value
Height in metres	1.66±0.08	1.65±0.08m	0.827

The mean height of the patients in group R was 1.66±0.08m while in group G was 1.65±0.08m. This was found to be comparable (p-value=0.827).

Graph 6: Weight of the patients in each group

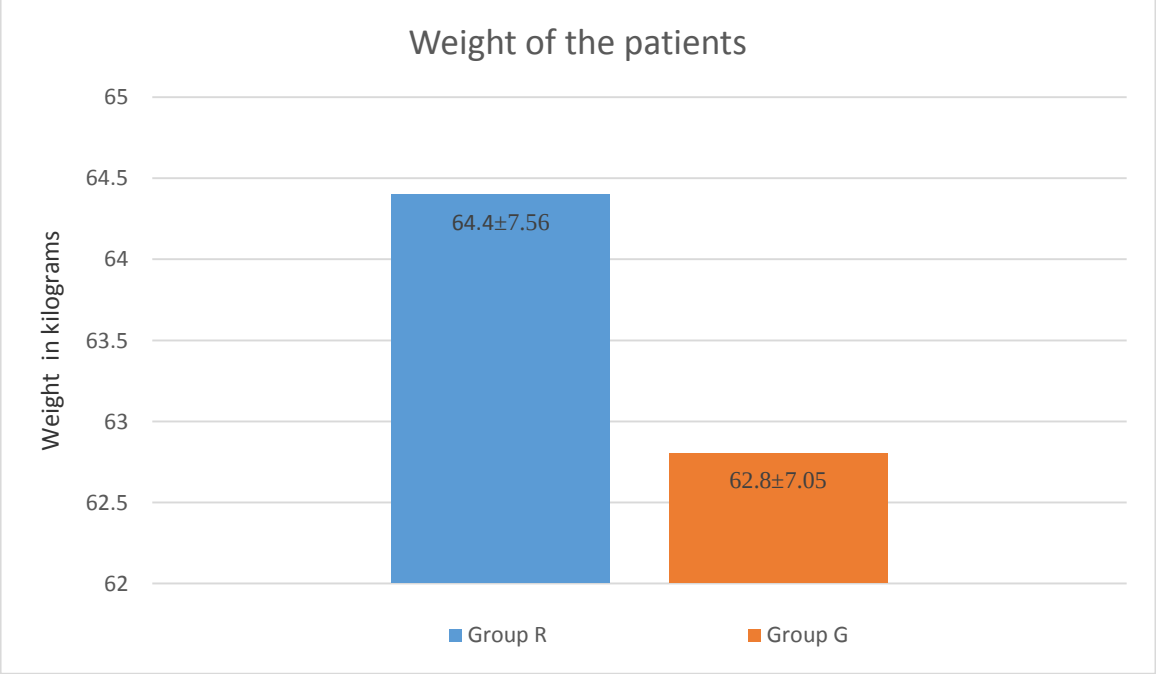


Table 6: Weight of the patients in each group

	Group R	Group G	p-value
Weight of the patients in kilograms	64.4±7.56	62.8±7.05	0.233

The mean weight of the patients in group R was 64.4±7.56kg while in group G was 62.8±7.05kg. This was found to be statistically comparable with a p-value of 0.233.

Graph 7: Duration of surgery in each group

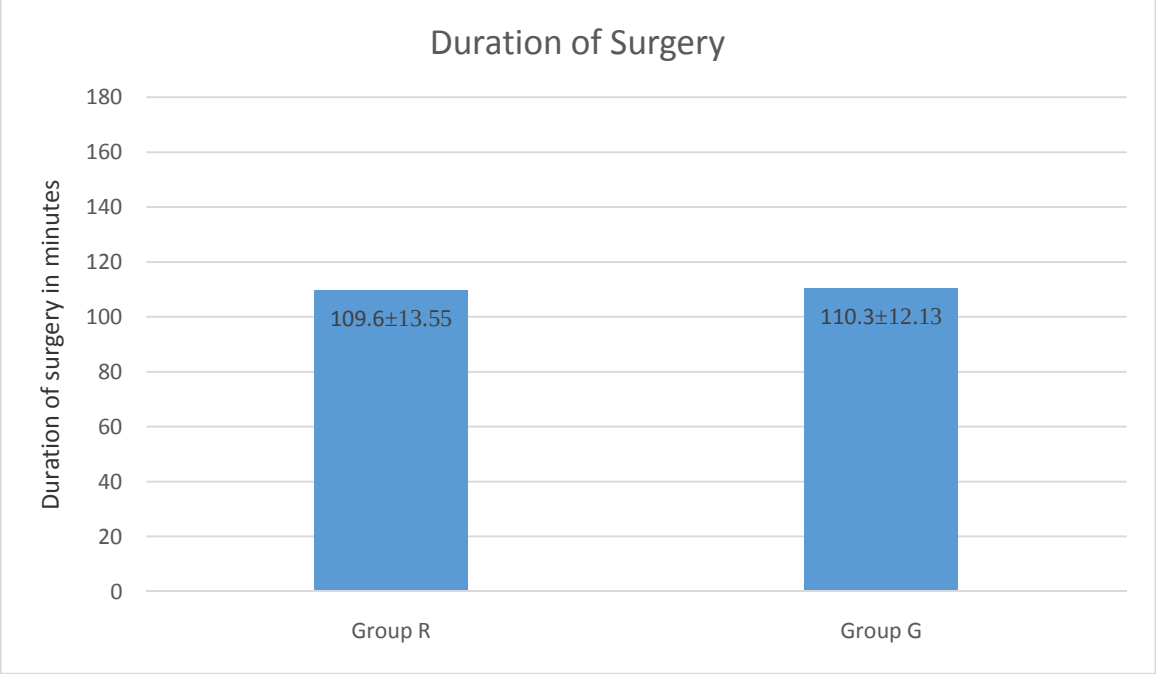


Table 7: Duration of surgery in each group

	Group R	Group G	p-value
Duration of surgery in minutes	109.63±13.55	110.34±12.13	0.776

The mean duration of the surgery in group R was 109.63±13.55 minutes. The mean duration of surgery in group G was 110.34±12.13 minutes. These were found to be comparable with p-value=0.776.

PONV Scores

In the first 0-6 hours in group R, 54(98.2%) patients did not have any nausea. This compares to 21 (38.2%) in group G. This is statistically significant with a p-value of <0.001.

1(1.8%) patient in group R had nausea compared to 31(56.4%) in group G. This difference is statistically significant.

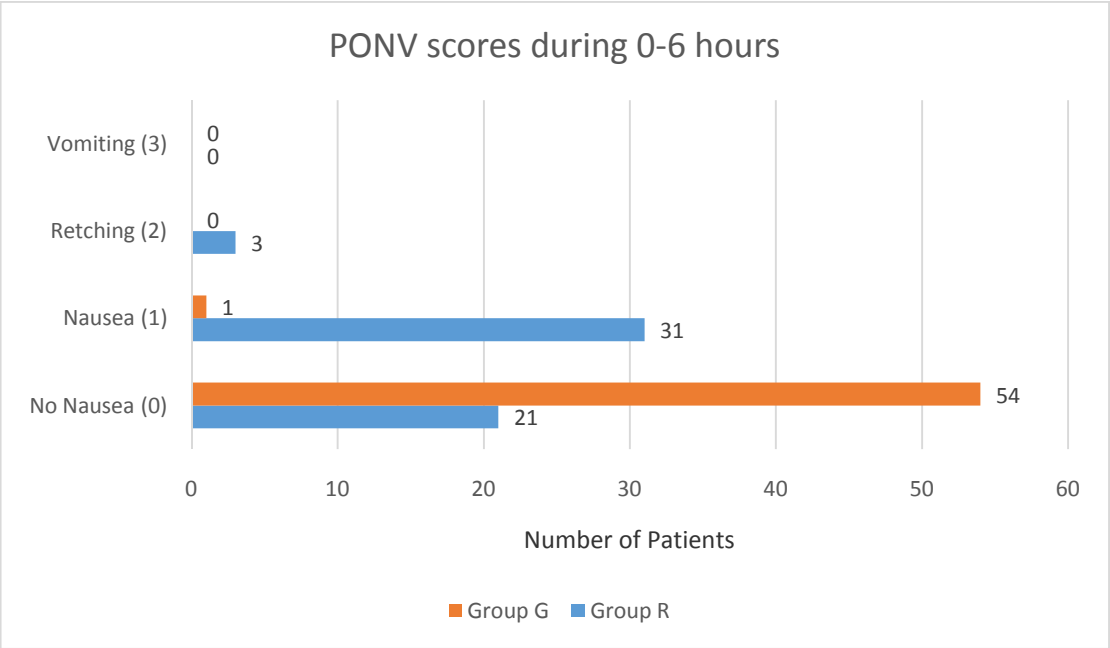
No patient in group R had retching while 3 (5.3%) in group G had retching. This is not statistically significant as the p-value is 0.082.

None of the patients had episodes of vomiting in either of the groups(p-value=1).

Table 8: PONV Scores in during 0-6 hours

PONV score in 0-6 hours	Group R	Group G	p-value
No nausea (0)	54(98.2%)	21(38.2%)	<0.001
Nausea (1)	1(1.8%)	31(56.4%)	<0.001
Retching (2)	0	3(5.4%)	0.82
Vomiting (3)	0	0	1

Graph 8: PONV Scores in during 0-6 hours



In the next 6-12 hours, 53 (96.4%) patients in group R had no nausea while 21 (38.2%) had no nausea in group G. This difference is statistically significant with a p-value <0.001.

In group R 2 patients (3.4%) had nausea compared to 32 patients (58.2%) in group G. This difference is statistically significant with a p-value <0.001.

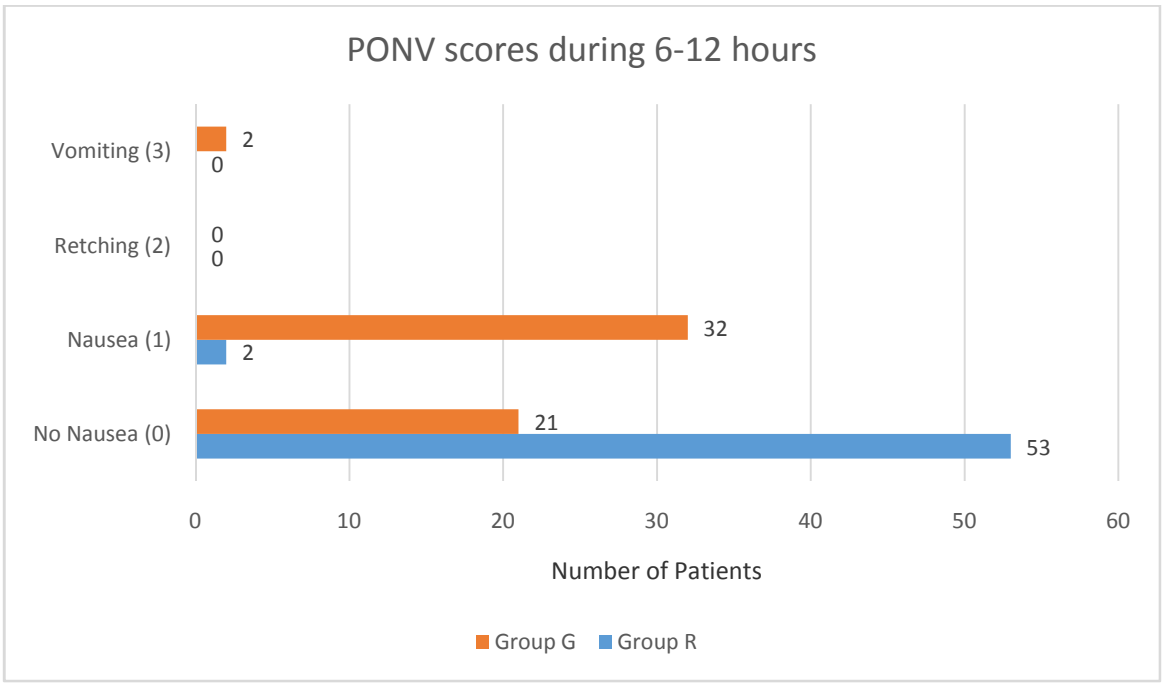
No patients had retching in either of the groups (p-value=1).

No patients in group R had vomiting while 2 patients (3.6%) in group G had vomiting. This is statistically not significant with a p-value of 0.158.

Table 9: PONV Scores during 6-12 hours

PONV score in 6-12 hours	Group R	Group G	p-value
No nausea (0)	53(96.4%)	21(38.2%)	<0.001
Nausea (1)	2(3.4%)	32(58.2%)	<0.001
Retching (2)	0	0	1
Vomiting (3)	0	2(3.6%)	0.158

Graph 9: PONV Scores during 6-12 hours



In the next 12-18 hours, 50 patients (90.9%) in group R had no nausea compared to 36 patients (65.5%) in group G. This difference is statistically significant with a p-value of 0.001.

5 patients (9.1%) in group R had nausea compared to 17 patients (30.9%) in group G. This is statistically significant with a p-value <0.001.

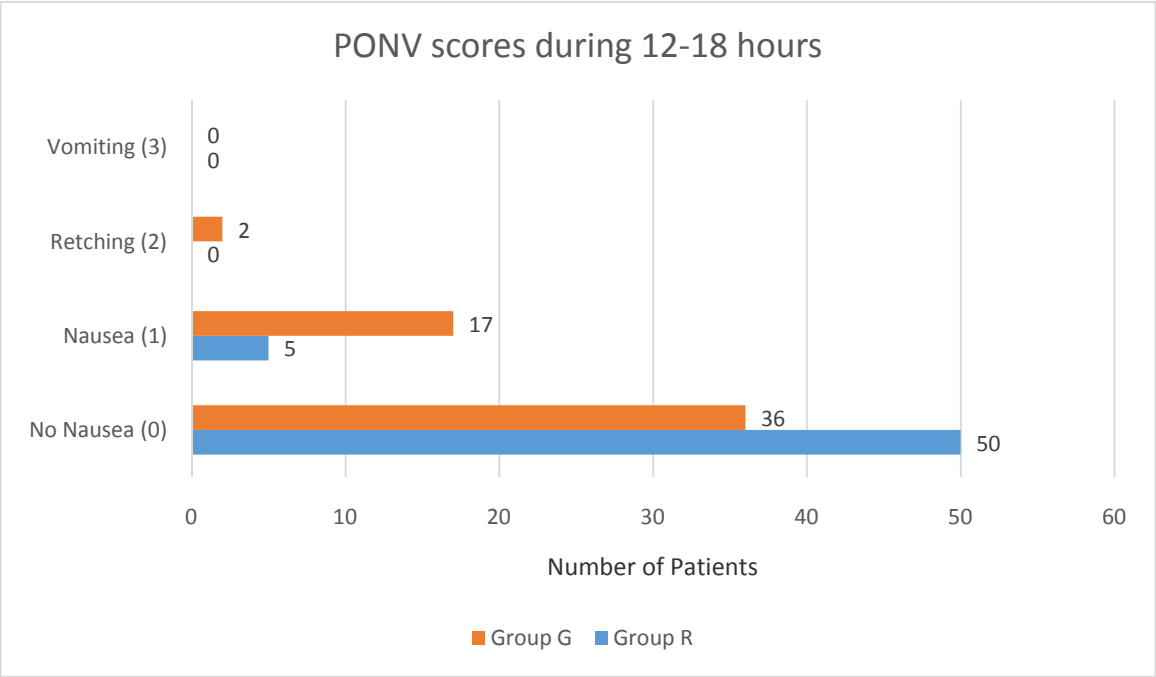
No patient in group R had retching compared to 2 patients (3.6%) in group G. This is not statistically significant with a p-value of 0.158.

No patients had vomiting in either of the groups (p-value=1).

Table 10: PONV Scores during 12-18 hours

PONV score in 12-18 hours	Group R	Group G	p-value
No nausea (0)	50(90.9%)	36(65.5%)	0.001
Nausea (1)	5(9.1%)	17(30.9%)	<0.001
Retching (2)	0	2(3.6%)	0.158
Vomiting (3)	0	0	1

Graph 10: PONV Scores during 12-18 hours



In the final 18-24 hours, 44 patients (80%) in group R had no nausea compared to 42 patients (76.4%) in group G. This is not statistically significant with a p-value of 0.644.

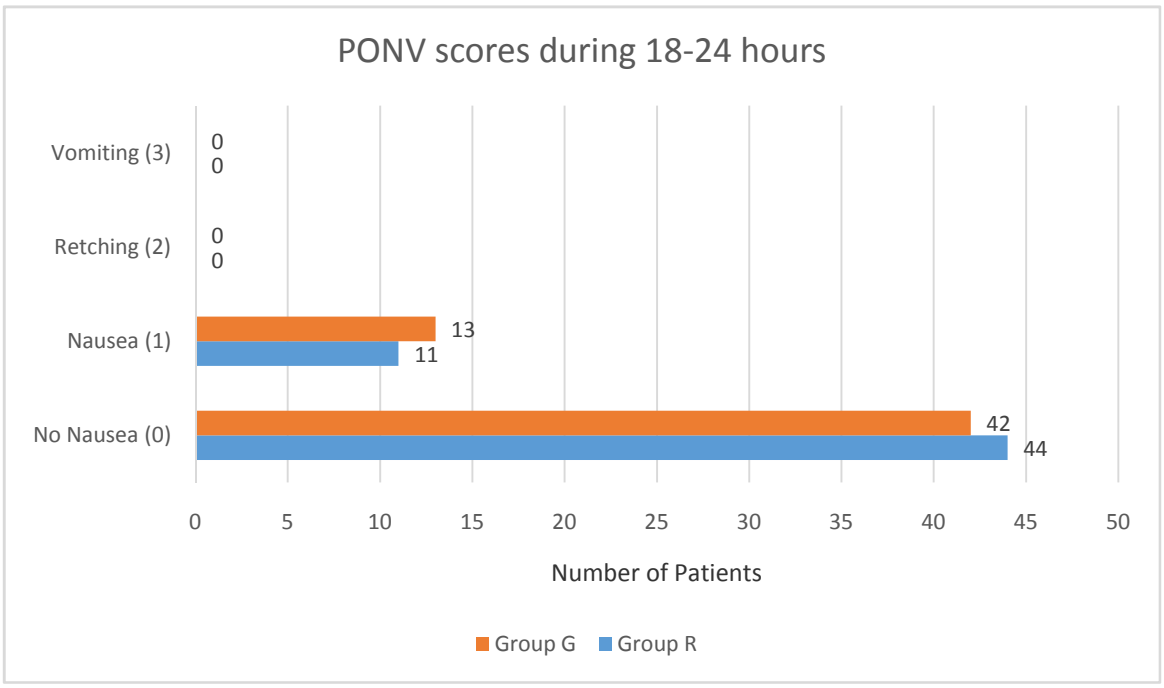
11 patients (20%) in group R had nausea compared to 13 patients (23.6%) in group G. This is not statistically significant with a p-value of 0.644.

None of the patients in either of the groups had retching or vomiting (p-value=1).

Table11: PONV Scores during 18-24 hours

PONV score in 18-24hours	Group R	Group G	p-value
No nausea (0)	44(80%)	42(76.4%)	0.644
Nausea (1)	11(20%)	13(23.6%)	0.644
Retching (2)	0	0	1
Vomiting (3)	0	0	1

Graph 11: PONV Scores during 18-24 hours

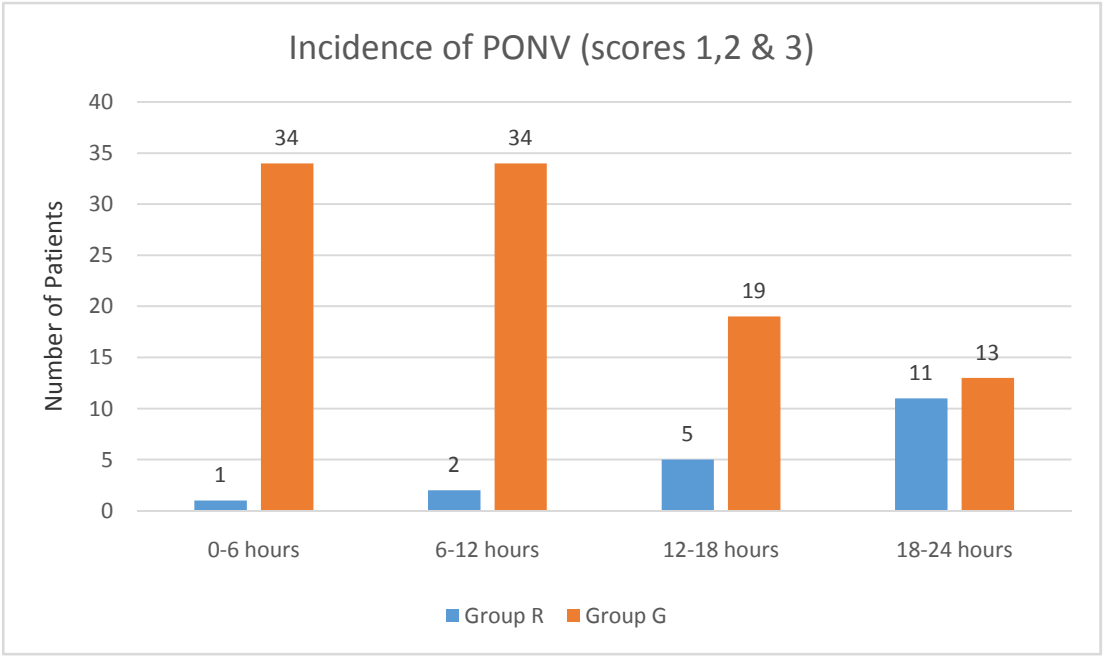


In group R incidence of PONV.ie. PONV score >0 was 1.5%, 3.6%, 9.1% and 20% while in group G it was 61.9%, 61.9%, 34.5% and 23.6% for 0-6 hours, 6-12 hours, 12-18 hours and 18-24 hours respectively. The difference was significant in the first three six hour periods.ie. the first 18 hours.

Table 12: Incidence of PONV (PONV scores 1,2 and 3) in both groups

PONV score – 1,2 & 3 combined	Group R	Group G	p-value
0-6 hours	1 (1.5%)	34 (61.9%)	<0.001
6-12 hours	2 (3.6%)	34 (61.9%)	<0.001
12-18 hours	5 (9.1%)	19 (34.5%)	0.001
18-24 hours	11 (20%)	13 (23.6%)	0.644

Graph 12: Incidence of PONV (PONV scores 1,2 and 3) in both groups

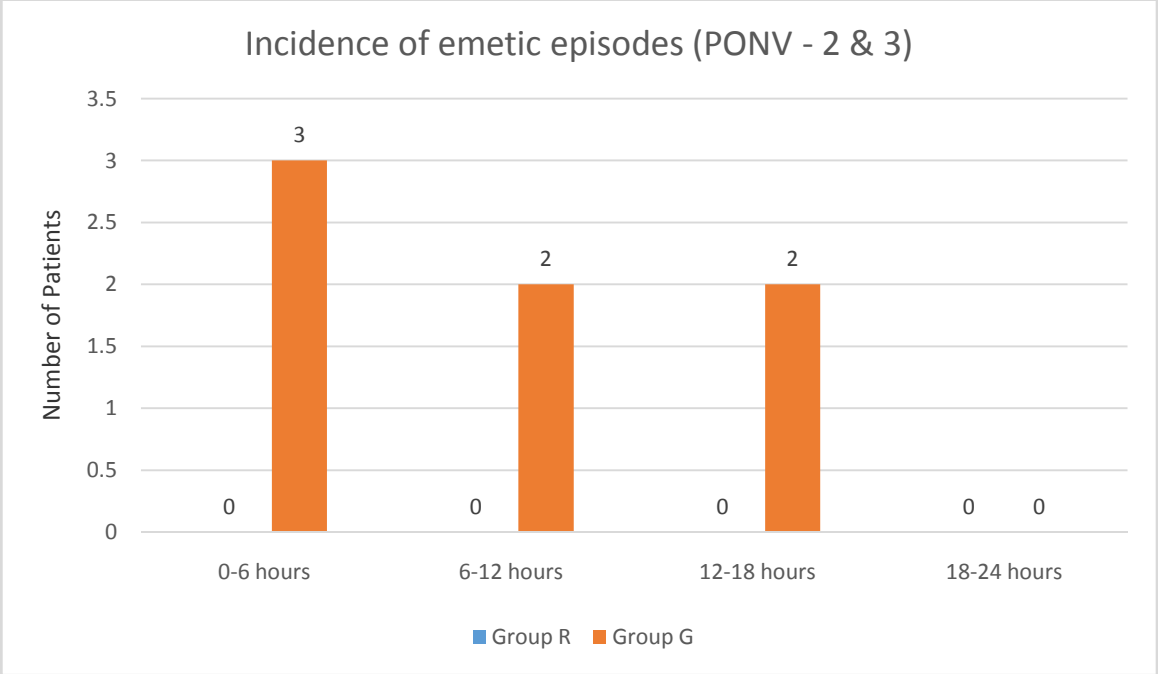


In group R incidence of emetic episodes.ie. PONV score >0 was 0%, 0%, 0% and 0% while in group G it was 5.5%, 3.6%, 3.6% and 0% for 0-6 hours, 6-12 hours, 12-18 hours and 18-24 hours respectively. The difference was not significant with a p-value>0.05 in all the time periods.

Table 13: Incidence of emetic episodes (PONV scores 2 &3)

PONV score -2 & 3 combined	Group R	Group G	p-value
0-6 hours	0	3 (5.5%)	0.052
6-12 hours	0	2 (3.6%)	0.158
12-18 hours	0	2 (3.6%)	0.158
18-24 hours	0	0	1

Graph 13: Incidence of emetic episodes (PONV scores 2 &3)



DISCUSSION

Post-operative nausea and vomiting (PONV) has been a problem which has troubled the anaesthesiologist, the surgeon and most importantly the patient since the very beginning of surgery and anaesthesia. It can range from a subtle sensation of nausea which discomforts the patient to repeated episodes of retching and vomiting causing wound dehiscence and bleeding.

The general incidence is about 20% to 30%, and the PONV rate can go up to 80% in subsets of high-risk patients[2, 46, 47]. PONV is frequent in abdominal surgeries leading to the recommendation of routine prophylactic administration of antiemetic drugs[48].

It has been a major cause of delayed discharge of the patients who have been admitted for day care surgeries. It thus increases the economic burden on the patient. Complications due to PONV include electrolyte imbalances, aspiration, tachycardia, pain, suture dehiscence, hematoma formation and so on.

5 HT_3 antagonists have proven to be a versatile tool in the arsenal of anaesthesiologists against PONV. Despite the well-known shared mechanism of action of 5-HT_3 antagonists, they have their own distinguished chemical structures and demonstrate variable receptor binding affinities, durations of action and dose responses[49].

Ramosetron, a selective 5-HT 3 receptor antagonist usually available as its hydrochloride salt, has been on the market as an antiemetic drug for cancer patients receiving chemotherapy[50, 51] in Japan and a number of other Asian countries. It has a longer half life compared to other $5HT_3$ antagonists.

Granisetron has been in the market for a little longer time than ramosetron and is used throughout the world. It has been found to be more effective than older 5-HT_3 antagonists like ondansetron and other older antiemetic drugs[52].

The aetiology of PONV after laparoscopic appendicectomy is not known but probably associated with operative factors including effect of intraperitoneal carbon dioxide insufflation on residual stretching and irritation of the peritoneum[53]. It is mostly believed to be multifactorial in origin[54].

There are certain risk factors associated with PONV. These are classified into factors that are patient related, surgery related, and anaesthesia related. Anaesthesia related risk factors are use of volatile anaesthetics, N_2O, postoperative opioids, postoperative pain, and intraoperative hypovolemia. In our study these factors were standardised for all patients.

Patients in both groups were found to be comparable in terms of age, height, weight, gender and ASA status with no statistical significance. This standardises the patient related risk factors.

All the patients underwent laparoscopic appendicectomy and the duration of the procedures was comparable with no statistical significance.

PONV scores when compared in the first 0-6 hours showed a significant difference between the two groups. The incidence of PONV score of 0 was 98.2% in the ramosetron group compared to 38.2% in the granisetron group. This was statistically significant with a p-value<0.001. This is in contrast to 18% in the ramosetron group and 12% in the granisetron group found by Waqar-ul-Nisa et al.[15]who compared the two drugs in patients undergoing thyroidectomy under general

anaesthesia. This may be due to the different nature of the surgeries and the surgical durations involved.

In the second 6-12 hours we observed a statistically significant difference in the incidence of nausea, 3.4% in the ramosetron group and 58.2% in the granisetron group (p-value<0.001). Nausea free state (PONV = 0) was observed in 96.4% of the patients and in 38.2% of the patient in the granisetron group (p-value<0.001).

I Bhat et al[12]. who compared ramosetron and granisetron in laparoscopic cholecystectomy under general anaesthesia found that there was no statistically significant difference till 12 hours post operatively. Another study by Newstar et al[55]. comparing the same two drugs for laparoscopic cholecystectomy found that ramosetron is as effective as granisetron in preventing early (0-2 hours) and late (2-24 hours) PONV. This may be due to the different nature of the surgeries involved.

From 12-18 hours post operatively we found that the incidence of nausea was much less with ramosetron (9%) compared to granisetron (30.9%) which is statistically significant (p<0.001). This is similar to the results by Waqar-ul-Nisa et al.[15] who studied the effect of drugs after thyroidectomy (ramosetron 12% vs granisetron 30%, p=0.0479).

From 18-24 hours we found that the difference in nausea was not significant between the two groups (ramosetron 20% vs granisetron 23.6%, p=0.644). This is different from what Waqar-ul-Nisa et al.[15] who studied the effect of drugs after thyroidectomy (ramosetron 10% vs granisetron 34%, p=0.007).

Overall incidence of PONV (scores 1,2 & 3) was also less in the ramosetron group when compared to the granisetron group. The difference was statistically significant in all the time periods except in the last 6 hours.

I Bhat et al[12]. who compared granisetron and ramosetron in prevention of PONV after laparoscopic cholecystectomy concluded that ramosetron is superior to granisetron in providing prolonged relief from PONV. This is similar to our findings where ramosetron performed better than granisetron.

Emetic episodes which include retching and vomiting can cause suture dehiscence and cause various other complications like surgical site bleeding, hematoma formation, raised intracranial pressure, raised intraocular pressure etc. They require a rescue anti-emetic drug. We used injection dexamethasone 0.1mg/kg IV stat. Incidence of such episodes (PONV scores 2 & 3) were more or less equal in the two groups. This shows that granisetron is as effective as ramosetron in preventing emetic episodes but not effective in preventing nausea.

The results we got are similar to the results obtained by Yoshita Fuji et al.[56] who concluded that ramosetron is superior to granisetron for prevention of PONV during laparoscopic cholecystectomy.

Thakur R et al.[17] did a comparative evaluation of the efficacy of ondansetron, granisetron and ramosetron in patients undergoing caesarean section and found that ramosetron followed by granisetron is better than ondansetron for PONV prophylaxis. This result is in accordance with our result where we found ramosetron to be better than granisetron.

Feng Yi Feng et al[57]. also found ramosetron to be superior to granisetron in preventing nausea and vomiting after chemotherapy. 5-HT_3 receptors are involved both in CINV and PONV[58]. So extrapolating their results ramosetron should be better than granisetron in preventing PONV. This is in accordance to our results.

Ramosetron has been marketed as a drug with a significantly long duration of action compared to granisetron, an already established anti-emetic. In this study the anti-emetic action of ramosetron was much better than granisetron in all the time periods except the last six hours where the difference was statistically not significant.

Granisetron has come across as a slightly inferior drug in this study. This might be due to the dose of the drug we used which, that is 1mg. Studies have been done where it has performed better when higher doses (up to 3mg) was used[14]. So perhaps even though granisetron is an efficient anti-emetic for other surgeries done under general anaesthesia the dose required for its use in laparoscopic appendicectomy under general anaesthesia may be higher. These higher doses may increase the side effects. Ramosetron is also a 58 times more potent than granisetron and its effect lasts 10.7 times longer in ferrets treated with cisplatin. This vast difference in potency may also explain the favourable result we got in favour of ramosetron[57].

Ramosetron has a high pharmacological bio-availability[59]. This results in antagonism of maximum number of 5-HT3 receptors. It also has a higher affinity for 5-HT_3 receptors than granisetron[60]. These facts can explain the better efficacy against PONV which we have observed.

Most anaesthesiologists use a standardized dose of an anti-emetic as part of their anaesthetic protocol. We recommend that further studies be done to find out the best dose of an anti-emetic drug for a particular surgery. We also recommend that studies be done to compare ramosetron with higher doses of granisetron to prevent PONV after laparoscopic appendicectomy under general anaesthesia.

Another difference is that we used halothane to maintain the general anaesthesia while other studies used sevoflurane or isoflurane. This was due to the limitations at the institute where the study was conducted. Anaesthesia maintained with agents like propofol and dexmedetomidine have shown to be better at reducing PONV[61].

In the end we conclude that ramosetron is better than granisetron at preventing PONV after laparoscopic appendicectomy under general anaesthesia. We also found that both drugs are equally effective at preventing emetic episodes.

CONCLUSION

From our study we conclude that ramosetron is better than granisetron at preventing PONV after laparoscopic appendicectomy under general anaesthesia. We also found that both are equally effective at preventing emetic episodes.

SUMMARY

We conducted a study to compare the efficacy of ramosetron with granisetron in preventing post-operative nausea and vomiting (PONV) in 110 patients undergoing laparoscopic appendicectomy under general anaesthesia.

The study was conducted after obtaining institutional ethical committee clearance & written informed consent from all the patients. Thorough pre- anaesthetic evaluation was done, investigations were noted. Patients were randomised into two groups of 55 patients (Group R & Group G) each using a computer generated randomization table.

Patients in group R received injection 0.3mg ramosetron IV while patients in group G received injection granisetron 1mg five minutes before induction of anaesthesia. Patients in both groups were administered general anaesthesia using the same anaesthetic protocol.

Patients were monitored in the post-operative period for PONV and scored every six hours using the PONV scoring system.

We observed that age, gender, height, weight, ASA status and duration of surgery were comparable in both the groups. Incidence of PONV (scores 1,2 & 3) were found to be lower in the ramosetron group and the difference was statistically significant. Incidence of emetic episodes (PONV scores 2 & 3) were comparable in both the groups.

So from our study we derive that ramosetron is better than granisetron at preventing PONV in patients undergoing laparoscopic appendicectomy under general anaesthesia. Both drugs are equally effective in preventing retching and vomiting.

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ANNEXURE – I – ETHICAL CLEARANCE LETTER

K.L.E.SOCIETY'S
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Ref: MDC/DOME/ 08.

Date: 30/11/2013

To,

PG student in M.D. Anaesthesiology,
J.N.Medical College,
BELGAUM.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled " **To compare the efficacy of ramosetron and granisetron in prevention of post operative nausea and vomiting in patients undergoing laparoscopic appendicectomy under general anesthesia – A one year RCT**" is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Hema Dhumale)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belgaum.

(Dr.Ganga Pilli)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belgaum.

ANNEXURE – II - CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____, we are requesting you to enrol yourself in study titled "TO COMPARE THE EFFICACY OF RAMOSETRON AND GRANISETRON IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANESTHESIA – A ONE YEAR RANDOMIZED CONTROLLED TRIAL" conducted by Dr. _____, Post Graduate in M.D. Anaesthesiology under the guidance of Dr_____ , Professor & Head, Department of Anaesthesiology, J.N. Medical College, Belagavi under KLE University, Belagavi.

Respected Sir/Madam we request you to enrol yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N. Medical College. If you decide to participate you are free to withdraw at any time.

The purpose of research is to compare the efficacy of the drugs ramosetron and granisetron in the prevention of post-operative nausea and vomiting.

Procedure Involved:

If you agree to enrol yourself in my study, you will be interviewed regarding your present, past and family history. Then you will be clinically examined in detail and investigated accordingly. You will receive either Inj. Ramosetron 0.3mg IV or Inj. Granisetron 1mg IV while undergoing general anaesthesia for the surgery. You will be assessed for episodes of nausea and vomiting for up to 24hrs after the surgery.

Benefits and Risks

The benefits of taking part in this research is that you will have a reduced incidence of nausea and vomiting and you will play an essential role in helping patients who undergo surgeries in the future. Side effects might include headache, dizziness, diarrhoea, muscle ache and drowsiness. Risks are minimal as both the drugs have a very safe pharmacological profile.

Voluntary participation / Withdrawal

Taking part in the study is voluntary; you may choose not to enrol in this study. Your decision will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital & MRC.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Confidentiality

All information collected about you during the course of the study will be kept confidential. The code numbers will identify you in this study. Records and the information from this study may be published but your identity will be confidential in any publication. The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to others without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury or complication related to the study, treatment will be made available at Dr. Prabhakar Kore Hospital and MRC, Belagavi. No reimbursement, compensation or free medical care will be given by law.

Queries/ Contact details

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. _____, Department of Anaesthesiology, J. N. Medical College. Dr. _____, Professor & Head, Dept. Of Anaesthesiology, J. N. Medical College.

If you have any queries about your rights as a study subject, you may call Dr. Ganga Pilli, Professor & Head of Pathology as Chairman of J. N. Medical College Institutional Ethics Committee on Human Subjects Research, Phone No.0831 2473777 ext-4052, 09448863866 at J. N. Medical College, Belagavi.

Consent for participation in research trial

I, _____ voluntarily agree for the participation as a subject of study. By signing this consent form, I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read form in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name: _____

Signature or the Left Thumb Print of Subject: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____

Investigators Name: _____

Signature: _____

Date: _____

Place : _____

ANNEXURE – III - PROFORMA

"TO COMPARE THE EFFICACY OF RAMOSETRON AND GRANISETRON IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANESTHESIA – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"

Patient Name:	IP No.:
Age:	Gender:
Occupation:	Address:
Date of Operation:	Anaesthesiologist:
Height:	Weight:

Pre-anaesthetic Evaluation:

Chief Complaints:

Past History:

a. HTN / DM / Asthma / Epilepsy / Drug allergy

b. Drug therapy

c. Previous exposure to anaesthesia

Family history:

General physical examination

Pallor / Icterus / Clubbing / Cyanosis / Lymphadenopathy / Oedema

PR:	BP:
RR:	Temp:
Jaw movements:	Teeth:
Airway assessment:	Spine:

Systemic Examination

RS: CNS:

CVS: Abdominal:

Investigations

Haemoglobin: Total Leukocyte Count:

Platelet Count:

Serum urea: Serum creatinine:

Urine routine:

Bleeding Time: Clotting Time:

ECG: Chest X-Ray:

Preoperative physical status: ASA Grade I II

Diagnosis:

Proposed Surgery:

Preoperative baseline values

HR: BP:

Monitors attached

Pulse oximetry: NIBP:

ECG:

Vital parameters:

Duration of the surgery:

Incidence of the emetic episodes will be compared in 2 groups according to nausea and vomiting score-

0=No emetic symptoms

1=Nausea

2=Retching

3=Vomiting.

Patient shall receive inj. Dexamethasone 0.1mg/kg IV as rescue medication.

Time in hours	0-6	6-12	12-18	18-24
PONV score				

ANNEXURE – IV - PHOTOGRAPHS

Photograph 1: Injection Ramosetron Hydrochloride 0.3mg per ml

Photograph 2: Injection Granisetron Hydrochloride 1mg per ml

ANNEXURE V – KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologist
F	-	Female
hrs	-	Hours
IP No.	-	In Patient Number
kg	-	Kilogram
M	-	Male
m	-	Metre
min	-	Minutes
PONV	-	Post-operative Nausea and Vomiting
Serial No.	-	Serial Number