"A RANDOMIZED CLINICAL TRIAL TO COMPARE PALONOSETRON AND ONDANSETRON FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING"

by

REGISTRATION NUMBER-BA0110004

Dissertation

Submitted to the
KLE UNIVERSITY, Belgaum, Karnataka,
In partial fulfillment
of the requirements for the degree of
M.D. (DOCTOR OF MEDICINE)
in
ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY
JAWAHARLAL NEHRU MEDICAL COLLEGE
BELGAUM – 590010

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ENDORSEMENT BY THE HEAD OF DEPARTMENT, PRINCIPAL OF THE INSTITUTION

This is to certify that the dissertation entitled **"A RANDOMISED CLINICAL TRIAL TO COMPARE PALONOSETRON AND ONDANSETRON FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING"** is a bonafide research work done by **THE CANDIDATE REG.NO**. **BA0110004.**

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ABBREVATIONS

5 HT	-	5 Hydroxy tryptamine
ASA	-	American Society of Anaesthesiologists,
CTZ	-	Chemoreceptor Trigger Zone
PONV	-	Post Operative Nausea Vomiting
CINV	-	Chemotherapy Induced Nausea and Vomiting
CR	-	Complete Remission
AVP	-	Arginine vasopressin
TRH	-	Thyroid releasing hormone
VIP	-	Vasoactive intestinal peptide
VIZ	-	Namely
Vs	-	Versus
i.v.	-	Intra Venous
i.m.	-	Intra Muscular
Hrs	-	Hours
Kg	-	Kilograms
Mg	-	Miligrams
Sec	-	Seconds
Cms	-	Centimeter
GIT	-	Gastro intestinal tract

ABSTRACT

BACK GROUND AND OBJECTIVES:

Nausea and vomiting have been associated for many years with the use of anaesthetic techniques for surgical procedure. Objective of the present study is to compare the efficacy of Palonosetron and Ondansetron for prevention of post operative nausea and vomiting in patients undergoing abdominal surgery under general anaesthesia.

METHODOLOGY:

The present one year randomized clinical trial was conducted in the Department of Anaesthesiology, K.L.E'S Hospital and M.R.C. Belgaum during the period of JAN 2011-DEC 2011 on 140 patients undergoing abdominal surgeries under GA. A thorough pre-anaesthetic evaluation was performed by taking history and clinical examination. Weight, basal heart rate, respiratory rate, blood pressure were recorded. Investigations like complete blood count, urine routine were done. Investigations like blood sugar, electrocardiogram and chest x-ray were performed if required. After explaining the anaesthetic procedure, written informed consent for participation in the study was obtained. The patients were randomly allocated into two groups, Group I(Control group) and Group II(Study group) of 70 each by computer generated randomization. Occurrence of PONV was noted and was scored for 24 hrs.

RESULTS:

The incidence of PONV was significantly lower in the Palonosetron group compared with the Ondansetron group (24.3% vs 78.6%, respectively). And emetic episodes were observed in 5.71% of patients in Palonosetron group compared to 61.4% of patients in Ondansetron group. The results were clinically and statistically significant.

INTERPRETATION AND CONCLUSION:

Incidence of ponv and emetic episodes is less in patients who had received iv Palonosetron in comparison to those who had received iv Ondansetron in patients undergoing abdominal surgeries under GA. From the study we conclude that Palonosetron is more efficacious than ondansetron for prevention of PONV in patients undergoing abdominal surgery under GA.

KEY WORDS: Post Operative Nausea and Vomiting, Palonosetron, Ondansetron.

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INTRODUCTION

Post operative nausea and vomiting remains a significant problem in the modern day anaesthesia practice and continues to be a significant challenge following many types of anaesthetics.[1]

During the past decade, anaesthesiologists have been modifying their anaesthetic techniques to ensure a more rapid and smooth recovery. There has been a general trend towards decrease in the incidence of the problem of PONV because of the use of less emetic anaesthetic agents, improved pre-operative and postoperative medication, refinement of operative techniques and identification of patient predictive factors[2, 3]. However inspite of these advances, nausea and vomiting still occurs with unacceptable frequency in association with surgery and anaesthesia and description of it as "the big little problem"[4] encapsulates much of the general perception.

Post operative nausea and vomiting in addition to being distressing and unpleasant to the patients, has a potential to adversely affect the patient in the form of delayed recovery, unexpected hospital stay, and can also cause post surgical morbidities like wound dehiscence, pulmonary aspiration, surgical site bleeding and dehydration[5].

This is not just "Big little problem" in post surgical patients, but it is true in cancer therapy patients also, where the choice of cytotoxic drugs or radiotherapy may be determined by the likelihood of severity in the incidence of vomiting rather than efficiency against the neoplasm.

Various drugs has been used to prevent PONV namely antihistamines, phenothiazine derivatives, anticholinergic and dopamine receptor antagonists. Use of these drugs is associated with unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness and tachycardia[6, 7, 8].

The management of nausea and vomiting has improved greatly in recent years, with the introduction of 5 Hydroxytyptamine ($5\text{-}HT_3$) receptor antagonists. The commonly used drug of this group is Ondansetron[9]. Ondansetron is being considered as a gold standard drug for treatment of PONV. 2^{nd} generation drug Palonosetron has been recently introduced and is believed to be more potent and longer acting than Ondansetron[5].

Hence the present study was undertaken to compare the antiemetic effects of Palonosetron and Ondansetron for prevention of post operative nausea and vomiting in patients undergoing abdominal surgeries under general anaesthesia.

OBJECTIVE

To compare efficacy of Palonosetron and Ondansetron for prevention of post operative nausea and vomiting, in patients undergoing abdominal surgeries under general anaesthesia.

REVIEW OF LITERATURE

Post-operative nausea and vomiting is a frequent complication of surgery, which can lead to patients discomfort and dissatisfaction as well as considerable medical and economic consequences.

Various drugs has been used to prevent PONV namely antihistamines, phenothiazine derivatives, anticholinergic and dopamine receptor antagonists[6]. Use of these drugs is associated with unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness and tachycardia[7, 8]. Recently introduced $5HT_3$ antagonists are devoid of such side effects and are highly effective in treatment of PONV.

In 1991 a study was done which showed that, the treatment of PONV with ondansetron significantly decreased post treatment nausea score without increasing sedation or producing changes in cardio-respiratory parameters. Only 43% of the ondansetron treated patient's required "rescue" antiemetic compared with 86% in the placebo group. Thus they showed that inj. Ondansetron 8 mg i.v was associated with decreased incidence of nausea and vomiting in outpatients undergoing laparoscopic procedure [10].

Another study was done in 1995 to compare the efficacy of Ondansetron 4mg and 8mg on 75 patients who underwent middle ear surgery under general anaesthesia. 75 patients were randomized into 3 groups receiving 4mg, 8mg i.v ondansetron or placebo. Study revealed that 12%, 12%, and 24% of the patients in the placebo group suffered from nausea, retching and vomiting respectively. The corresponding values in Ondansetron 4mg group were 16%, 4%, and 8% and in 8mg group was 4%, 16%,

16%. 12 patients in the placebo group needed "rescue" antiemetic (droperidol 10µ/Kg). But only 6 and 7 patients required it in the ondansetron group with 4mg and 8 mg respectively. Study revealed that dose less than 8mg is safe and effective antiemetic for treating postoperative nausea and vomiting [11].

Another study was done in 1997, to evaluate the efficacy and safety of injection Ondansetron 4mg or 0.1mg/Kg i.v. in children. The study was done in 427 children undergoing tonsillectomy with or without adenoidectomy in the age group of 1-12 yrs. Emesis and nausea were analyzed separately .Compared with placebo treated children, significantly more Ondansetron treated children had no emetic episodes i.e. 127/212 (60%) vs. 108/213 (51%) with P=0.004 and experienced no postoperative nausea (135/211, (64%) vs. 108/213 (51%) p=0.004) in the first 24 hrs. No significant side effects were being observed in the children who received ondansetron[12].

A study was conducted in 1999 on 54 women undergoing modified radical mastectomy (MRM). Following surgery patients received either saline placebo or ondansetron 4 mg i.v. The study showed 24 hour incidence of PONV (81.5% vs 33%) was significantly lower in ondansetron group and only 15% of patients treated with Ondansetron required a 'rescue' antiemetic compared with 59% in placebo group. Thus the study showed that injection Ondansetron 4mg i.v was associated with decreased incidence of nausea and vomiting in patients undergoing modified radical mastectomy[13].

Following Ondansetron a number of superior $5HT_3$ antagonists were introduced. Newer one being Palonosetron hydrochloride.

A study was done in the year 2008 which assessed the efficacy and safety of 3 different doses of Palonosetron, compared with placebo, on the incidence and severity of PONV for 72 hours post-surgery. The study was done on 574 patients undergoing either outpatient abdominal or gynaecological laparoscopic surgery. Complete response (CR: no emetic episodes and no rescue medication) during 0-24 and 24-72 hours post-operative time intervals were studied.CR of PONV for first 24hrs with Palonosetron 0.075 was 43% and 26% with placebo and 49% and 41% for 24-72hrs.Compared with placebo Palonosetron 0.075mg was associated with significant downward shift towards less intense nausea and with significant reduction in impact of PONV on patients functioning during 0-24hrs interval[14].

In 2008, a multicenteric study was done on 544 patients undergoing elective gynaecological or breast surgery to evaluate efficacy and safety of 3 different doses of Palonosetron versus placebo in preventing PONV over 72 hrs period .Complete response rates for placebo and palonosetron 0.075 mg were 36% and 56% for 0-24hrs, 52% and 70% for 24-72 hrs, 36% and 52% for 0-72 hrs time interval. The study showed that a single 0.075 mg i.v dose of palonosetron effectively reduced severity of nausea and delayed the time to emesis and treatment failure in the inpatient surgical setting[15].

Palonosetron is also a promising drug in treatment of chemotherapy induced nausea and vomiting when compared to ondansetron. A study was done in 2006 on 667 patients who were scheduled to receive a single dose of highly emetogenic chemotherapy. Patients randomly received single i.v dose of Palonosetron 0.025 mg or 0.075 mg, or Ondansetron 32 mg prior to highly emetogenic chemotherapy.

Dexamethasone pre-treatment was used at investigator discretion. The study showed that single dose palonosetron was as effective as ondansetron in preventing acute chemotherapy induced nausea and vomiting (CINV) following highly emetic chemotherapy, and with dexamethasone pre-treatment, its effectiveness was significantly increased over ondansetron throughout the 5 day post chemotherapy period[16].

The role of i.v dexamethasone in treatment of PONV has been extensively studied. Data was collected from 1,946 patients from 17 trials and was analyzed. Dexamethasone was compared with placebo in 4 trials in adults and 3 trials in children. The study proved that use of i.v dexamethasone was associated with reduced incidence of PONV[17]. Hence 8 mg i.v dexamethasone is used as rescue anti emetic in the study.

A prospective randomized double blind study to compare the antiemetic effect of Ondansetron and Palonosetron in patients undergoing thyroidectomy was done in the year 2012 on 100 female patients. The result showed that incidence of PONV during the 24 hrs postoperative period was lower in the Palonosetron group than in the Ondansetron group(42% vs 62%, P=0.045). Incidence of nausea and vomiting and nausea severity were significantly lower in palonosetron group than in ondansetron group during 2-24 hrs. The difference in the use of rescue antiemetic was at 2-24 hrs(10% with Palonosetron compared with 28% with Ondansetron, P=0.02). The study concluded that palonosetron is more effective than ondansetron for high risk patients receiving fentanyl based PCA after thyroidectomy, especially 2-24 hrs after surgery[18].

However, literature regarding comparison of efficacy of Palonosetron and Ondansetron for prevention of PONV among patients undergoing abdominal surgeries is scant. Hence this study was undertaken to compare the efficacy of Palonosetron and Ondansetron for prevention of PONV in patients undergoing abdominal surgery under general anaesthesia.

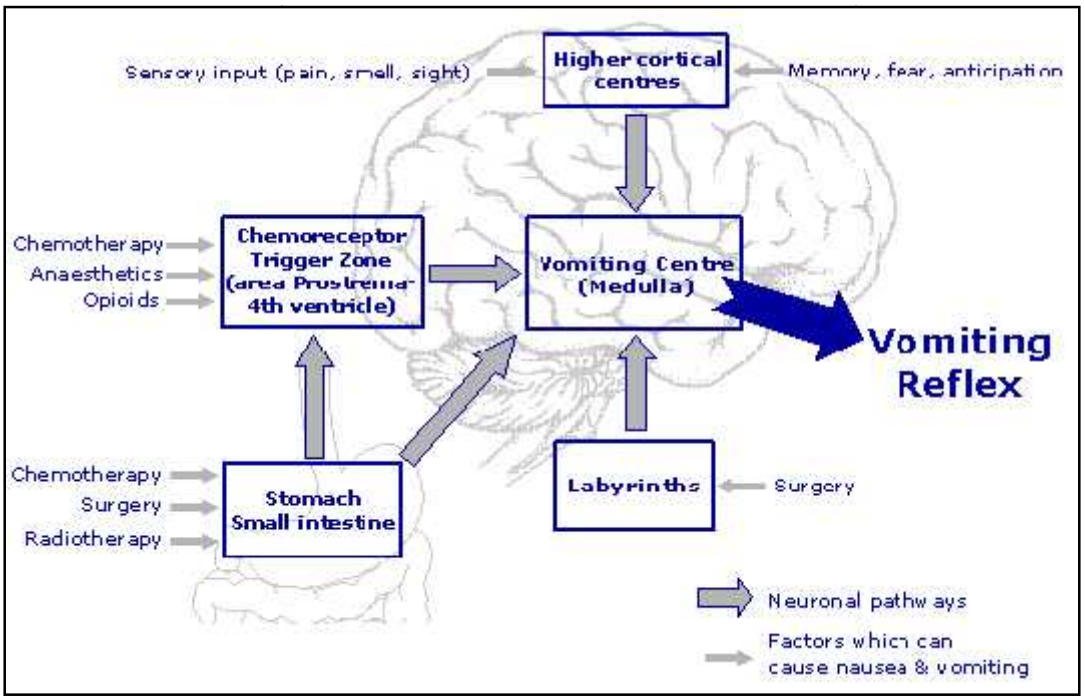
PHYSIOLOGY OF VOMITING

Definitions:

Term Nausea is derived from Greek word “nautia” meaning seasickness. Nausea is defined as a subjective sensation of unease and discomfort in the stomach with an urge to vomit referred to 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.



General Mechanism of Vomiting.

GENERAL MECHANISM OF EMESIS:

Vomiting reflex has 3 major components, these are

Emetic detectors

Integrative mechanism

Motor components

EMETIC DETECTORS: are the various pathways for the nausea and vomiting

A) Abdominal visceral afferents: Gut wall has a system which is capable of detecting the accidental ingestion of toxins and is capable of activating vomiting reflex. For this vagus is the motor nerve, and in its abdominal course it contains 80-90% afferent fibres. Electrical stimulation of the abdominal vagal afferents induces vomiting within 20 seconds[19].

Vagal afferent fibers are of 2 types

I) Mechanoreceptors: These are located in the muscular layer of the gut and are activated by the contraction or distension of the gut. Eg(By over eating or obstruction.)

II) Chemoreceptors: located in the mucosa of the upper gut. They respond to mucosal stroking, acid, alkali, hyper tonic solutions, temperature and irritants[20].

B) Area postrema:

Area Postrema is a u shaped structure. It contains chemoreceptor trigger zone (CRTZ). CRTZ is a circumventricular organ at the bottom of the 4^{th} ventricle in the region of obex. It is devoid of blood - brain barrier and CSF – brain barrier and hence is able to detect various emetogenic substances in the blood stream. Borison and Wang demonstrated that various stimuli were detected by cells of CRTZ which in turn sent emetogenic trigger to the brain stem's vomiting center to activate the vomiting reflex.

C) 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 center and influence emetic 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 uvula and nodule of the cerebellum, the signals are transmitted to CTZ and then to emetic center to cause vomiting.

D) Higher centers:

Input from higher centers (i.e. Limbic system) can induce nausea and vomiting. They mainly have facilitating role in modulating the sensitivity of brain stem emetic mechanism[21].

E) Miscellaneous inputs:

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:

Vomiting centre:

Vomiting is a stereotyped motor programme involving co-ordination between the autonomic and somatic components of the nervous system. The complex act of vomiting involves co-ordination of respiratory, gastro-intestinal and abdominal

musculature. Anatomic studies show that the parvicellular reticular formation has access to motor pathways responsible for the visceral and somatic output involved in vomiting. This area is situated in the lateral reticular formation in the brainstem, close to tractus solitaries and is thought to be the vomiting center[22].The nucleus tractus solitaries is rich in enkephalin, histaminic and muscarinic cholinergic receptors

MOTOR COMPONENTS OF VOMITING

The act of emesis is divided into three phases.

Pre ejection phase

Ejection phase

Post ejection phase

Pre-ejection phase (Prodromal phase):

Is dominated by nausea along with autonomic and gastrointestinal changes. Autonomic symptoms include heavy salivation, swallowing, cold sweating, pallor, tachycardia and papillary dilation. Low level stimulation of vomiting pathways may result in nausea without vomiting. Pre- ejection phase may last minutes, hours, or even days; as seen with pregnancy, chemotherapy and space sickness. Autonomic manifestations often precede active vomiting and may result from the proximity of vomiting centers to vagal and regulatory nuclei.

Gastro intestinal changes in this phase include profound relaxation of the proximal stomach mediated by vagal afferent nerves. Along with this, a retrograde giant contraction originates in mid small intestine and travels towards stomach. This antiperistaltic wave travels backwards up the intestine at a rate of 2 to 3 cm/ sec. As a result duodenum becomes over distended. The distension is the main exciting factor that initiates the actual vomiting act .Strong intrinsic contractions occur both in

duodenum and stomach, along with the beginning of relaxation of lower oesophageal sphincter. This allows vomitus to begin moving into oesophagus. From here on specific vomiting act occurs.

Ejection phase:

Impulses are transmitted by both vagal and sympathetic afferents to the bilateral vomiting centers of the medulla. Appropriate motor reactions begin. The motor impulses transmitted from vomiting center 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.

Vomiting Reflex:

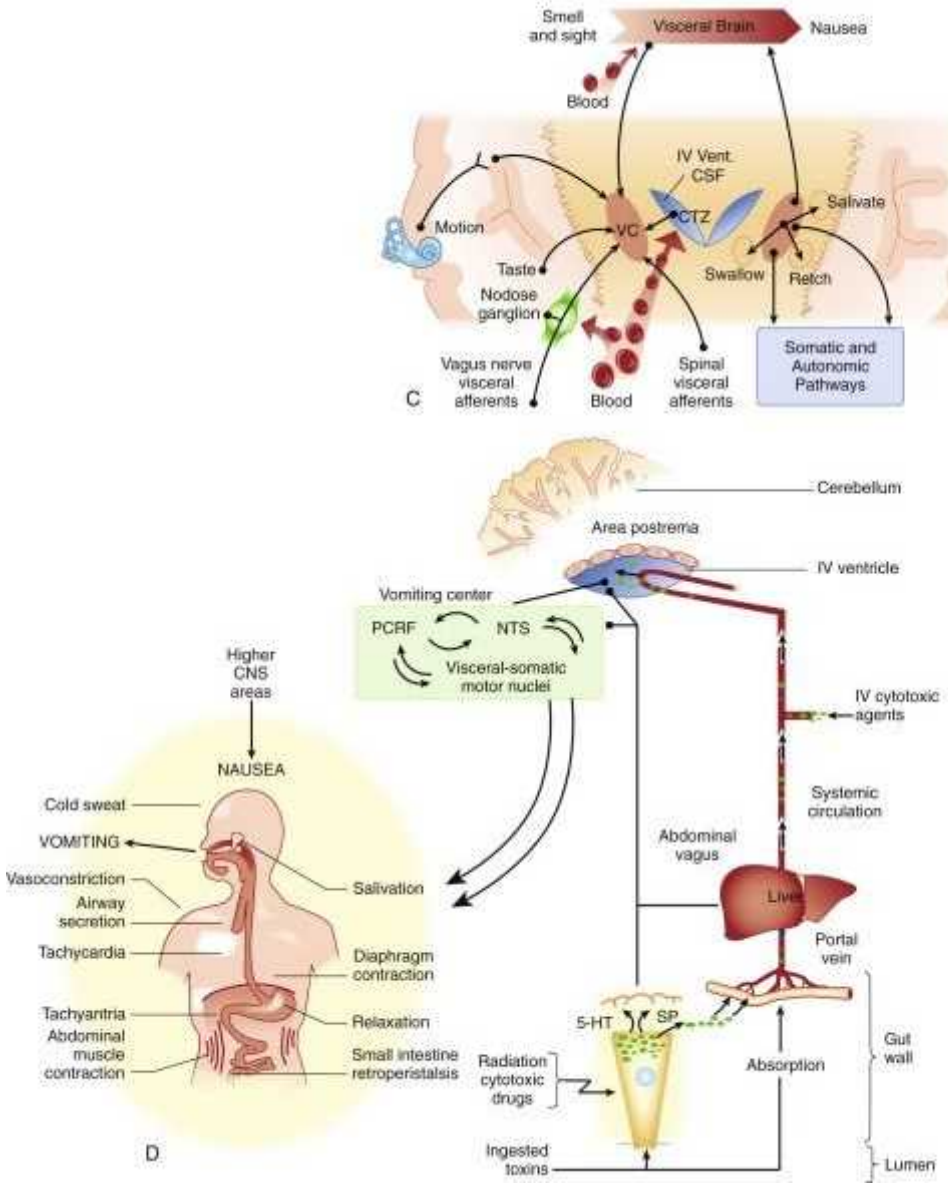
It is a complex act involving both the striated and visceral muscles. When the vomiting center is stimulated, there occurs deep inspiration, rising of the hyoid bone and larynx to pull the crico-oesophageal sphincter open, elevation of the soft palate to close nasopharynx and glottis. Proximal stomach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

Finally contraction of oesophageal muscle pulls the stomach into thorax, forming a 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].



Etiological Factors involved in Vomiting.

Causes for Post operative nausea and vomiting

Causes are multi factorial and are classified as

I. Pre operative factor

II. Intraoperative factors

III. Postoperative factors.

PREOPERATIVE FACTORS:

1) Food:

Anaesthetising the patient after meals is associated with emesis both during induction and post operative period. Food induces abdominal vagal afferent activation by its volume and chemical composition. This in combination with central emetic effect of anaesthetics provides a sufficient emetic drive. Hormones released by gut like (gastrin, peptide, and motilin) sensitize area postrema to effects of other stimuli.

2) Pre existing conditions:

Pre existing conditions like Diabetes Mellitus, Uraemia, intra cranial hypertension, pregnancy, motion sickness, and abdominal disorders predisposes patient to nausea and vomiting. Female patients, young age , emergency operation , type of surgery , history of previous post operative nausea and vomiting and obesity increases the risk of nausea and vomiting.

3) Anxiety and stress:

Increases risk of emesis by increasing the releases of catecholamines or by excessive air swallowing[25]. Increased circulating stress hormones delays gastric emptying and increases the gastric fluid volume.

4) Premedication:

Atropine causes delayed gastric emptying leading to post surgical stasis. Opioids decreases gastric emptying by increasing duodenal tone. They act on the

vestibular nucleus releasing leuenkephalin and thereby sensitizing the vestibular system. Opoids also enhance release of 5HT3 from small intestine by disinhibition of tonically inhibiting neural pathways to the enterochromaffin cells. The emetic effect is via action on opioid receptors (probably mu) present in area postrema

5) Intubation:

Intubation leads to Stimulation of pharyngeal mechanoreceptor afferents which will project to the glossopharyngeal nerve, and evokes gag reflex leading to nausea and vomiting[21].

INTRA OPERATIVE FACTORS

A. Anaesthesia:

During anaesthesia, patient is in recumbent position with immobile head. This causes decrease in tonic discharge from vestibular labyrinth. On awakening the head often moves first, leading to sudden vestibular discharge. In addition nystagmus and papillary dilatation which has not returned to normal after anticholinergic pre medication, causes vestibule visual mismatch leading to vomiting.

B. Anaesthetics:

I) Pharmacological effects of anaesthetics: Interaction of anaesthetic agents with adrenergic receptors and their adrenomimetic 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 center, present in the brain stem when active will inhibit the vomiting center. 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 center.

II) Physical effects of anaesthetics:

Mask ventilation will lead to gastric distension

Gut distension can occur with gases like nitrous oxide

Reduction in intestinal motility can occur and suppression of belching reflex occur[25].

Irritation of gastric mucosa occurs with agents like ether.

III) Physiological effects of anaesthetics:

Endocrine effects: Peptide hormones like Angiotensin, AVP, bombesin, gastrin, somatostatin, insulin, neuropeptide Y, TRH, neurotensin, VIP released during anaesthesia and surgery activates area postrema and cause ponv.

Cardiovascular effects: Hypotension causes large sympathetic discharge releasing adrenaline from adrenal medulla thus inducing vomiting. Vagal afferent mechanoreceptors located in the ventricles of the heart are activated by tachycardia with hypovolemia. This occurs when the patient sits upright causing venous pooling in the lower body.

C. Surgery:

General effects of surgery:

Reduced gastro intestinal motility and increased concentrations of vasopressin predisposes to post operative nausea and vomiting.

Specific effects of surgery:

Certain surgical procedures are associated with increased incidence of post operative nausea and vomiting. Examples like;

Ocular surgery especially squint surgery has high incidence because of oculoemetic and oculogastric reflex. Traction on the extraocular muscles during surgery stimulates afferent neural pathways to the vomiting centre via the ciliary ganglion or labyrinthine pathway.

In middle ear surgery, there is high incidence of emesis because of activation of vestibular afferent pathway and stimulation of Arnold's nerve. Mechanical stimulation of the pharynx results in the activation of the glossopharyngeal nerve which is afferent in vomiting reflex. Nasal surgery evokes emesis by stimulation of gastric and pharyngeal afferents by the swallowed blood.

Intra abdominal surgeries cause more vomiting than extra abdominal ones. The gut, mesentery, kidney, bladder and uterus are innervated by vagal and splanchnic afferents that can be activated by mechanical stimulation[20]. Along with this manipulation of these organs induces release of serotonin from enterochromaffin cells which increases risk of vomiting.

Gynaecological surgery especially laproscopic surgery has very high incidence of vomiting. Women are more sensitive than men in response to emetic stimuli. Vomiting depends on the prevailing hormonal status of the woman with four fold increase in incidence during menstruation and lower incidence postmenopausally[26]. Vomiting sickness in pregnancy is a state in which the central emetic mechanism is sensitised[27]. Incidence is higher with dilatation and curettage. Afferents supplying uterus, broad ligament, and vaginal cervix are sensitive to gentle probing, rubbing and ischemic stimuli. Bradykinin and serotonin that are released are more sensitive in oestrous tissues.

POST OPERATIVE FACTORS:

I) Residual effect of drugs and anaesthetics

Opioids still being present in the blood during the post operative period induce vomiting by stimulation of CTZ, by sensitizing the vestibular system and delaying the gastric emptying. Neostigmine used for reversal of neuromuscular blocked is also associated with increased incidence of vomiting because of marked stimulation of

gastric motility, which in turn will activate vagal afferents and triggers central emetic mechanism sensitised by other factors.[28] Prolonged disruption of gastric function causes gastric stasis and reduced intestinal motility leading to post operative nausea and vomiting.

II) Perioperative pain:

Clinical studies have shown that pain is associated with sensation of nausea rather than frank vomiting.[25, 29] The mechanism involved in nociceptor induced nausea is not clearly known, but current knowledge points towards two mechanisms

1) Pain causes general arousal or alertness of the central nervous system, making them to experience nausea generated by other inputs.

2) Activation of nociceptors alters the threshold for emesis by sensitisation of the afferents at both central and peripheral sites. Central sensitization is caused by the release of afferent neurotransmitters and excitatory amino acids that prolongs the synaptic potentials. Peripheral sensitization is caused by release of serotonin, histamine and cytokines.

COMPLICATIONS OF POST OPERATIVE NAUSEA AND VOMITING

Post operative nausea and vomiting has adverse consequences like[5]

1. Delayed recovery
2. Unexpected hospital stays and delayed return to work of ambulatory patients
3. Post surgical morbidities such as wound dehiscence, pulmonary aspiration, surgical site bleeding, dehydration and electrolyte disturbances can occur.

MECHANISM OF ACTION OF ANTIEMETIC AGENTS

Neurotransmitters which play important role in mediating emetic response are:

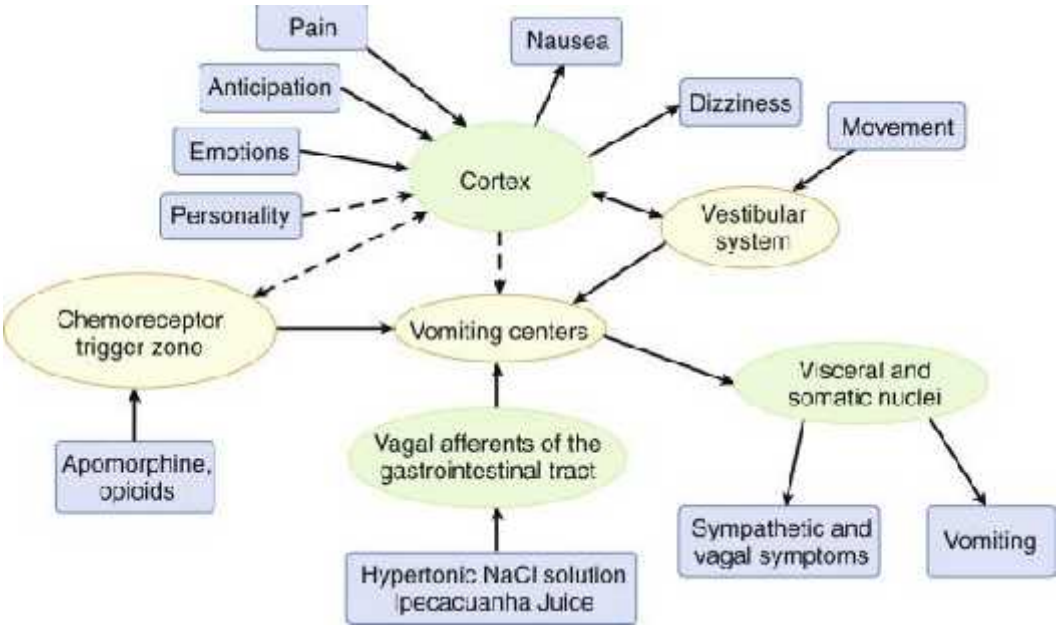
Dopaminergic (D_2)

Histaminergic (H_1)

Cholinergic muscarinic

Serotonin ($5HT_3$)

Area postrema is rich in dopamine, opioid, serotonin receptors. Nucleus tractus solitarius is rich in enkephalin, histamine and cholinergic muscarinic receptors. Vomiting center 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 have greater antiemetic action than a single drug. Drugs acting on Dopaminergic, Histaminergic and Cholinergic muscarinic receptors caused sedation, dizziness, dry mouth and muscular dystonias as side effects. Drugs acting on 5HT3 receptors had favourable side effect profile; this made them popular choice in both adult and paediatric surgical population.



Pathways for nausea and vomiting.

PHYSIOLOGY AND PHARMACOLOGY OF 5-HYDROXYTRYPTAMINE

The potential value of 5-hydroxytryptamine receptor antagonists was discovered through study of metoclopramide in 1980's. The exact mechanism through which 5-hydroxytryptamine (5-HT) and 5-HT3 receptors contribute to the control of PONV are unknown. But their involvement is demonstrated by the antiemetic effect of ondansetron, $5HT_3$ receptor antagonists. 5-HT is a naturally occurring neurotransmitter, found widely in both plants and animals.

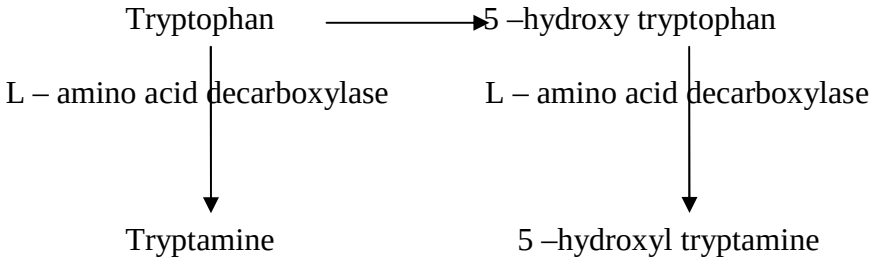
ENDOGENOUS 5- HT:

About 90% of body's content of 5-HT is located in enterochromaffin cells of intestines; most of the rest is in platelets and brain.

Synthesis, Uptake and Storage:

5-HT is β-aminoethyl-5-hydroxyindole and is synthesised in situ by 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[30].

Synthesis and degradation of 5-HT



Mechanism of action of 5-HT:

All 5-HT receptors are G-protein coupled receptors which functions through decreasing (5-HT_1) or increasing (5-HT_4, 5-HT_6, 5-HT_7) cAMP production or by generating IP3/DAG (5-HT2) as second messenger.

$5HT_3$ receptors are ligand gated cation selective channels. It mediates membrane depolarisation and increases Na, K conductance by opening the ion channels and neuronal excitation.

Absorption, metabolism and excretion:

Most of the 5- HT, either endogenous or ingested undergoes oxidative deamination by monoamine oxidase (MAO) to form 5-hydroxyindole acetaldehyde. This inturn is degraded by oxidation to 5-hydroxyindole acetic acid (5-HIAA) by acetaldehyde dehydrogenase. Again by aldehyde dehyrogenase 5-HIAA is reduced to 5- hydroxyl tryptophol (5-HTOL). The principal metabolite is 5-HIAA and is excreted in the urine (2 to 10 mg /24 hrs).

Classification of 5-HT receptors:

There are 4 families of 5-HT receptors comprising of 14 receptor subtypes.

5-HT receptors family

5-HT1	5-HT2	5-HT3	5-HT4
5-HT 1A	5-HT 2A		
5-HT 1B	5-HT 2B		
5-HT 1D	5-HT 2C		
5-HT 1E			
5-HT 1F			

Functions of Endogenous 5-HT:

Major function of 5-HT is to serve as neurotransmitter in brain. It is involved in sleep, temperature regulation, cognitive functions, behaviour and mood. Enterochromaffin cells and 5-HT containing neurons regulate peristalsis and local reflexes in the gut. 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 and its action on 5-HT_3 receptors in the gut, area postrema and nucleus tractus solitarious.

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.

5-HT_4 Antagonists: Renzapride.

5-HT and emesis:

Of all 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 blocks the depolarising action of 5-HT through 5-HT_3 receptors on vagal afferents in the GIT as well as in NTS and CTZ[31].

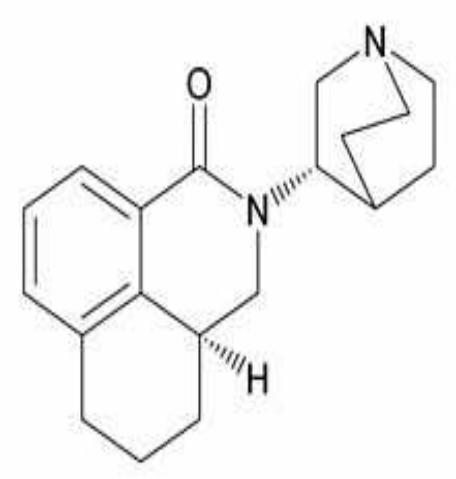
Cytotoxic drugs /radiation produce nausea and vomiting by causing cellular damage, release of mediators including 5-HT from the intestinal mucosa, activation of vagal afferents in the gut, emetogenic impulses to the NTS and CTZ. 5-HT_3 receptor antagonists block emetogenic impulses both at their peripheral and central relay[31].

PHARMACOLOGICAL PROFILE OF PALONOSETRON

Palonosetron is the latest 5-HT_3 antagonists and is the first of a 'second generation' of 5-HT_3 antagonists. It is the only drug of its class approved for prophylaxis against both acute and delayed chemotherapy induced nausea and vomiting. Palonosetron has also been approved for its use in prevention of PONV. Palonosetron has got far higher receptor affinity and a much longer half life than other 5-HT_3 antagonists and confers a prolonged duration of action

CHEMICAL STRUCTURE:

Palonosetron is a single stereoisomer isoquinoline based on a fused tricyclic ring system attached to a quinuclidine moiety. Palonosetron Hydrochloride is hexahydro-1-oxo-1Hbenz (de) isoquinoline hydrochloride. The empirical formula is C19H24N2O HCl, with a molecular weight of 332.87.



Structure of Palonosetron

Pharmacology:

Palonosetron is a potent, reversible and competitive antagonist of 5-HT_3 receptor.

Anti emetic action:

Anti emetic action is through competitive antagonism of 5HT3 receptors. 5HT3 receptors are found in the gut and in areas of the central nervous system associated with the regulation of nausea and vomiting, being abundant in the

chemoreceptor trigger zone of the area postrema which has projections to the vomiting center located in the lateral reticular formation of the medulla oblongata. Stimulation of these receptors initiates the vomiting reflex.

Peripheral $5HT_3$ receptors are located in vagal nerve terminals, which are linked to the vomiting center via the nucleus tractus solitarius. Competitive antagonism with 5-HT_3 receptor antagonists at these sites, and probably others, can block initiation of the vomiting reflex caused by emetogenic stimuli.

PHARMACODYNAMICS:

Receptor binding is the most important factor influencing the duration of action of the 5-HT_3 antagonists. Palonosetron shows avid binding for 5-HT_3 receptors, with a pK of 10.4, which far exceeds other 5-HT_3 antagonists. Binding affinity is more than 30 times the potency of granisetron and 100 times that of Ondansetron.

Unlike other 5-HT_3 Antagonists, Chemical structure of Palonosetron is dissimilar to serotonin, so palonosetron binds to the 5-HT receptor at an allosteric site, different to other antagonists that bind at the orthosteric site occupied by serotonin. This interaction at the allosteric site may prevent attachment of serotonin at its orthosteric site, explaining the insurmountable binding noted in vitro.

High receptor affinity is accompanied by high selectivity, with low affinity (pK <6.0) for various other receptors including 5-HT $_{1A, 1D, 2A, 2C.}$ This makes it unlikely that palonosetron will produce unwanted effects at other receptor sites.

PHARMACOKINETICS:

A single dose of 10 µ/Kg i.v is widely distributed in the tissues. Volume of distribution is 8.3± 2.4 L/Kg. Palonosetron is moderately bound to plasma proteins (62%). It is primarily metabolised in the liver by cytochrome P450 enzyme system. The main metabolites, N-oxide –palonosetron, 6-(s)-hydroxy- palonosetron and small

amount of 6-keto –N-oxo-palonosetron display less than 1% of palonosetron's activity at 5-HT_3 receptors. 40 % of the administered drug is excreted unchanged in the urine. Total body clearance in healthy individuals is approximately 160ml/h/kg. The slower elimination resulted in longer half life of 40 hrs, which is in contrast with previous 5-HT_3 antagonists such as ondansetron (3-5hrs) and granisetron (5-8 hrs). Dose adjustment need not to be done in elderly patients.

DRUG INTERACTIONS:

Palonosetron does not cause inhibition or induction of the main hepatic enzyme system, so the risk of significant drug interaction is low. But it reacts with Apomorphine causing profound Hypotension and altered consciousness.

ADVERSE EFFECTS:

Palonosetron share the similar safety profile as that of other 5-HT_3 Antagonists. The most common side effects that are seen are non-serious and short duration headache (9%), constipation (5%) and dizziness (1%).

Cardiac conduction:

In common with other 5-HT3 antagonists palonosetron slightly increases QTc interval, the mean increase after a bolus i.v dose lies between 1 and 3 ms which is less than that caused by ondansetron (5 ms) and dolasetron (5.4 ms).

Use in pregnant and lactating women:

There is currently no clinical experience with palonosetron in pregnant or lactating women. Studies of teratogenicity in animal models show no evidence of interference with fertility or fetal development. But caution is advised until safety in these populations is established.

Contraindications: Palonosetron is contraindicated in the patients previously sensitive to the drug components or to any of the excipients of the product.

Use in children:

There is little experience to date to determine the safety of palonosetron in children, however emerging evidence suggests that it is effective and appears safe.

Pharmacological Information:

Palonosetron is a clear, colourless, sterile, nonpyrogenic, aqueous solution for intravenous administration. Palonosetron hydrochloride is available in 1.5 ml glass vial and is available in concentration of 0.075 mg for single use.

Dosage:

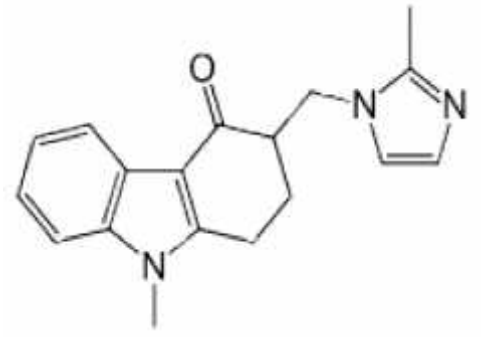
1µg/Kg and 30µg/Kg doses produce significantly better complete response in first 24 hours. For prevention of nausea and vomiting in adults, a single dose of 0.075 mg of palonosetron is given over 10 sec immediately before induction of anaesthesia.

PHARMACOLOGY OF ONDANSETRON

Ondansetron is the prototype of a new class of antiemetic drugs developed to control cancer chemotherapy / radiotherapy induced vomiting and later was found to be highly effective in post operative nausea and vomiting as well.

hemical structure:

Ondansetron is a synthetic structurally novel carbazole derivative



Structure of Ondansetron.

Mechanism of action:

Ondansetron is a potent, reversible and competitive antagonist of 5-HT_3 receptors. Ondansetron blocks the depolarising action of 5-HT through 5-HT_3 receptors on the vagal afferents in the G.I.T. as well as in NTS and CTZ. Cytotoxic drugs and radiation produce nausea and vomiting by causing cellular damage and release of mediators including 5-HT from the intestinal mucosa. This results in the activation of vagal afferents in the gut and sends emetogenic impulses both at their peripheral origin and central relay.

PHARMACODYNAMICS:

Ondansetron is reported to have very weak affinity at 5-HT_{3C} , alpha1and opioid binding sites. It has no action on other 5-HT receptors, alpha 2 and beta adrenoreceptors, muscarinic and nicotinic cholinergic receptors, GABA A receptors, H_1 and H_2 Histamine receptors, dopamine D2 receptors and NK1, NK2, and NK3 neurokinin receptors. So ondansetron produces very less side effects.

OTHER ACTIONS:

Ondansetron prolongs colonic transit time in healthy volunteers. It also enhances gastric emptying time. From animal models there is good evidence that 5-HT_3 receptor may be involved in anxiety, schizophrenia, cognitive dysfunction and drug dependency states.

PHARMACOKINETICS:

The bioavailability of ondansetron following oral administration in healthy volunteers is 60-70% because of first pass metabolism. It is 70-76% bound to plasma proteins. In healthy volunteers, oral administration of Ondansetron 8 mg produces a peak plasma concentration of approximately 30 ng/ ml in one to one and half hours

post administration. An intravenous infusion of 8 mg ondansetron over 5 min gives peak plasma values of 80-100 ng/m. The apparent volume of distribution is 160L.

METABOLISM AND ELIMINATION:

Ondansetron undergoes extensive hepatic metabolism. It is metabolised by Hepatic cytochrome P-450 enzyme. 40% of a single dose is oxidized to β-hydroxyl ondansetron and 20% to 7-hydroxy ondansetron. It is eliminated in urine and faeces, mostly as metabolites. Half life being 3-5 hrs and duration of action is 4-5 hrs. Ondansetron clearance is reduced in elderly patients. The half life in these patients is increased to about 5 hrs. But dose reduction does not appear to be necessary in this patient group.

DRUG INTERACTIONS:

Clinical evidences indicate that Ondansetron has got wide therapeutic index, no interactions with commonly prescribed drugs and no dependence liability.

ADVERSE EFFECTS:

Ondansetron is generally well tolerated; the only common side effect is headache. Mild constipation or diarrhoea and abdominal discomfort occur in few patients. Rashes and allergic reactions can occur after i.v injection. Transient elevation of aminotransferases and bilirubin was observed with Ondansetron. Elevation in aminotransferase levels were 2-3 times the upper limit of normal values and usually occur 24 hrs after antiemetic treatment. And the values returned to normal one week later.

Other adverse reactions include bronchospasm, hypotension, urticaria, tachycardia, angina, ECG alteration, transient blurred vision, xerostomia. Sedation and extra pyramidal effects like Acute dystonic reaction are very rarely seen.

CONTRAINDICATIONS:

Ondansetron is contraindicated in patients known to have hypersensitivity to the drug.

USE IN PREGNANCY:

Animal studies have revealed no evidence of impaired fertility or harm to the foetus due to Ondansetron. No adequate and well controlled studies in pregnant women are available. So the drug should be used cautiously in both pregnant women and lactating females.

USE IN CHILDREN:

There are very little studies to determine safety of ondansetron in children, but the emerging studies have shown it to be safe and effective.

PHARMACEUTICAL INFORMATION:

Ondansetron injection is aqueous isotonic solution of 2 mg /ml with ondansetron base as the hydrochloride dehydrates. The injection is maintained at pH 3.5 with citrate buffer and isotonicity is maintained by inclusion of sodium chloride.

It is also available in the form of 4mg and 8 mg tablets.

Injections of 1ml=2 mg. 2ml and 4ml ampoules are available.

Injections have a shelf life of 2 years. Several infusion fluids are compatible with Ondansetron injection, viz sodium chloride 0.9%, dextrose 5%, mannitol 10 %, ringer lactate, potassium chloride 0.3%.

DOSAGE:

In children - 0.1 to 0.15 mg /Kg/ day

In adults – 0.1 to 0.15 mg /Kg/ day

METHODOLOGY

The present study was conducted in department of anaesthesiology, KLE'S Dr Prabhakar Kore's Hospital and Medical Research center, Belgaum.

Source of Data

Patients undergoing abdominal surgeries under GA at K.LE'S Dr Prabhakar Kore Hospital and M.R.C , Belgaum.

Sample size

A total of 140 cases were taken as sample size, with 70 in each group.

Sample size calculation

Sample size was calculated using the formula

$$N = 2\frac{(Z\alpha + Z\beta)^2\ P(1-P)}{(P_0 - P_1)^2} \qquad P = \frac{P_0 + P_1}{2}$$

$\alpha = 0.05$, $\beta = 0.2$, Power = 80%, $P_0 = 36\%$, P1 = 60%, P = 48%,

$Z\alpha = 1.96$, $Z\beta = 0.84$.

SELECTION CRITERIA

Inclusion Criteria

1. Patients of either sex aged between 18 to 60 years undergoing abdominal surgeries under general anaesthesia.

2. American Society of Anaesthesiologist (ASA) Grade I and II Patients.

3. Presence of one of the following PONV risk factors.

a. Female gender

b. History of PONV or motion sickness

c. Nonsmoking status

Exclusion Criteria.

1. Inability to understand or cooperate with study procedure as determined by investigator\

2. Women who are pregnant, nursing or planning to become pregnant.

3. Patient who are having vomiting, retching and nausea 24hrs preceding the administration of anaesthesia

4. Patients who have taken any antiemetic drug 24hrs before the anaesthetic procedure.

PRE- ANAESTHETIC EVALUATION

A thorough pre-anaesthetic evaluation was performed by taking history and clinical examination. In all the patients weight, basal heart rate, respiratory rate, blood pressure were recorded. Investigations like complete blood count, urine routine, blood sugar, blood urea, serum creatinine were done. Investigations like electrocardiogram and chest x- ray were performed if required.

METHOD OF STUDY

A One year Randomized clinical trial.

METHOD OF COLLECTION OF DATA

After obtaining written informed consent and confirming inclusion and exclusion criteria. Patients were randomly divided into 2 groups.

Group I – received inj Ondansetron n=70

Group II – received inj Palonosetron n=70

Using computer generated randomization table.

On the day of surgery intravenous access was secured with intravenous cannula half an hour before surgery. In the operation theatre routine monitories such as ECG, NIBP, pulse oxymeter were connected and base line reading obtained.

Patients in Group I received 8 mg of Ondansetron and Patients in group II received 0.075 mg /of Palonosetron Hydrochloride 5 min before induction of general anaesthesia.

Patient were premedicated with injection glycopyrrolate 0.004mg/Kg, injection midazolam 0.05mg/kg and injection Fentanyl 2µ /kg body weight i.v. Following pre oxygenation anaesthesia was Induced with injection thiopentone sodium 5mg/kg and intubation was facilitated with injection Suxamethonium 2mg/kg. Endotracheal intubation was done with appropriate size endotracheal tube. Anaesthesia was maintained with N_2O 50% and oxygen 50% and vecuronium 0.1 mg/kg. Neuromuscular blocked was reversed with injection glycopyrrolate 0.04mg/kg nd neostigmine 0.05mg/kg. Pulse rate, blood pressure, SPO2 and $ETCO_2$ were monitored throughout perioperative period. Post operative analgesia was provided by diclofenac sodium 75 mg IM or with paracetamol infusion of 10 mg/ kg four times day depending on patients profile.

Post operatively patients were monitored for Nausea and vomiting every hourly for first 24 hours. Incidence of the emetic episodes was compared in 2 groups according to nausea and vomiting score.

0 = No emetic symptoms

1 = Nausea

2 = Retching and

3 = Vomiting.

Patients received intravenous Dexamethasone 0.1mg/kg as rescue antiemetic and was administered when PONV score was ≥ 2.

STATISTICAL ANALYSIS

All data is expressed as mean +/- standard deviation. Demographic data is analyzed using unpaired ‘t’ test. Efficacy of drugs is compared using chi square test. P value of < 0.05 is considered significant.

The study was done on 140 patients undergoing abdominal surgeries under general anaesthesia at K.L.E's Dr Prabhakar Kore Hospital and Medical Research Center, Belgaum. The patients were grouped in Group I and Group II according to computer generated randomization.

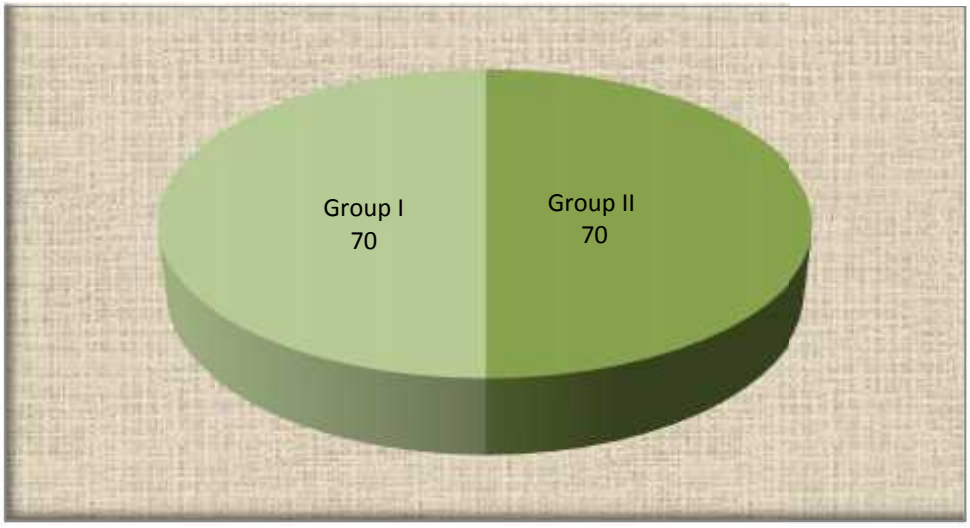
The demographic data was analyzed using student 't' test. The observed data were analyzed using unpaired student 't' test and data was presented as mean ± S.D based on 'P' value.

The following observations were recorded and results are tabulated as below.

Table No. 1: Group wise distribution of the patients

Group	Group I	Group II
No. of Patients.	70	70

Graph No. 1: Group wise distribution of the patients

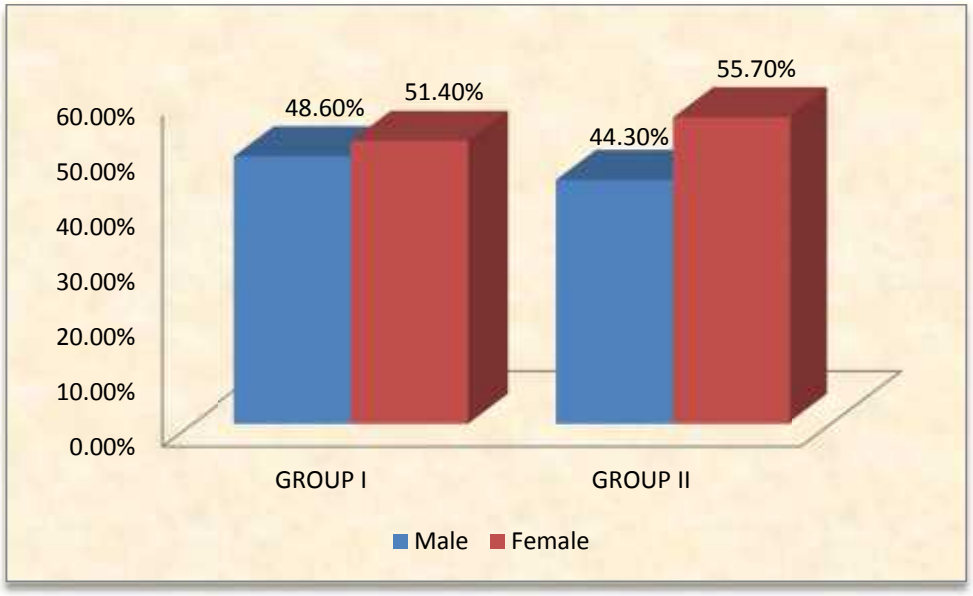


In the present study out of 140 patients, 70 patients received injection Ondansetron 8 mg i.v and were grouped under Group I and another 70 received injection Palonosetron 0.075 mg i.v. and were grouped under Group II. (Table No.1 and Graph No.1)

Table No. 2: Sex wise distribution of the patients

SEX	GROUP I		GROUP II	
	Number	Percentage	Number	Percentage
Male	34	48.6%	31	44.3%
Female	36	51.4%	39	55.7%
Total	70	100%	70	100%

Graph No. 2: Sex wise Distribution of the patients

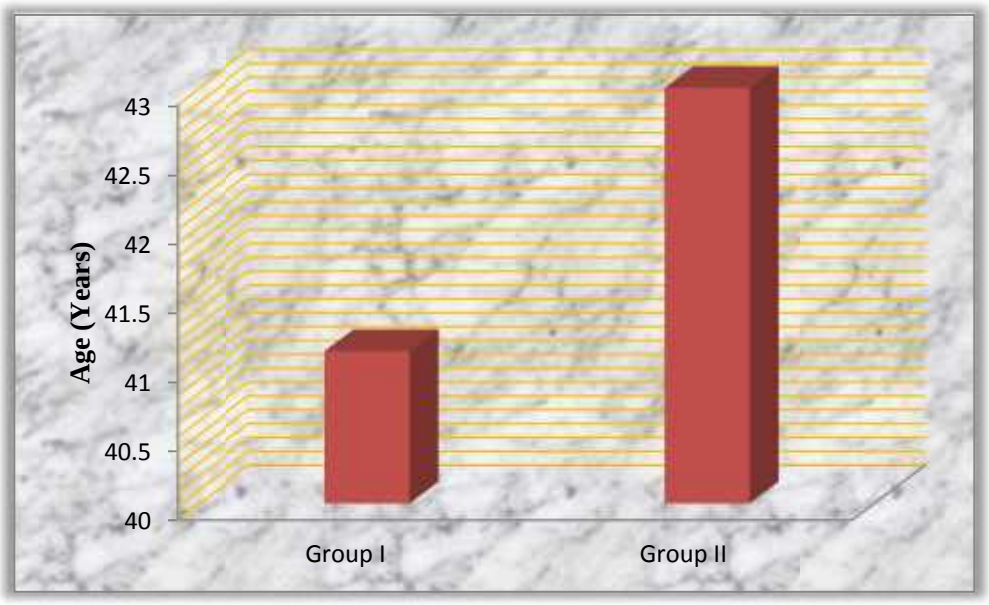


In the above study it was observed that there are 49% and 44% males in group I and group II respectively as compared to 51 % and 56% of females in group I and group II respectively. There was no difference in sex ratio of the study groups (p= 0.611), (Table No.2 and Graph No.2).

Table No. 3: Mean age in two groups

Groups	Group I	Group II
Age (Years)	**41.1±15.16 yrs**	**43±13.86 yrs**

Graph No. 3: Mean age in two groups

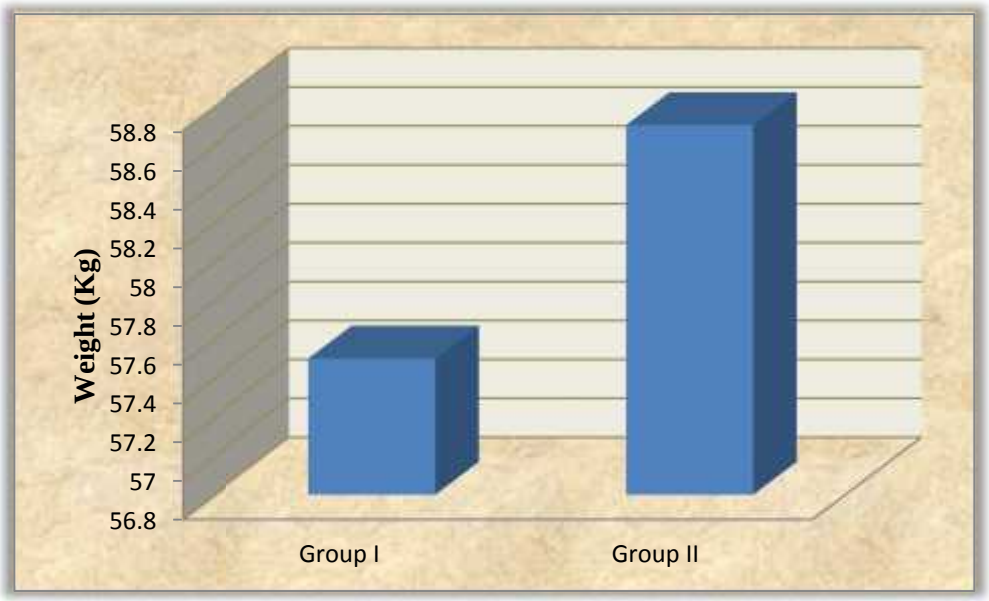


There was no significant difference in mean age of both the groups (P= 0.444). (Table No.3 and Graph No.3).

Table. No. 4: Mean body weight of the patients

Groups	Group I	Group II
Body Weight (in Kg)	**57.5±8.57 Kg**	**58.7±8.11 Kg**

Graph No. 4: Mean body weight of the patients



All the patients in the two groups were comparable according to the body weight. (P=0.13) (Table No.4 and Graph No.4).

Table No. 5: Distribution of patients according to ASA Grade.

	ASA Grade I	ASA Grade II
Group I	**45.7% (32)**	**54.7% (38)**
Group II	**45.7% (32)**	**54.7% (38)**

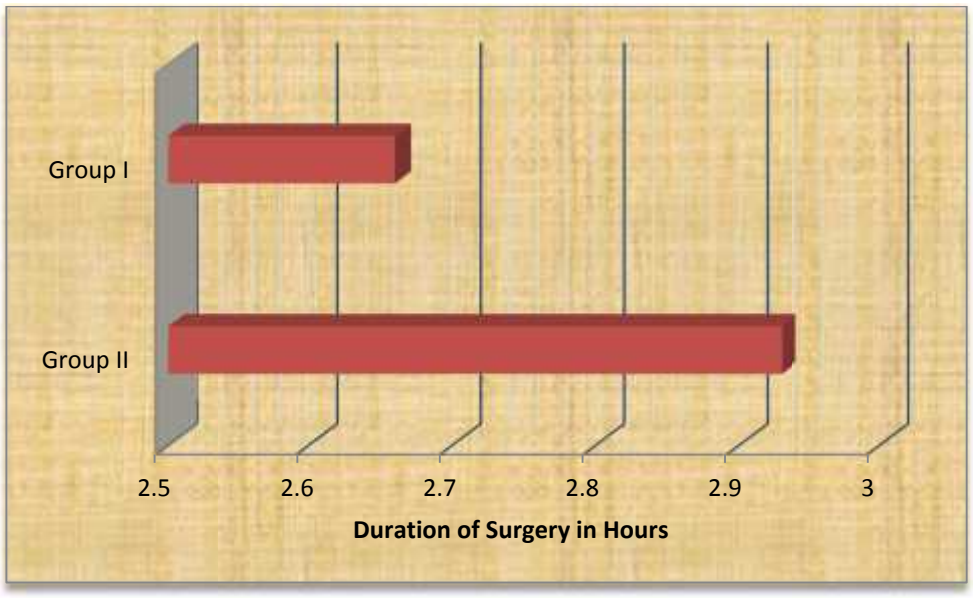
Graph No. 5: Distribution of patients according to ASA Grade

Statistically both the groups were comparable according to the ASA Grading (P=1). (Table No.5 and Graph No.5)

Table No.6: Duration of the surgery and Anaesthesia

Group I	**2.66±0.83 hrs**
Group II	**2.93±0.82 hrs**

Graph No.6: Duration of the surgery and Anaesthesia

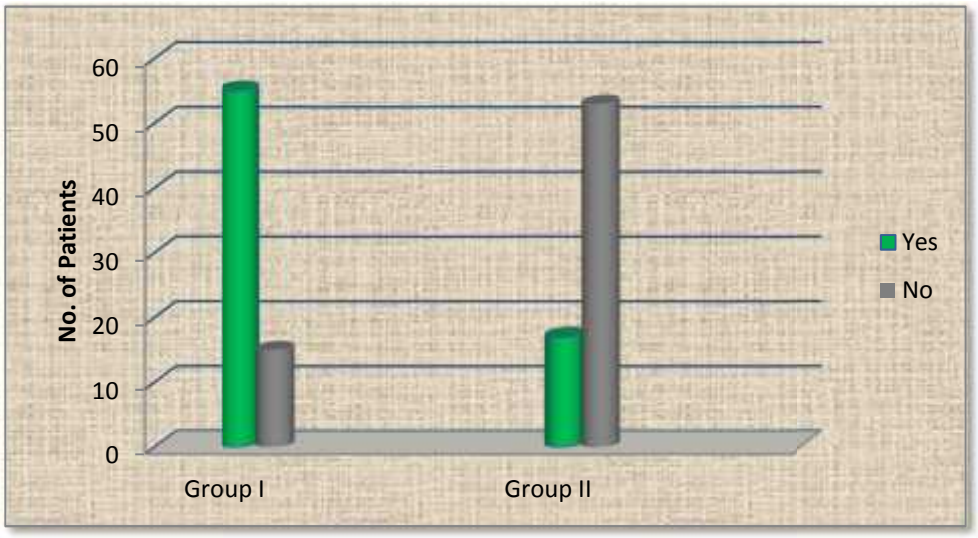


In the present study mean duration of surgery and anaesthesia in hours was 2.66 in group I and 2.93 in group II with a 'P' value of 0.055, which was statistically insignificant. (Table No.6 and Graph No.6).

Table No. 7: Incidence of post operative nausea and vomiting

Nausea & Vomiting	Group I		Group II	
	Number	%	Number	%
Yes	55	78.57	17	24.29
No	15	21.43	53	75.71
Total	70	100	70	100

Graph No. 7: Incidence of post operative nausea and vomiting

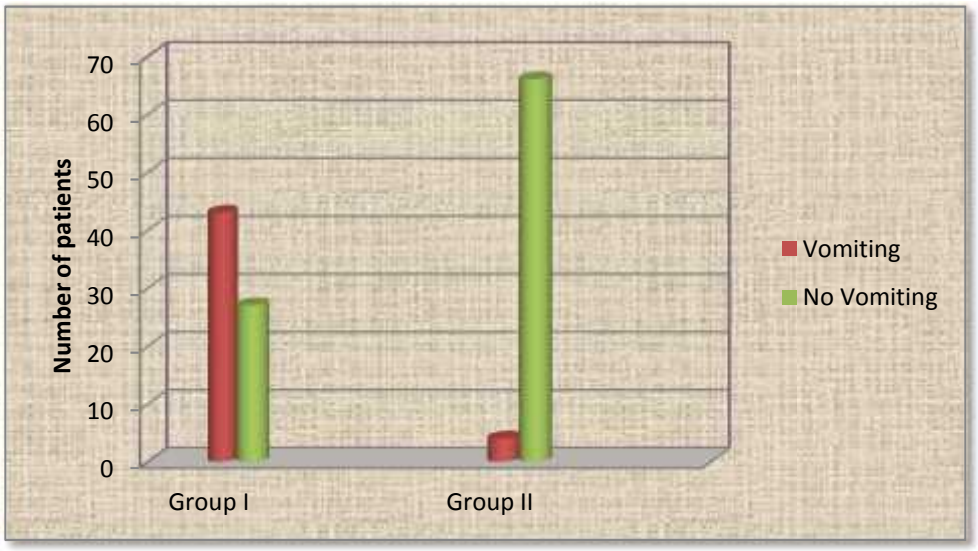


It was observed that the incidence of post operative nausea and vomiting in group I is 78.57% (55) as compared to 24.29% (17) in group II is out of 70 patients each, with p value < 0.001 which is statistically significant. (Table No.7 and Graph No.7).

Table No.8: Incidence of Emetic episodes

Emetic episodes	Group I		Group II	
	Number	%	Number	%
Vomiting	43	61.43	04	5.71
No Vomiting	27	38.57	66	94.29
Total	70	100	70	100

Graph No.8: Incidence of Emetic episodes



It was observed that the incidence of vomiting in group I is 61.43% (43) as compared to 5.71% (04) in group II, out of 70 patients each. with 'P' value of <0.001 which is statistically significant. (Table No.8 and Graph No.8).

DISCUSSION

Post operative nausea and vomiting (PONV) is very common sequelae of general anaesthesia and is very unpleasant and distressing for the patient. It is leading cause of delayed discharge of unanticipated hospital admission after ambulatory surgical procedure[32]. Incidence of postoperative nausea and vomiting in an untreated adult surgical population receiving general anaesthesia is around 20-30%, but it increases up to 80% in patients with high risk for PONV. PONV is very frequent in abdominal surgeries leading to the recommendation of routine prophylactic administration of antiemetics[33]. The etiology of nausea and vomiting after abdominal surgeries under GA are multifactorial in origin. Age, type of surgery, anaesthetic procedure and duration of surgery may influence PONV.

The complex act of vomiting involves coordination of respiratory, gastrointestinal and abdominal musculature and is controlled by the emetic center situated in the lateral reticular formation close to the tractus solitarius in the brain stem. Stimuli from several areas within the central nervous system can affect the emetic center[8, 34]. These include afferents from the pharynx, gastrointestinal tract and mediastinum, as well as afferents from the higher cortical center (including the visual center and the vestibular portion of the eight cranial nerves) and the chemoreceptor trigger zone (CTZ) in the area postrema. The area postrema of the brain is rich in Dopamine, Opioid and Serotonin or 5-hydroxytryptamine (5-HT_3) receptors[8].

Major neurotransmitter systems which play important role in mediating emetic reflex are Dopaminergic, Histaminic (H_1), Muscarinic and 5-HT_3. So an ideal antiemetic agent should be able to block all these 4 receptors. But the present antiemetic agents have prominent action at one or two receptors only[8, 34].

Numerous interventional methods have been studied for the prevention of nausea and vomiting. Non pharmacological methods include acupuncture, electropuncture, transcutaneous electrical nerve stimulation, acupoint stimulation and acupressure. Pharmacological methods include Dopamine receptor antagonists (phenothiazines, buterophenones and benzamides), Histamine receptor antagonists (dimenhydrinate), Muscarinic receptor antagonists (scopolamine), and serotonin receptor antagonists (ondansetron). Miscellaneous drugs like propofol, clonidine, dexamethasone and ephedrine are also tried for prevention of nausea and vomiting. Above drugs are effective in reducing PONV with varying efficacy and are associated with unwanted side effects.

Hence introduction of 5-HT_3 receptor antagonists in 1990s was heralded as the major advance in prophylaxis of PONV as they lack the major adverse effects which were observed commonly with traditionally used antiemetic drugs[34, 35]. These 5-HT_3 receptor antagonists produced no sedation, extrapyramidal reactions, adverse effects on vital signs or laboratory tests or drug interactions[36].

5-HT_3 receptors antagonists are routinely used nowadays to prevent post operative nausea and vomiting in the patients undergoing abdominal surgeries under general anaesthesia. Currently available 5-HT_3 antagonists include Ondansetron, Granisetron, Dolasetron, Topisetron and Palonosetron[36]. FDA has approved the use of palonosetron for prophylaxis of PONV in 2008 and is now available in India. All 5-HT_3 receptor antagonists have the same basic double nitrogen ring backbone for their chemical structure. This may be the clinical site of action of the 5-HT_3 receptor antagonists on serotonin. Half life of Ondansetron is 3.5 to 5.5 hrs and that of Palonosetron is 40 hrs[5], this confers Palonosetron prolonged duration of action and less frequent dosing as compared to Ondansetron.

A randomized study was done by PAVENTI S et al. in the year 2001 to compare the efficacy of ondansetron 4 mg and ondansetron 8 mg for the prevention of postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy in 60 patients. The study showed that during the first 6 hrs postoperatively, the incidence of PONV with ondansetron 4 mg and 8 mg were similar ($p < 0.001$). After 6 hrs the incidence of PONV increased significantly in patients who had received ondansetron 4 mg ($p = 0.01$) and was greater than that in patients who had received ondansetron 8 mg ($p = 0.001$). The study concluded that, single-dose ondansetron 8 mg is more effective than ondansetron 4 mg in the prevention of PONV after laparoscopic cholecystectomy. So Ondansetron 8 mg was considered as an optimal dose for the study[37].

Study to optimise the dose of Palonosetron was done in 2008 by Kovac AL et al. In the study palonosetron in dose of 0.025 mg, 0.05 mg and 0.075 mg was used and were compared in 546 patients undergoing laparoscopic surgery. Only the highest 0.075 mg dose showed a significantly improved rate of complete response compared with placebo in the 0-6 hrs, 0-24hrs, and 0-72hrs, periods (49% vs 37%; 43% vs 26%; 39% vs 24% for each periods respectively, p<(0.05). The palonosetron 0.075mg dose was statistically superior to placebo for all end points during the first 24 hrs, including CR (complete remission), emesis, nausea rates and reduction in nausea severity. Also palonosetron 0.075 mg was associated with significantly longer median time to first emesis and a significantly longer time to treatment failure. Based on the above study minimum effective dose of palonosetron in the setting of PONV is 0.075mg[15].

Studies were also done to evaluate efficacy of palonosetron for chemotherapy induced nausea and vomiting (CINV) by Aapro MS et al in 2006. Studies proved Palonosetron to be an excellent drug and were effective against both acute and

delayed CINV. It is effective after a single dose and thus provided a simpler and convenient treatment option[38]. An outstanding feature of palonosetron is improved nausea control, which does not seem to be adequately controlled with older 5-HT3 receptor antagonists or with new class of NK1 receptor antagonists. The study also showed the the dose of palonosetron (0.075 mg) was very less in comparison with ondansetron (32mg) used for prevention of CINV. Moreover ondansetron has shorter half life of 4 hrs, where as palonosetron has half life of 40 hrs signifying less frequent dosing in preventing nausea and vomiting. The binding affinity of Palonosetron to 5-HT3 receptor is 100 times that of ondansetron which makes it unlikely that palonosetron will produce unwanted effects at the other receptor sites[38].

Present study was done to compare the efficacy of palonosetron 0.075mg and ondansetron 8mg for prevention of PONV administered 5 min prior to the induction of anaesthesia in the patients undergoing abdominal surgeries under general anaesthesia.

The study was designed in such a way as to control all the factors that can interfere with the interpretation of the results of the study with a standardized anaesthesia regimen like (avoiding use of propofol for induction, avoiding use of tramadol and opoids for post operative analgesia). The duration of anaesthesia, surgery and the anaesthetic used were similar in both the groups. Therefore it is likely that the difference in the incidence of emetic episodes in both the groups were attributable to Ondansetron and Palonosetron.

In our study, in group I there were 48.6% of males and 51.4% of females and in group II males were 44.3% and females 55.7%. Both the groups were comparable with respect to sex of the patients($p=0.611$). (Table No.2). All the male patients in both the groups were non smokers.

The mean age in group I is 41.1± 15.16 yrs and in group II 43± 13.86 yrs. According to age both the groups are comparable (p=0.444). (Table No.3).

With respect to body weight both the groups were comparable (p=0.13). Mean body weight in group I is 57.5± 8.57 kg and group II 58.7 ± 8.11 Kg.(Table No.4).

Both the groups were comparable with respect to ASA grading (p=1). (Table No.5).

The mean duration of anaesthesia and surgery in group I was 2.66±0.83 hrs compared to 2.93±0.82 hrs in group II. Both the groups were comparable (p=0.075) (Table no.6).The duration of anaesthesia and surgery has a bearing on post operative nausea and vomiting as prolonged duration of surgery with frequent bowel handling will increase the incidence of post operative nausea and vomiting, hence increasing the requirement of antiemetic.

Patients of both the groups were observed and assessed for 24 hrs every hourly, after recovery from anaesthesia by means of nausea and vomiting score. IV dexamethasone 0.1mg /Kg was used as a rescue antiemetic when the nausea and vomiting score was 2 or more than 2.

Incidence of nausea and emetic episodes were compared in the two groups according to nausea and vomiting score,

0= no emetic symptoms

1= nausea

2= retching

3= vomiting.

In the present study it was found that the incidence of PONV was 79% in Ondansetron group and 24% in Palonosetron group (P value = <0.001). The results were both clinically and statistically significant (Table no.7). The study confirms the

finding that Palonosetron at a dose of 0.07 mg improves the control of nausea and vomiting. Control over nausea and vomiting is even seen to extend over second and third day, an effect that may be most marked after major operations requiring inpatient stay. From the study we can also say that Palonosetron 0.075mg reduces the severity of delayed nausea, which is particularly relevant in day surgery population, in whom it is difficult to identify those at risk of post discharge PONV and for whom early return to normal activities is important.

From the study it was also found that the incidence of emetic episodes were 6% in Paolnosetron group and 61% in Ondansetron group (p value = <0.001), in 24 hrs post operative period in the patients undergoing abdominal surgeries under general anaesthesia. The results were both clinically and statistically significant. In the study it was noticed that incidence of vomiting was high in the Ondansetron group mainly between 3-6 hours. This is mainly due to its relative short life of 3.5 to 5 hrs. In the patients who received Palonosetron, the incidence of vomiting was less because it has longer duration of action of 40 hrs.

Both Palonosetron and Ondansetron has non serious adverse effects like short duration head ache, constipation, dizziness and prolongation of QTc interval. But no side effects were observed in patients of both the groups in our study.

The above observations agree with the following studies;

A randomized, placebo- controlled, double blind study conducted in 2008 by Kovac AL at el, on 544 female patients undergoing elective gynaecological or breast surgery under general anaesthesia and observed for over 72 hrs, the showed that iv Palonosetron in dose of 0.075mg (10µ/Kg) was an effective antiemetic with an incidence of vomiting of 40 % as compared to 60% in the placebo group (Patients

here has received normal saline). This corresponds to relative risk reduction of 34% for patients treated with Palonosetron 0.075mg[15].

In another study conducted by Candiotti KA in 2008, on 574 patients undergoing either outpatient abdominal or gynaecological laparoscopic surgery showed that the incidence of vomiting was 33% in those patients who has received iv Palonosetron 0.075 mg compared to 44% in those who has received placebo. Patients had no nausea in larger proportion of the patients who had received Palonosetron 0.075 mg ($p = 0.033$) as compared to the patients who received placebo[14].

A double blind study was done in 2011by Park SK to compare the efficacy of iv ondansetron 8 mg and Palonosetron 0.075 mg on 90 patients who are undergoing gynecological laparoscopic procedure. The study showed that incidence of PONV (42.2% vs 66.7%) was significantly lower in the palonosetron group than in the ondansetron group during the overall 0 – 24 h time interval ($P < 0.05$). More patients in the palonosetron group had a complete response (no PONV and no rescue antiemetic) compared with the ondansetron group this difference was statistically significant for the 0 – 24 h time interval ($P <0.05$)[39].

Moon .Y.E et al did a prospective randomized double blind study to compare the antiemetic effect of Ondansetron and Palonosetron in patients undergoing thyroidectomy in the year 2012. Here the patients were receiving opioid based patient controlled analgesia (PCA). A total of 100 female non smoking subjects were randomly assigned into Palonosetron or ondansetron group. Ondansetron group received 8 mg bolus and 16 mg was added to the i.v PCA mixture. Palonosetron group received a single bolus injection of 0.075mg. The result showed that incidence of PONV during the 24 hrs postoperative period was lower in the Palonosetron group than in the Ondansetron group (42% vs 62%, P=0.045). Incidence of nausea and

vomiting and nausea severity were significantly lower in palonosetron group than in ondansetron group during 2-24 hrs. The difference in the use of rescue antiemetic was at 2-24 hrs(10% with Palonosetron compared with 28% with Ondansetron, P=0.02). The study concluded that palonosetron is more effective than ondansetron for high risk patients receiving fentanyl based PCA after thyroidectomy, especially 2-24 hrs after surgery[18].

In the present study we compared the efficacy of Ondansetron 8mg and only one dose of Palonosetron i.e 0.075mg. We did not evaluate the efficacy of 0.025mg and 0.05mg of Palonosetron which can also decrease incidence of PONV.

On the basis of promising results for combination therapy with Palonosetron in CINV, similar combination studies can be done for prevention of PONV in surgical patients. Combination of Palonosetron with Dexamethasone is very effective in prevention of nausea, and when neurokinin–1 antagonists such as Aprepitant is added to the above combination, incidence of vomiting is still further reduced to low levels even in high risk patients. Hence effect of combination therapy can be studied to decrease PONV. All antiemetic have effect on the incidence of vomiting on different phases of menstrual cycle, with the studies showing the incidence of vomiting less in women in postovulatory phase. Hence study can be done comparing incidence of PONV in specific phase of menstrual cycle.

So from the results of the present study, it can be concluded that Palonosetron is more effective than Ondansetron to prevent post operative nausea and vomiting in patients undergoing abdominal surgeries under general anaesthesia.

CONCLUSION

From the above study we can conclude that Palonosetron is more effective than Ondansetron for prevention of post operative nausea and vomiting in patients undergoing abdominal surgeries under general anaesthesia.

Nausea and vomiting remains till today as one of the most unpleasant and distressing aspect of anaesthesia, contributing to the patients morbidity, since the discovery of anaesthesia.

The present study was done to compare the efficacy of Palonosetron 0.075mg and Ondansetron 8 mg for prevention of post operative nausea and vomiting in patients undergoing abdominal surgery under general anaesthesia for 24 hrs. 140 patients (ASA I and ASA II) undergoing abdominal surgeries under GA were randomly allocated into two groups according to the computer generated randomization table. Group I (n=70) received inj.Ondansetron 8mg i.v, Group II received inj. Palonosetron 0.075mg i.v 5 min before the induction of GA. Anaesthetic procedure was standardized and was common to all the patients. Nausea and emetic episodes in 24 hours were recorded and compared in different study groups. Results were analysed by student't' test and chi square test (X2), with p value < 0.05 was considered to be significant.

Nausea and emetic episodes were observed in 79% of patients in Ondansetron group and 24% of patients in Palonosetron group. Emesis was seen in 6% of patients in Palonosetron group and 61% of patients in Ondansetron group. Both the results were clinically and statistically significant. In our study, no side effects were noticed with both the drugs.

So from study we could derive that, there were minimal emetic episodes in the post operative period of 24 hrs in, those patients who had received inj Palonosetron in comparison to those who had received inj Ondansetron. So we conclude that Palonosetron is more efficacious than Ondansetron in prevention of post operative nausea and vomiting in the patients undergoing abdominal surgeries under general anaesthesia.

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Figure1.Palanosetron

Figure 2. Ondansetron

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr./Mrs./Miss._____ we are requesting you to enroll yourself in study titled **"A RANDOMIZED CLINICAL TRIAL TO COMPARE PALONOSETRON AND ONDANSETRON FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING" a Clinical trial at KLES DR. Prabhakar Kore Hospital and Medical Research Centre,** conducted by Dr. BA0110004, Post Graduate at J.N. Medical College, KLE university, Belgaum.

Respected Sir/Madam we request you to enroll 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.

RESEARCH BEING DONE

To compare the efficacy of iv Palonosetron with iv Ondansetron to prevent post operative nausea and vomiting.

PURPOSE OF THE RESEARCH

To compare the antiemetic effects of palonosetron and ondansetron for prevention of post-operative nausea and vomiting.

Procedure involved.

You will be randomly allocated either into study group or control group, if you are in study group then you will be given iv Palonosetron 0.075mg 5 min before induction and if you are in control group then you will be given iv Ondansetron 4mg. Emetic episodes will be assessed post operatively at hourly interval for 24 hours.

Potential risks and discomforts:

No serious side effects.

Benefits of taking part in this research:

Prevention of post-operative nausea and vomiting.

Lesser gastric discomfort.

Decline from participation

You have the option to decline from participation in the study without any discrimination and you will be treated as per the existing protocol for your condition.

New information

All information collected during the study from the participants will be told as and when required.

Privacy and confidentiality

Privacy of the individual will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Injury as a result of participation

There will neither be any compensation to or for the patient and his or her relatives nor there any monetary benefits for the damage incurred.

Cost of participation in this research

Participation is free of cost.

Reimbursement for any expenses for participation in research

No reimbursement for any of your expenditures

Withdrawal or be removed:

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered

to you at K.L.E.S hospital. Researcher can remove you from the study if circumstances arise.

Whom to contact

For any information about the study during the study or after that may be collected from Dr BA0110004 Postgraduate student at, JNMC, Belgaum. Ph.No._____

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 for me 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 : _____

KLE UNIVERSITY'S DEPARTMENT OF ANAESTHESIOLOGY, JAWAHARLAL NEHRU MEDICAL COLLEGE,BELGAUM.

"A RANDOMIZED CLINICAL TRIAL TO COMPARE PALONOSETRON AND ONDANSETRON FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING."

PROFORMA

Name & Address of the patient: _____

_____

Age of the Patient: _____ Years IP. No. _____

Anaesthesiologist: _____ Surgeon: _____

PREANAESTHETIC EVALUATION :

Chief Complaints:

Past History:

1. History of Hypertension, Diabetes Mellitus, Asthma, Epilepsy, Drug allergy.
2. History of drug intake.
3. Previous exposure to anaesthesia.
4. History of PONV or motion sickness or smoking.

Family History:

General Physical Examination:

Weight: Temperature: Pallor: Height:

Cyanosis: Pedal Edema: Clubbing:

Pulse : B.P: RR:

Musculoskeletal system examination:

Jaw movements: Teeth:

Airway assessment: Spine:

SYSTEMIC EXAMINATION:

Respiratory System: Cardiovascular System:

Central Nervous system: Per Abdomen:

INVESTIGATIONS:

Hemoglobin,

Random blood sugar,

Serum creatinine,

Chest x-ray,

ECG if age > 40 years if required

Pre-operative physical status: ASA grade

Inclusion Criteria:

1. Patients of either sex aged between 18 to 60 years undergoing abdominal surgeries under general anaesthesia.

2. American Society of Anaesthesiologist (ASA) Grade I and II Patients.

3. Presence of one of the following PONV risk factors.

a. Female gender

b. History of PONV or motion sickness

c. Nonsmoking status

Exclusion Criteria:

1. Inability to understand or cooperate with study procedure as determined by investigator

2. Women who are pregnant, nursing or planning to become pregnant.

3. Patient who are having vomiting, retching and nausea 24hrs preceding the administration of anesthesia

4. Patients who have taken any antiemetic drug 24hrs before the anesthetic procedure.

Diagnosis:

Proposed surgery: Patients will be allocated by computer generated randomization into group I and group II**.** On the day of surgery, i.v. line secured with 18g branula for males, 20g branula for females in a peripheral vein.

Preoperative baseline

Heart rate

Blood pressure

Monitors attached:

Pulse oximeter Noninvasive blood pressure ECG

Group II patients will be given i.v. Palonosetron 0.075mg and Group I will receive i.v. Ondansetron 4 mg 5 minutes before induction. Premedication with Glycopyrrolate 0.004 mg/kg, Midazolam 0.05 mg/kg and Fentany 2µ/kg will be given.

Induction of Anaesthesia will be with i.v. thiopentone 5 mg/kg intubation facilitated with suxamethonoum 1mg/kg. Maintenance with N_2O 50% + O_2 50%, Vecurionium 0.05 to 0.08 mg/kg. Neuromuscular blockade will be reversed with inj

Glycopyrrolate 0.0025mg/kg +Neostigmine 0.05mg/kg. Extubation will be done after through suctioning.

The patients of both the groups will be monitored for 24 hours every hourly after recovery from anaesthesia by means of nausea and vomiting score.

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 and

3=Vomiting.

Patient shall receive inj. Dexamethasone 8mg i.v. as rescue medication.

Time (hrs)	1-4	5-8	9-12	13-16	17-20	21-24
Ponv score						

Place:

Date: Signature

Group II

Sl.no	Ip.No	Age	Sex	Wt (Kg)	ASA grade	Diagnosis	Proposed Surgery	Duration (Hrs)	PONV SCORE					
									1-4 hrs	5-8 hrs	9-12 hrs	13-16 hrs	17-20 hrs	21-24 hrs
1	4E+05	30	F	46	I	Pain Abdomen	Diagnostic Laproscopy	2	0	0	0	0	0	0
2	4E+05	63	M	60	II	Intestinal Obstruction	Exploratory Laprotomy	4	0	0	0	0	1	0
3	4E+05	62	M	69	II	Epigastric Hernia	Mesh Repair	3	0	0	0	0	0	0
4	4E+05	50	F	84	I	Chronic Cholecystitis	Lap cholecystectomy	3.3	0	0	1	0	0	0
5	4E+05	38	F	60	I	Chronic Cholecystitis	Lap cholecystectomy	4	0	0	0	0	0	0
6	4E+05	51	F	67	II	Cholelithiasis	Lap cholecystectomy	3.3	0	0	0	0	0	0
7	4E+05	27	F	56	II	ITP with Hypersplenism	Splenectomy	4	0	0	0	0	0	0
8	4E+05	51	F	60	II	Cholelithiasis	Lap cholecystectomy	3	0	0	0	1	0	0
9	4E+05	27	M	54	II	Pseudopancreatic cyst	Cystojejunostomy	3.3	0	0	2	0	0	0
10	4E+05	60	M	58	II	Calculous Cholecystitis	Lap cholecystectomy	4	0	0	0	0	0	0
11	4E+05	40	F	64	I	DUB	LAVH	4	0	0	0	0	0	0
12	4E+05	32	M	67	I	Chronic Cholecystitis	Lap cholecystectomy	3	0	0	0	0	0	0
13	4E+05	38	F	63	I	Cholelithiasis	Lap cholecystectomy	2.3	0	0	0	0	0	0
14	4E+05	28	M	58	I	Diverticulosis	Exploratory Laprotomy	3.3	0	0	0	0	0	0
15	4E+05	21	F	51	I	Para Duodenal Hernia	Exploratory Laprotomy	3	0	0	0	0	0	0
16	4E+05	20	F	54	I	Ovaraian cyst	Laprotomy	2.3	0	0	0	1	0	0
17	4E+05	27	F	49	I	Chronic Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
18	4E+05	28	M	54	II	Pseudopancreatic cyst	Pancreatico jejunostomy	4	0	0	3	0	0	0
19	4E+05	23	F	56	I	Pain Abdomen	Diagnostic Laproscopy	3	0	1	0	0	0	0
20	4E+05	50	F	50	II	Chronic PID	LAVH	4	0	0	0	0	0	0
21	4E+05	30	F	48	I	Recurrent Appendicitis	Lap Appendicetomy	2.3	0	0	0	0	0	0
22	4E+05	55	F	60	II	Biliary Peritonitis	Laprotomy	3	0	0	0	0	0	0
23	4E+05	55	M	67	II	Calculous Cholecystitis	Open Cholecystectomy	2.3	0	0	0	0	0	0
24	4E+05	50	F	70	II	Calculous Cholecystitis	Open Cholecystectomy	3	0	0	0	0	0	0

Group II

25	4E+05	18	F	43	I	Ovaraian cyst	Excision	2	0	0	0	0	0	0
26	4E+05	23	F	56	I	Appendicitis	Lap Appendicetomy	1.3	0	0	0	0	0	0
27	4E+05	28	F	50	II	Splenomegaly with ITP	Lap splenectomy	4	0	0	0	0	0	0
28	4E+05	64	M	68	II	Acute cholecystitis	Open Cholecystectomy	3	0	0	0	0	0	0
29	4E+05	59	M	67	II	Ca colon	Resection anastomosis	4	0	1	0	0	0	0
30	4E+05	29	F	51	I	ovarian mass	Laprotomy and resection	2.3	0	0	0	0	0	0
31	4E+05	28	F	58	II	Unruptured ectopic pregnancy	Laproscopy and proceed	3	0	0	0	0	0	0
32	4E+05	36	M	65	II	Intestinal Obstruction	Exploratory Laprotomy	4	0	0	3	0	0	0
33	4E+05	63	M	59	II	Stricture urethra	Pyeloplasty	4	0	0	0	0	0	0
34	4E+05	60	M	61	II	Duodenal Perforation	Repair	3	0	0	0	0	0	0
35	4E+05	28	M	65	I	Pain Abdomen	Diagnostic Laproscopy	2	0	0	0	0	0	0
36	4E+05	47	M	60	II	Blunt injury to abdomen	Exploratory Laprotomy	4	0	2	0	0	0	0
37	4E+05	56	F	68	II	Fibroid Uterus	Abdonimal Hysterectomy	2	0	0	0	0	0	0
38	4E+05	28	M	50	I	Recurrent Appendicitis	Lap Appendicetomy	1.3	0	0	0	0	0	0
39	4E+05	61	M	58	II	Strangulated inginal hernia	Bowel resection & repair	3.3	1	0	0	0	0	0
40	4E+05	55	M	68	II	Ca Stomach	Jejunostomy	3	0	0	0	0	0	0
41	4E+05	40	F	57	I	Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
42	4E+05	47	M	69	II	Renal calculi	PCNL	3	0	0	0	0	0	0
43	4E+05	59	M	78	I	Inguinal Hernia+ IHD	Mesh Repair	2.3	0	0	0	0	0	0
44	4E+05	64	M	70	II	Intestinal Obstruction	Exploratory Laprotomy	4	2	0	0	0	0	0
45	4E+05	46	M	70	II	Cholecystitis	Lap cholecystectomy	3	0	0	0	0	0	0
46	4E+05	60	F	69	II	Cholelithiasis	Lap cholecystectomy	4	3	0	0	0	0	0
47	4E+05	56	F	74	II	Cholelithiasis	Lap cholecystectomy	3	0	0	0	0	0	0
48	4E+05	54	M	76	II	Inguinal hernia+ Cholelithiasis	Lap Chole + Mesh Repair	4.3	0	0	0	0	0	0

Group II

49	4E+05	26	F	45	I	Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
50	4E+05	41	F	56	I	DUB	LAVH	4	0	0	0	0	0	0
51	4E+05	60	F	67	II	Cholelithiasis	Lap cholecystectomy	3	0	0	0	0	0	0
52	4E+05	54	M	59	II	Chronic Pancretitis	Laprotomy and proceed	4	1	0	0	0	0	0
53	4E+05	65	F	72	II	Pain Abdomen	Lap and proceed	2	0	0	0	0	0	0
54	4E+05	38	F	64	I	Cholelithiasis	Lap cholecystectomy	3.3	0	0	0	0	0	0
55	4E+05	32	F	63	I	Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
56	4E+05	48	F	62	II	Acute Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
57	4E+05	43	F	69	I	Cholelithiasis	Lap cholecystectomy	3.3	0	0	0	0	0	0
58	4E+05	45	M	64	II	Renal calculi	PCNL	2	0	0	0	0	0	0
59	4E+05	54	M	67	II	Inguinal Hernia + IHD	Mesh Repair	2	0	0	0	0	0	0
60	4E+05	51	M	61	II	Intestinal Obstruction	Exploratory Laprotomy	4	3	0	0	0	0	0
61	4E+05	40	M	67	I	Chronic Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
62	4E+05	31	M	61	I	Recurrent Appendicitis	Lap Appendicetomy	1.3	0	0	0	0	0	0
63	4E+05	18	F	58	I	Pain Abdomen	Diagnostic Laproscopy	2	0	0	0	0	0	0
64	4E+05	55	F	70	II	Cholecystitis	Lap cholecystectomy	3.3	0	0	0	0	0	0
65	4E+05	42	M	69	I	Cholelithiasis	Lap cholecystectomy	3	0	0	0	0	0	0
66	4E+05	46	F	65	I	Chronic Cholecystitis	Open Cholecystectomy	2	2	0	0	0	0	0
67	4E+05	50	F	70	II	Incisional Hernia	Mesh Repair	3	0	0	0	0	0	0
68	4E+05	48	F	61	I	Fibroid Uterus	Abdonimal Hysterectomy	3	0	0	0	1	0	0
69	4E+05	35	F	64	I	Ch. Cholecystitis	Lap cholecystectomy	3	0	0	0	0	0	0
70	4E+05	24	M	56	I	Recurrent Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0

Group II

sl.no	Ip.No	Age	Sex	Wt (Kg)	ASA grade	Diagnosis	Proposed Surgery	Duration (Hrs)	PONV SCORE					
									1-4 hrs	5-8 hrs	9-12 hrs	13-16 hrs	17-20 hrs	21-24 hrs
1	4E+05	30	F	46	I	Pain Abdomen	Diagnostic Laproscopy	2	0	0	0	0	0	0
2	4E+05	63	M	60	II	Intestinal Obstruction	Exploratory Laprotomy	4	0	0	0	0	1	0
3	4E+05	62	M	69	II	Epigastric Hernia	Mesh Repair	3	0	0	0	0	0	0
4	4E+05	50	F	84	I	Chronic Cholecystitis	Lap cholecystectomy	3.3	0	0	1	0	0	0
5	4E+05	38	F	60	I	Chronic Cholecystitis	Lap cholecystectomy	4	0	0	0	0	0	0
6	4E+05	51	F	67	II	Cholelithiasis	Lap cholecystectomy	3.3	0	0	0	0	0	0
7	4E+05	27	F	56	II	ITP with Hypersplenism	Splenectomy	4	0	0	0	0	0	0
8	4E+05	51	F	60	II	Cholelithiasis	Lap cholecystectomy	3	0	0	0	1	0	0
9	4E+05	27	M	54	II	Pseudopancreatic cyst	Cystojejunostomy	3.3	0	0	2	0	0	0
10	4E+05	60	M	58	II	Calculous Cholecystitis	Lap cholecystectomy	4	0	0	0	0	0	0
11	4E+05	40	F	64	I	DUB	LAVH	4	0	0	0	0	0	0
12	4E+05	32	M	67	I	Chronic Cholecystitis	Lap cholecystectomy	3	0	0	0	0	0	0
13	4E+05	38	F	63	I	Cholelithiasis	Lap cholecystectomy	2.3	0	0	0	0	0	0
14	4E+05	28	M	58	I	Diverticulosis	Exploratory Laprotomy	3.3	0	0	0	0	0	0
15	4E+05	21	F	51	I	Para Duodenal Hernia	Exploratory Laprotomy	3	0	0	0	0	0	0
16	4E+05	20	F	54	I	Ovaraian cyst	Laprotomy	2.3	0	0	0	1	0	0
17	4E+05	27	F	49	I	Chronic Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
18	4E+05	28	M	54	II	Pseudopancreatic cyst	Pancreatico jejunostomy	4	0	0	3	0	0	0
19	4E+05	23	F	56	I	Pain Abdomen	Diagnostic Laproscopy	3	0	1	0	0	0	0
20	4E+05	50	F	50	II	Chronic PID	LAVH	4	0	0	0	0	0	0
21	4E+05	30	F	48	I	Recurrent Appendicitis	Lap Appendicetomy	2.3	0	0	0	0	0	0
22	4E+05	55	F	60	II	Biliary Peritonitis	Laprotomy	3	0	0	0	0	0	0
23	4E+05	55	M	67	II	Calculous Cholecystitis	Open Cholecystectomy	2.3	0	0	0	0	0	0
24	4E+05	50	F	70	II	Calculous Cholecystitis	Open Cholecystectomy	3	0	0	0	0	0	0

Group II

25	4E+05	18	F	43	I	Ovaraian cyst	Excision	2	0	0	0	0	0	0
26	4E+05	23	F	56	I	Appendicitis	Lap Appendicetomy	1.3	0	0	0	0	0	0
27	4E+05	28	F	50	II	Splenomegaly with ITP	Lap splenectomy	4	0	0	0	0	0	0
28	4E+05	64	M	68	II	Acute cholecystitis	Open Cholecystectomy	3	0	0	0	0	0	0
29	4E+05	59	M	67	II	Ca colon	Resection anastomosis	4	0	1	0	0	0	0
30	4E+05	29	F	51	I	ovarian mass	Laprotomy and resection	2.3	0	0	0	0	0	0
31	4E+05	28	F	58	II	Unruptured ectopic pregnancy	Laproscopy and proceed	3	0	0	0	0	0	0
32	4E+05	36	M	65	II	Intestinal Obstruction	Exploratory Laprotomy	4	0	0	3	0	0	0
33	4E+05	63	M	59	II	Stricture urethra	Pyeloplasty	4	0	0	0	0	0	0
34	4E+05	60	M	61	II	Duodenal Perforation	Repair	3	0	0	0	0	0	0
35	4E+05	28	M	65	I	Pain Abdomen	Diagnostic Laproscopy	2	0	0	0	0	0	0
36	4E+05	47	M	60	II	Blunt injury to abdomen	Exploratory Laprotomy	4	0	2	0	0	0	0
37	4E+05	56	F	68	II	Fibroid Uterus	Abdonimal Hysterectomy	2	0	0	0	0	0	0
38	4E+05	28	M	50	I	Recurrent Appendicitis	Lap Appendicetomy	1.3	0	0	0	0	0	0
39	4E+05	61	M	58	II	Strangulated inginal hernia	Bowel resection & repair	3.3	1	0	0	0	0	0
40	4E+05	55	M	68	II	Ca Stomach	Jejunostomy	3	0	0	0	0	0	0
41	4E+05	40	F	57	I	Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
42	4E+05	47	M	69	II	Renal calculi	PCNL	3	0	0	0	0	0	0
43	4E+05	59	M	78	I	Inguinal Hernia+ IHD	Mesh Repair	2.3	0	0	0	0	0	0
44	4E+05	64	M	70	II	Intestinal Obstruction	Exploratory Laprotomy	4	2	0	0	0	0	0
45	4E+05	46	M	70	II	Cholecystitis	Lap cholecystectomy	3	0	0	0	0	0	0
46	4E+05	60	F	69	II	Cholelithiasis	Lap cholecystectomy	4	3	0	0	0	0	0
47	4E+05	56	F	74	II	Cholelithiasis	Lap cholecystectomy	3	0	0	0	0	0	0
48	4E+05	54	M	76	II	Inguinal hernia+ Cholelithiasis	Lap Chole + Mesh Repair	4.3	0	0	0	0	0	0

Group II

49	4E+05	26	F	45	I	Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
50	4E+05	41	F	56	I	DUB	LAVH	4	0	0	0	0	0	0
51	4E+05	60	F	67	II	Cholelithiasis	Lap cholecystectomy	3	0	0	0	0	0	0
52	4E+05	54	M	59	II	Chronic Pancretitis	Laprotomy and proceed	4	1	0	0	0	0	0
53	4E+05	65	F	72	II	Pain Abdomen	Lap and proceed	2	0	0	0	0	0	0
54	4E+05	38	F	64	I	Cholelithiasis	Lap cholecystectomy	3.3	0	0	0	0	0	0
55	4E+05	32	F	63	I	Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
56	4E+05	48	F	62	II	Acute Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
57	4E+05	43	F	69	I	Cholelithiasis	Lap cholecystectomy	3.3	0	0	0	0	0	0
58	4E+05	45	M	64	II	Renal calculi	PCNL	2	0	0	0	0	0	0
59	4E+05	54	M	67	II	Inguinal Hernia + IHD	Mesh Repair	2	0	0	0	0	0	0
60	4E+05	51	M	61	II	Intestinal Obstruction	Exploratory Laprotomy	4	3	0	0	0	0	0
61	4E+05	40	M	67	I	Chronic Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0
62	4E+05	31	M	61	I	Recurrent Appendicitis	Lap Appendicetomy	1.3	0	0	0	0	0	0
63	4E+05	18	F	58	I	Pain Abdomen	Diagnostic Laproscopy	2	0	0	0	0	0	0
64	4E+05	55	F	70	II	Cholecystitis	Lap cholecystectomy	3.3	0	0	0	0	0	0
65	4E+05	42	M	69	I	Cholelithiasis	Lap cholecystectomy	3	0	0	0	0	0	0
66	4E+05	46	F	65	I	Chronic Cholecystitis	Open Cholecystectomy	2	2	0	0	0	0	0
67	4E+05	50	F	70	II	Incisional Hernia	Mesh Repair	3	0	0	0	0	0	0
68	4E+05	48	F	61	I	Fibroid Uterus	Abdonimal Hysterectomy	3	0	0	0	1	0	0
69	4E+05	35	F	64	I	Ch. Cholecystitis	Lap cholecystectomy	3	0	0	0	0	0	0
70	4E+05	24	M	56	I	Recurrent Appendicitis	Lap Appendicetomy	2	0	0	0	0	0	0