**DISSERTATION ON**

# "TO STUDY EFFICACY AND SAFETY OF INTRAVENOUS PALONOSETRON AGAINST ONDANSETRON IN POST SURGICAL PATIENTS UNDERGOING GENERAL ANAESTHESIA"

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## CERTIFICATE

This is to certify that Dr. Sunil M. Vishwasrao, a Post Graduate student in the Department of Pharmacology has carried out the work titled *"***TO STUDY EFFICACY AND SAFETY OF INTRAVENOUS PALONOSETRON AGAINST ONDANSETRON IN POST SURGICAL PATIENTS UNDERGOING GENERAL ANAESTHESIA"** under the guidance of Dr. JACOB VERGHESE, M.D., PROFESSOR, Department of Pharmacology, towards the partial fulfilment of regulations laid down by The Tamilnadu Dr. M.G.R Medical University, Guindy, Chennai, Tamilnadu, India for the award of Doctor of Medicine (M.D.) in Pharmacology.

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## DECLARATION

I declare that dissertation entitled **"TO STUDY EFFICACY AND SAFETY OF INTRAVENOUS PALONOSETRON AGAINST ONDANSETRON IN POST SURGICAL PATIENTS UNDERGOING GENERAL ANAESTHESIA"** submitted by me for the Degree of M.D. is the record work carried out by me during the period of January 2015 to February 2016 under the guidance of Dr. JACOB VERGHESE, PROFESSOR of Pharmacology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre and has not formed the basis of any Degree, Diploma, Fellowship, titles in this or any other University or other similar Institution of Higher learning.

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Date:

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# 1. INTRODUCTION

# INTRODUCTION

Post operative nausea vomiting (PONV) is an alarming surgical complication[1] with critical clinical consequences leading to delayed recovery in patients undergoing general anaesthesia. PONV continues to rank as most undesirable surgical outcome despite of multiple advances in recent years with use of non-pharmacological and pharmacological strategies to reduce its incidence to certain extent. Since the inception of general anaesthesia, PONV remains an important complication after surgery for which no complete solution is available till date. PONV had gained more attention in 1991 after Kapur has described this issue as big "little problem" [2]. It is distressing for patient as well as for the treating physician as it affects post-operative care and recovery substantially. PONV is an unpleasant sensation which patient often describes it as worse than post-operative pain.

Causes of PONV are multi factorial which are primarily categorised into patient related factors, pre- surgical factors and post-surgical factors. Due to various factors contributing to development of PONV quantification of risk of PONV in individual patient is difficult. Apfel and colleagues[3] mentioned major predictors of PONV that include age, obesity[4], female patient,[5,6] past history of PONV or motion sickness[7] , use of opioids[8] as an adjunct to anaesthesia and non smoker group[9]. Other pre-surgical and intra-surgical factors that contribute to PONV are pre-operative anxiety, underlying medical condition, hydration status, use of volatile anaesthetics, type and duration of surgery and type of anaesthesia[3, 6, 10]. In general population, incidence of PONV is very high (i.e.30-40%) and which increases further in high risk individuals up to 80%[7]**.** In addition to such

displeasing sensation PONV may have adverse consequences like pulmonary aspiration, Hypovolemia, electrolyte imbalance and wound dehiscence which prolongs post operative as well as total hospital stay and increase hospital cost[11]. The Prevention of above said complications improve quality of life and reduce unexpected hospital admissions and duration of hospital stay leading to overall decrease in financial burden to the patient.

Patho-physiological mechanism of PONV is complex due to involvement of different neurotransmitters at different sites. Activation of vomiting centre mainly occurs due to stimulation of chemoreceptor trigger zone (CTZ) situated at the floor of fourth ventricle. CTZ constitutes receptor for dopamine, serotonin, opioids, acetylcholine and neurotransmitter substance P. Each of these receptors innervates the pathway that stimulate vomiting centre. At least three nerves and seven neurotransmitters play role in causation of PONV. There are several classes of drugs that constitute basic of anti-emetic therapy. Several pharmacological agents[1] like anti-histaminics, butyrophenones, dopamine receptor antagonist and dexamethasone has been tried for the prevention of PONV but none of them found to be superior. Despite extensive research and introduction of new classes of anti-emetic agents with better safety and efficacy profile, there seems to be little progress in reducing incidence of PONV. As single agent has not been proved to be complete solution to tackle this problem; recent research has advanced the use of

combination anti-emetic therapy acting at more than one molecular site to control PONV. Use of more than two anti-emetic drugs has its own

disadvantages in the form of added side effects and drug interactions. Therefore development of single molecule with prolonged action and lesser side effects is encouraged.

Ondansetron, a $5HT_3$ receptor antagonist is used as antiemetic in patients of malignancy along with chemotherapy [11] and also approved in prevention of PONV. Palonosetron is considered to be second generation latest 5 $HT_3$ receptor antagonist with unique action and much longer half life than other $5HT_3$ antagonists offering flexibility to use as once a day. It has higher receptor affinity compared to other $5HT_3$ antagonists and requires much smaller dose (0.075mg I.V) [12] than ondansetron for the prophylaxis of PONV.

Safety and efficacy of Palonosetron in comparison to ondansetron has been well established in recent studies in patients undergoing specific surgeries like laparoscopic cholecystectomy, gynaecological laparoscopic surgery, paediatric surgery and lower segment caesarean section but most of the studies are restricted to laparoscopic or gynaecological or thyroid surgeries. Very minimal data is available on efficacy of palonosetron in all different types of surgeries under individual research. Hence Palonosetron study was undertaken to compare its safety and efficacy with ondansetron in all adult patients planned for surgical procedures under general anaesthesia.

# 2. AIMS AND OBJECTIVES

# AIMS AND OBJECTIVES

## Primary objectives:

- To assess the efficacy of IV Palonosetron in preventing post operative nausea vomiting (PONV) in comparison with IV ondansetron
- To assess safety of IV Palonosetron compared to IV ondansetron in relation to adverse effects in post surgical patients undergoing GA

## Secondary objective:

- To find whether both drugs are comparable with demographic parameters like age, sex, height and weight

# 3. REVIEW OF LITERATURE

## REVIEW OF LITERATURE

**PONV definition:** PONV is the second most common complaint after post-operative pain. One of the first extensive descriptions of phenomenon of nausea and vomiting was by John Snow, published in 1848 with one and half years of chloroform discovery as anaesthetic agent in Britain. The term PONV became more popular in 1992 after landmark review by Watcha and White[1]. The word "vomiting" is developed from Latin word "vomitorium"[13] meaning fast exit. The word "nausea"[14] derived from a Greek word "nautia" is source for word nausea which means seasickness. It is described as discomfort in the stomach with the need to vomit. The retching means reverse movements of contents of oesophagus as well as stomach without vomiting. By definition PONV is nausea, retching or vomiting observed during first 24-48 hours of surgery. A well designed study conducted in United States[15] and Europe[16] showed that patients are willing to pay from their pocket for efficacious anti-emetic agent to get rid of unpleasant experience which could be worse than post-operative pain.

**Epidemiology:** Though PONV is one of the leading complications after anaesthesia and is a most important factor in determining the length of hospital stay, its exact incidence has not been quantified[17, 18]. Incidence of PONV is variable and it ranges from 30-40% which further increases up to 80%[7] in high risk patients. Higher incidence of PONV is seen in patient with use of opoid analgesics, laparoscopic surgery, breast surgery and strabismus surgery. Greatest incidence is observed in young non-smoking women[19]. High incidence of PONV can be reduced by propofol anaesthesia.

In view of need to improve treatment strategies in PONV almost 3000 randomized controlled studies have been published in numerous journals and 300 new studies are being published every year[14]. This recent information can be very much handy and useful for Clinicians and Anaesthetists in managing PONV more effectively in their day to day practice.

**Aetiology: Pathways for Nausea and Vomiting**

Nausea and vomiting may be induced by various pathways involving complex interaction between area postrema (CTZ), vomiting centre (nucleus of tractus solitarius), cortex, thalamus, hypothalamus, vestibular apparatus and two cranial nerves namely VIII$^{th}$ and X$^{th}$ nerve.

Various receptors that have been found in the vomiting centre are responsible for act of emesis are: Muscarinic ($M_1$), Histamine ($H_1$), serotonin ($5HT_3$) and neurokinin 1 ($NK_1$) receptors. Vomiting centre receives four afferent inputs[20] from following area:

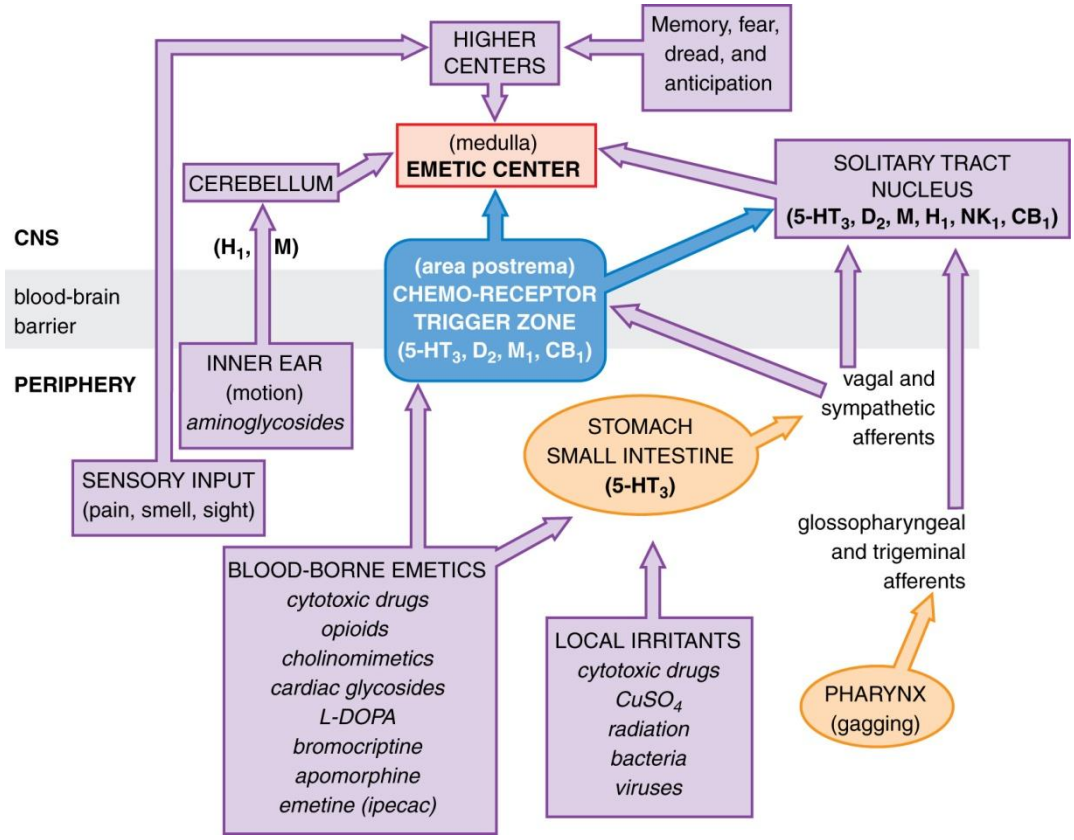
1. CTZ: is located at the base of fourth ventricle and constitutes $D_2$, opioid, $5HT_3$ and $NK_1$ receptors.
2. Vestibular apparatus: is rich in $M_1$ and $H_1$ receptors and plays important role in motion sickness through VIII$^{th}$ cranial nerve.

3. GIT: irritation of GI mucosa by chemotherapy, radiotherapy, gastric distension, and acute gastroenteritis leads to release of serotonin and

activation of 5HT3 receptors carries afferent information through vagal nerve to vomiting centre and CTZ.

4. CNS: Afferent from cortex, hypothalamus, and thalamus are carried to the CTZ after stimulation of these organs by sense of smell, severe pain, sight of vomiting and emotional factors.

   Neurologic pathway responsible for genesis of emesis is shown in following diagram[21].




**<u>Risk Factors</u>:**

The term risk factor was first mentioned by Framingham study in relation to heart disease. Certain factors like high blood pressure, *dyslipidemia* and smoking[22] were assessed to find likely causal relation for development of heart disease. Information of risk factors is valuable for development of risk assessment tools which can predict risk of particular disease. In PONV, females

have more risk than males as they are more susceptible to certain stimuli[23, 24] like motion, opoids, chemotherapy and anaesthetic agents given through inhalational route.

Risk of PONV in females is thrice[25] more than males. If both genders are equal then incidence of PONV for female to male would be 45% and 15%. Major surgical procedures in female population increases incidence up to 50-60% while in small gynaecological procedures incidence could be as low as 7% [26]. A female with non smoking status and received opioids will have further increase in risk hence it is more useful to consider PONV as a multi-factorial in origin. Risk factors can be classified into three independent predictors which have been elaborated below.

I. **Patient related independent predictors:**

1. Female gender: risk of PONV is high in females compared to males irrespective of anaesthetic technique used. Exact cause is not known but probably may be due to lower threshold to motion sickness[27] and emotional tolerability than males. It is highly specific predictor of PONV with odds ratio of 2.6[28].
2. Non smoking status: individuals always develop nausea to their first cigarette due to nicotinic effects on body. One can expect higher incidence of PONV in smokers than non smokers. Interestingly findings from few Studies are contradictory. Cohen and associates mentioned 1.8 times[25] more risk to non smokers than smokers. This study was further strengthened by large meta-analysis study[28].

3. History of PONV, nausea or migraine: there will be variable response to emetogenic stimuli and patient may not recollect previous history correctly. Hence PONV history predictor is having only 50% sensitivity[29].
4. Age: incidence of PONV reduces with increase in age. Eberhart and associates have conducted study in children and concluded that at the age of 3 years or after PONV incidence is increased[30].
5. Anxiety: anxiety may affect PONV but study results are conflicting. A small cohort study in children[31] is not supportive and large randomized control trial in adults[32] also showed weak association. Anxiety may not be useful parameter for predicting PONV.

**II) Anaesthesia related independent predictors:**

1. Use of opioids: Opioid use before surgery showed no difference in PONV when compared with meperidine but showed more frequency of PONV in comparison to barbiturates[33]. During intra-operative stage, different type of opioid showed different results. One article mentioned that alfentanil was associated with less PONV compared with sufentanil or fentanyl [34]. While another study stated that no significant difference was observed in remifentanil and fentanyl comparative study. Cann C and colleagues[35] concluded that morphine-6-glucoronide is found effective than morphine in reducing PONV but in another comparative study conducted by Hanna M H and associates[36] showed no statistically significant difference. Use of opioids post-operatively increase the risk twice[3] but rather than type of opioid, dose[37]plays more important role in increased incidence of PONV.

Non-opioids reduce PONV incidence and thereby decreasing use of opioids by 30-50%[38].

2. Propofol and inhaled anaesthetic agents: Propofol has anti-emetic property and may reduce incidence of PONV. Scuderi and colleagues[39] conducted trial where small dose propofol was given as IV infusion in females planned for laparoscopy. Author could not be able to prove anti-emetic effect of propofol. In another randomized trial[40], healthy individuals were received propofol, midazolam or placebo and then apomorphine was given by infusion. There was increase in threshold for nausea in sedative dose but not for non-sedative dose. With these inconsistent results, concrete conclusion on anti-emetic effect of propofol cannot be drawn. As compared to regional anaesthesia, general anaesthesia brings higher risk of PONV which indirectly indicate contribution of inhalational anaesthetics for higher incidence[26] of PONV. A study conducted with sevoflurane[41] showed increased incidence of PONV up to 80% that clearly supports emetogenic property of inhalational agents. A meta-analysis study conducted by Gupta[42] and associates demonstrated no difference in PONV among volatile agents like isoflurane, sevoflurane and desflurane. Similar types of conclusions were observed by Macario[43] and colleagues study as well as Wallenborn[44]

   and co-worker study. Emetogenic effect of nitrous oxide has been demonstrated in various studies[45, 46] but effect may not be as strong as volatile anaesthetics[47]. More than emetogenic potential, nitrous oxide trials showed serious complications like hypoxia, wound infections and fever.

3. Duration of anaesthesia: Incidence of PONV is associated with duration of anaesthesia[26, 44, 47] but varies widely in extent. In addition to this, other factors like use of inhaled anaesthetics[26], opoids further aggravate magnitude of PONV. In general longer duration surgical procedures are associated with more incidence of PONV.

**III) Surgery related independent predictors:**

Various types of surgical intervention may be associated with high incidence of PONV. Laparoscopic procedures, ENT surgeries (Tympanoplasty, adeno-tonsillectomy and vestibular stimulation), gynaecological procedures and breast surgeries[48-50] have an increased risk of PONV up to 50%. But many times other underlying patient related or anaesthesia related factors contribute to higher incidence of PONV. Hence risk assessment should be done on underlying independent predictors. Several studies describe the fact that type of surgery is not independent factor for development of PONV[51-54]. However some article identified that different type of surgical procedures are independent predictors of PONV[26,29,32]. Strabismus surgery is not predictive factor in adult but well documented in PONV in children.

**<u>Risk Assessment</u>:**

As PONV is multifactorial, patient's risk can be better judged by logistic regression analysis. Palazzo and Evans[55] were the first to apply multiple logistic regressions while Koivuranta and co-workers[56] were the first to publish

predictive models on the basis of above mentioned study. By using strong predictors[56] like female sex, history of motion sickness, past history of PONV, operative time more than one hour and non-smokers, simplified models were developed. Factor positivity from 1 to 5 showed risk of PONV from 18%, 42%, 54%,74% and 87% respectively[56]. However for point zero, predictor risk of PONV was 17%. Of many PONV logistic models; Afpel's PONV score is used frequently for its simplicity.

Simplified risk score[3] predicting PONV for adults:

| Risk Factors | Points |
|---|---|
| Female gender | 1 |
| Non-smoker | 1 |
| History of PONV | 1 |
| Post-operative opioids | 1 |
| Risk score | 0...4 |

**Absolute risk difference**: is effectiveness of anti-emetic drug with specific risk profile. Suppose, PONV incidence in high risk group is 80% and use of $5HT_3$ antagonist reduced incidence up to 60% then relative risk difference is 20%. So if $5HT_3$ antagonists are given in all 100 high risk individuals, 20% of them will have reduced risk. In short 1 out of 5 will be benefited with $5HT_3$ antagonists. In other words to prevent PONV in one patient, 5 patients should be treated prophylactically.

Hence number needed to treat (NNT) =1/ARD

Relative risk reduction ratio is calculated as one minus relative risk reduction.

**Measurement of PONV:**

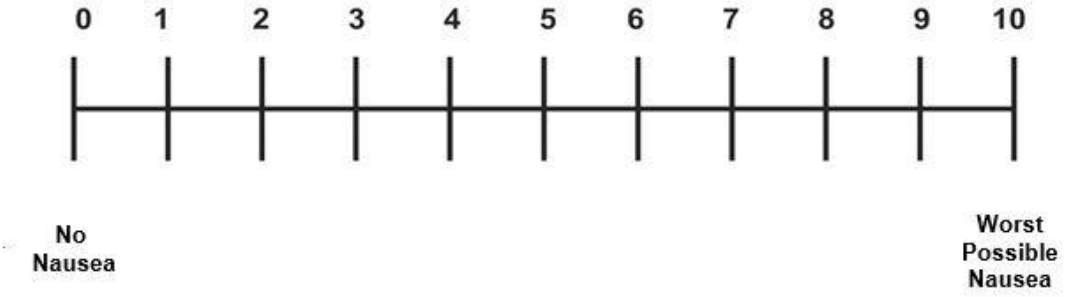
As nausea, vomiting and retching can occur separately or in combination, assessment should be done independently. Hence various scales are used for assessment of PONV are inadequate. VAS[14, 19] (Visual Analogue Scale) is most commonly used for measurement of PONV in which there is 10cm horizontal line with left side corresponds to no nausea and right side to imaginable nausea.

Another ways of assessment of nausea is by numeric rating scale[14] where patient rates his nausea from 0 to 10 with 0 corresponds to no nausea and 10 for worst possible nausea.

Another easy approach for assessing Nausea is verbal rating scale where patients describe their symptoms as no nausea, mild, moderate or severe nausea and scores are given as [0],[1-3],[4-6] and [7-10] respectively. As intensity of nausea varies from time to time, repeated scoring is required for assessment of PONV. Hence it is better to take average of the score.

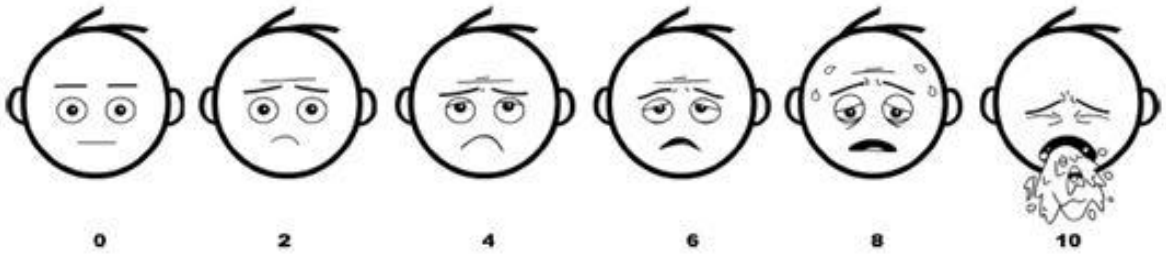
Several types of scales to rate severity of nausea are shown below:

**Visual Analogue Scale for nausea**




**(www.rch.org.au)**

**Baxter Retching Faces Nausea Scale**




**(www.rch.org.au)**

**<u>Prophylactic anti-emetic Policies</u>:**

PONV treatment is mainly classified into

1) Non-pharmacological strategies

2) Contemporary strategies

3) Pharmacological Strategies

1. **Non-pharmacological strategies:**

   Few non-pharmacological techniques like acupressure[57] and acupuncture[57, 58] have been tried in prevention of PONV but did not gain much popularity.

**2. Contemporary strategies:**

i) **Peri-operative pain management**: is most important strategy in anaesthetic practice to reduce complications of anaesthesia. Also right choice of analgesic agent is necessary to control post operative pain. Frequent use of opioids during intra and post operative period can increase the risk of PONV. Under such situation it is wise to use non opioid analgesics for post operative pain relief.[38] A systematic review by Marrett et al [38] demonstrated significant reduction in PONV with use of Non opioids.

ii) **Use of regional or local anaesthesia**: Use of general anaesthetic agents can lead to increased risk of PONV hence with use of regional or local anaesthesia can be good alternative in patients undergoing general anaesthesia provided surgery can be attainable by using regional or local anaesthesia. However risk of developing nausea and vomiting after spinal anaesthesia is not less but pathophysiology is slightly different. Few independent predictors responsible for post-spinal PONV are female sex, intra-operative tachycardia, use of opioids and hypotension[59, 60].

**3 . Pharmacological Strategies:**

**(1) Dopamine Antagonists**: Metoclopramide has been used since olden days to prevent PONV due to its anti-emetic as well as established pro-kinetic properties[61] but major issue with metoclopramide is development of extra-pyramidal symptoms seen in almost 10% of individuals. Although it can be

treated with anti-histaminics and benzodiazepines [62] dopamine antagonists are not frequently used for treatment of PONV.

Droperidol is another drug of choice for PONV with potent anti-emetic property and similar efficacy with smaller dose[63] (0.625 to 1.25 mg) than metoclopramide. Even though many studies have investigated its pharmacokinetic properties, its minimal effective dose and ideal time of administration has not been established well. Also it is contraindicated in patients with prolonged QT interval. Haloperidol has advantage over droperidol due to its relative safety and is considered being as effective as ondansetron[64]. Other drugs like alizapride, prochlorperazine and few neuroleptic agents are rarely used.

Domperidone is an antique drug similar to metoclopramide used in vomiting caused by cytotoxic agent and for gastrointestinal symptoms like nausea, retching. As it does not cross blood brain barrier, central side effects are less observed[13].

**(2) Histamine Antagonists**: As these drugs have been proved their successful use in motion sickness and with additional anti-cholinergic activity, Diphenhydramine, dimenhydinate, cyclizine and promethazine are used in prevention of PONV in selected individuals. Their use is limited by frequent side effects like urinary retention, blurring of vision and extra-pyramidal syndrome[14, 65].

**(3) Anti-cholinergics**: Of many anti-cholinergic agents scopolamine is well established agent in treatment of motion sickness and specialized delivery of scopolamine through trans-dermal route appears to be effective in treatment of PONV[66] when patch is applied a night prior to surgery or early morning on the day of surgery. As trans-dermal scopolamine causes pupillary dilation, its use in neurological surgeries is restricted where evaluation of pupillary reaction is vital in post operative management.

**(4) Neurokinin Antagonists**: Substance P binds to $NK_1$ receptor and induce emetogenic pathway. Some studies have proved efficacy of $NK_1$ antagonists against PONV. Diemunsch and co workers[67] demonstrated efficacy of $NK_1$ antagonist GR205171 in a pilot study conducted in patients undergoing gynaecological surgeries. Gan et al[68] conducted randomized controlled trial with $NK_1$ antagonists using dose of 40mg and 120 mg and ondansetron with dose of 4 mg. In this triple arm study author remarked that aprepitant; a $NK_1$ antagonist is superior to ondansetron in controlling PONV in first 24 and 48 hrs. Another newer $NK_1$ antagonist casopitant is in pipeline to prove its superiority over ondansetron[69]. Synthetic cannabinol (nobilone) also have been proved to be effective where vomiting is primarily due to CTZ stimulation[13].

**(5) Corticosteroids like Dexamethasone**: Dexamethasone has been used in animal experiment and proved to produce antiemetic effect through inhibition of nucleus of tractus solitarii rather than area postrema[70]. Carlisle and colleagues[71] has opined that dexamethasone is having similar efficacy to ondansetron. As

dexamethasone is having slow onset of action, it is not common practice to use dexamethasone alone in PONV.

**(6) Benzodiazepines:** although lorazepam and alprazolam are not anti-emetic agents but due to sedative, anxiolytic and amnesic effect they help in reducing anticipatory component of nausea and vomiting in patients[21].

**(7) Serotonin antagonists:** 5 $HT_3$ antagonists principally used for treatment of chemotherapy induced nausea vomiting (CINV) as well as treatment of PONV.[13] The primary site of action of these drugs is on CTZ. They are precisely used in vomiting than nausea that encounter after surgery. Due to additional safety profile compared to other anti-emetic agents they have gained more popularity in managing PONV. Commonly used $5HT_3$ antagonists are: ondansetron, palonosetron, granisetron and dolasetron. The most widely prescribed $5HT_3$ antagonist is ondansetron which is a prototype drug. The main difference among these agents are related to chemical structures, receptor affinity and pharmacokinetic profile.[21]

All $5HT_3$ antagonists act as competitive antagonist by binding to extracellular binding site except palonosetron which display allosteric binding. This distinguishable binding makes palonosetron unique in anti-emetic property with strong receptor affinity.

Anti-emetic agents are also classified depending upon their potency[72].

- Most Potent: Palonosetron, ondansetron, granisetron and metoclopramide
- Moderately Potent: Phenothiazines, droperidol and cannabinoids

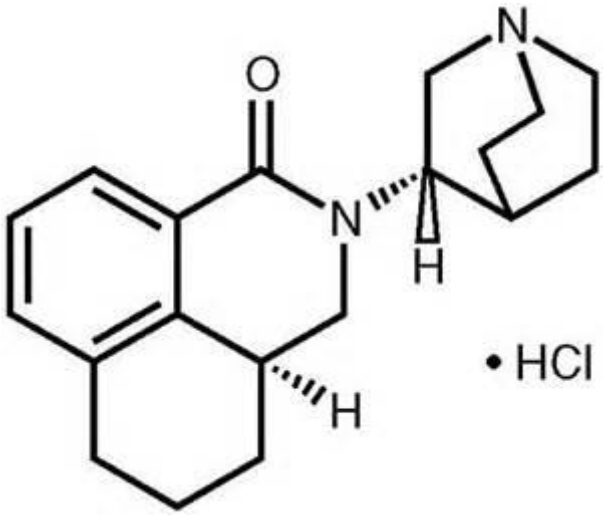
- Weak Anti-emetic agent: Anti-cholinergics, anti-histaminics and benzodiazepines.
- Adjunctive agents: Dexamethasone

Until recently ondansetron was the drug of choice for treatment of PONV and CINV, but various comparative studies had been in the favour of palonosetron in term of safety and efficacy. Even though ondansetron is less expensive, cost benefit ratio[73] proved superiority of palonosetron over ondansetron.

**Pharmacology of Palonosetron:**

**Chemical structure:**

Palonosetron hydrochloride exists as single isomer and posses following structural formula[74].




Chemically , palonosetron hydrochloride is (3aS)-2-(3S)-1-Azabicyclo[2.2.2]oct-3-yl-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinoline-1-one monohydro-chloride. The molecular formula for palonosetron is $C_{19}H_{24}N_2OHCl$ and molecular weight is 332.87.

**Mechanism of action:**

Palonosetron acts by binding to $5HT_3$ receptor as an antagonist[13]. $5HT_3$ receptor is a pentamer with a centrally permeable cylindrical body. Various genes for $5HT_3$ subtype had been identified. $5HT_{3A}$ and 5 $HT_{3B}$ receptor subunits[75] are expressed in area postrema, nucleus tractus solitarii and entero-chromaffin cells of GIT. All 5 HT receptors are G-Protein Coupled Receptors and 5 $HT_3$ receptors are inotropic ligand gated ion channels.

Activation of pre-synaptic $5HT_3$ receptor leads to rapid rise in $Ca^{2+}$ inside the cell which produces biological response through series of events. In addition, $5HT_3$ receptor also modulates release of various neurotransmitters like serotonin, dopamine, neurokinin, cholecystokinin and acetylcholine which are capable of inducing PONV after their activation.

**Pharmacokinetics of Palonosetron:**

There is not much significant difference in pharmacokinetics of palonosetron in comparison to other 5 $HT_3$ antagonists. After intravenous administration, it achieves adequate plasma concentration and 62% binds to plasma proteins[75]. It has volume of distribution of 8.3±2.5 L/kg and is metabolised in liver by oxidation and hydroxylation producing two primary inactive compounds: N-oxide palonosetron and 6-S-hydroxy palonosetron. Almost 40% of drug is excreted unchanged in urine. Palonosetron exhibit high receptor binding property (Pki=10.45) and prolonged elimination half life about 40 hours[74].

**Dose and route of administration**[12, 73]

Each 1.5 ml vial of palonosetron contains 0.075mg of palonosetron hydrochloride. It is preferably given as intravenous route 10-30 minutes before induction of anaesthesia.

**Safety of palonosetron:**

The safety of all 5 $HT_3$ antagonists is very well proved in various randomized[76]studies. Common side effects are constipation, headache, rashes and prolongation of QT interval leading to arrhythmias. Palonosetron showed less incidence of QT prolongation even with increasing dose. Transient increase in hepatic enzyme has been mentioned but occurs less frequently.

**Drug interactions:**

As palonosetron is neither enzyme inducer nor enzyme inhibitor, its drug interaction potential appears to be low[73]. However adverse reaction with apomorphine demonstrated profound hypotension and unconsciousness.

**Use in specific population:**

Pregnancy: Teratogenicity has been confirmed in animal studies but not well controlled studies observed in pregnant women. It is contraindicated in pregnancy with category B evidence[73]. As palonosetron is excreted through milk, serious adverse reaction in infants can occur hence it is not advised in nursing mothers[14]. Also its safety below 18 years has not been established.

**Studies in accordance with our study:**

Many studies assessed comparison of palonosetron versus ondansetron or other $5HT_3$ antagonists and have revealed superiority of palonosetron in term of safety and efficacy.

**Kovac and colleagues**[77] demonstrated safety and efficacy of various doses of palonosetron in female patients undergoing elective gynaecological or breast surgery. A multicentric trial was conducted among 544 patients. After random allocation, patients were divided into three groups. Primary efficacy end point was assessed by number of complete responders (CR) in all three groups who received either of three different doses of palonosetron (0.025mg, 0.050 mg and 0.075mg). The study concluded that single dose of 0.075 mg of palonosetron was effective in preventing PONV and not lower doses.

**Loha and associates**[78] conducted a single blinded parallel group study where 98 patients were allocated to either palonosetron group or ondansetron group. The surgical technique, type of anaesthesia and anaesthetic regimen was unique. The primary effectiveness was measured by frequency of nausea vomiting and number of CR and secondary safety end points were assessed by observing any adverse drug reactions. The study concluded that palonosetron was comparable to ondansetron for prophylaxis of PONV in laparoscopic cholecystectomy when intravenous palonosetron given as single dose just before induction.

**Moon and co-authors**[79] have evaluated efficacy of palonosetron versus ondansetron in a hundred non smoking females who were allocated randomly to either group. One group received 8 mg of ondansetron as a bolus followed by 16mg combined with patient controlled analgesia (PCA) regimen. Another group received intravenous 0.075mg palonosetron. Patients were treated with opioid analgesics like fentanyl to alleviate post operative pain. Incidence of PONV, adverse effects, severity of nausea and effect of rescue medication use were measured at 0-2 and 2-24 hrs. In a final conclusion, author remarked that palonosetron was more effective than ondansetron in high risk group where post operative opioids were used to control pain.

**Bajwa et al**[80] conducted a comparative clinical study in 60 patients undergoing day care surgery were randomly assigned in groups received 8mg of ondansetron or 0.075 mg of palonosetron just before induction of anaesthesia. All patients were observed for first 6 hours for PONV episodes and number of time rescue medication used. Patients were followed up on phone and statistical analysis was done. In palonosetron group 6.66% and 3.33% had nausea and vomiting respectively while in ondansetron group it was 20% and 13.33% respectively which was statistically significant. Author opined that palonosetron is better drug in comparison with ondansetron in controlling PONV in day care surgeries.

**Bhattacharjee and co-workers**[81] demonstrated the efficacy of palonosetron against granisetron in 60 female patients who had undergone laparoscopic cholecystectomy. Patients were randomly assigned to group P or group G and

received 75 µgm of palonosetron and 2.5 mg of granisetron respectively. Incidence of complete response (CR) and adverse effects were assessed statistically. From statistical observations author remarked that palonosetron was more effective as a prophylactic anti-emetic agent when compared with granisetron. However no statistical difference between two groups had been observed in relation to incidence of side effects.

**Chun and associates**[82] concluded the superiority of palonosetron in reducing PONV during first 72 hrs of post operative period among 204 patients. Two groups were assigned after randomization where one group received placebo (normal saline) and other group received 0.075mg palonosetron. Nausea severity, PONV incidence and rescue medication were the main parameters to assess efficacy. A conclusive remark by author mentioned that palonosetron helps in reducing incidence of PONV during post operative period.

**Sadaba et al**[83] opined about bioavailability of I.V. palonosetron in comparison with sc route and found equal bioavailability through both the routes. In their study appropriate patients were selected where platinum based chemotherapy was induced from October 2009 to July 2010. Patients were randomized to receive palonosetron either intravenous or subcutaneous route and primary end point for assessment was bioavailability. In a cross over designed study patient's blood samples were collected at required intervals and statistical analysis was performed by ANOVA. Author revealed that there was no statistical difference in AUC.

**Candiotti and colleagues**[84] organised open label study to compare better choice of rescue anti-emetics between first generation and second generation $5HT_3$ antagonists in reducing PONV. In this multicenter trial outpatients planned for abdominal or gynaecological surgery by laparoscopic method were selected and received ondansetron 4 mg intravenously just before anaesthesia. By randomization, patients were allotted to receive rescue treatment either with palonosetron 0.075mg or ondansetron 4 mg through intravenous route. Out of enrolled 220 patients 98 patients received rescue medication (48 palonosetron and 50 ondansetron). Complete control assessed at 72 hours of drug treatment found no statistical significance in both groups (25% in palonosetron group against 18% in ondansetron group). Even though not much significant difference was observed in two active arms, author did not forget to mention about down going trend in palonosetron group towards decrease in episodes of vomiting. Author further suggested that larger studies are necessary to prove superiority of palonosetron as a rescue anti-emetic agent.

**Sharma and co-workers**[85] compared efficacy of palonosetron with ondansetron in a prospective study where 90 patients undergoing hysterectomy by laparoscopic approach were selected. Patients were randomized into group I who received intravenous 0.075mg palonosetron with 8 mg of dexamethasone. In group II, 4 mg of ondansetron with same dose of dexamethasone were injected. In group I, during first 2 hrs no one had nausea, three had vomiting and 4% required rescue medication. While in group II, 8 had nausea (P=0.013) and vomiting and 20% needed rescue antiemetic therapy. After 24 hrs, neither

group had either nausea or vomiting. From above observations author derived conclusion that combination therapy with dexamethasone and palonosetron was more beneficial in treating early as well as late cases of PONV.

**Mansour**[86] has conducted study in high risk individuals with ASA (American Society of Anaesthesiologists) grade I or II. After randomization and blinding of patient as well as investigator, study was conducted in one hundred and fifty patients. Three equal groups were assigned for study in which one group received Dexamethasone and normal saline, second group received dexamethasone and metoclopramide and third group received dexamethasone and palonosetron. Author concluded that combination of palonosetron and dexamethasone was safe in early as well as late phase of PONV[1].

**Kim et al**[87] conducted a comparative study between palonosetron and ondansetron in non smoking females scheduled for gynaecologic surgery by laparoscopic manner. About 100 patients of ASA grade I or II were randomized into palonosetron group and ondansetron group. In ondansetron group, 8 mg of ondansetron was given intravenously followed by continuous infusion of 16 mg which was added in patient controlled analgesia regimen. Intravenous 0.075 mg of palonosetron was administered just before induction of anaesthesia in palonosetron group and normal saline was added in patient controlled analgesia regimen. PONV episodes were recorded at 2, 24, 48 and 72 hrs of post operative period. Overall incidence of PONV was 52% in ondansetron group and 48% in palonosetron group in 0-72 hr after surgery.

Author inferred from observations that no benefit of one drug over the other in preventing PONV.

**Morrow et al**[88] demonstrated superiority of palonosetron over other first generation $5HT_3$ antagonists. In this analytic study, different types of cancer patients who were about to receive emetogenic chemotherapy from four different trials were selected. Eligible patients from four study groups were grouped into two where first arm received single dose of 0.25mg or 0.75mg of IV palonosetron. In second arm either 32 mg of ondansetron,100 mg of dolasetron or 40 µgm/kg of granisetron was given half an hour before induction of chemotherapy. In a large study population of 2913 malignancy patients, complete control for palonosetron was 66% and 46% in acute and late phase while in ondansetron arm it was 63% and 43% respectively. Author drawn concluding remark mentioning that palonosetron received group were free of nausea on every day and very few had severe nausea. In addition, requirement of rescue medication was also less in palonosetron group.

**Mattiuzzi et al**[89] compared two doses of palonosetron with ondansetron in patients of AML undergoing chemotherapy. Forty seven patients enrolled in one group received ondansetron 8 mg stat and then 24 mg continuous infusion. Another two groups having 48 patients in each arm received either palonosetron 0.25 mg daily for 5 days or same dose of palonosetron on alternate day (Day1,3, and 5). In each group 77% were without nausea on first day and percentage of nausea from second to fifth day was reduced in all groups. On day 6and 7, patients from group who received palonosetron daily were free from nausea.

(p=0.01) Author remarked that daily palonosetron was superior to ondansetron in prophylaxis of late CINV.

**Moon et al**[90] derived conclusion from a study where 93 patients were planned to undergo gynaecologic laparoscopic procedures. Patients were randomized into two groups to receive 0.075 mg of IV palonosetron or 40 mg oral aprepitant. In a double blinded study complete response was assessed 1-48 hours of surgery. At 0 and 2 hrs, severity of nausea was significantly less ($p<0.05$) in aprepitant group. Although consumption of fentanyl was less in aprepitant group, large amount of rescue analgesics required to control pain in this group. In final comment author stated that palonosetron and aprepitant both are effective in PONV prophylaxis and further suggested that combined use of these drugs would provide more benefit compared to single use alone.

In a randomized study done by **Bicer et al** [91] where about 150 children under 2 to 12 years of age group undergoing strabismus surgery were assigned to receive palonosetron with dose of 0.5,1.0,1.5 µgm/kg. All patients were assessed at four different intervals (0-2 hrs, 2-6 hrs, 6-24 hrs and 24-48n hrs) for episodes of nausea, vomiting or retching. Nausea severity was assessed by numerical scale. Percentage of PONV in children received 0.5 or 1 µgm/kg of palonosetron was 24% while PONV incidence was 4% less in children receiving 1.5µgm/kg of palonosetron. Author mentioned efficacy of different doses of palonosetron in controlling PONV and stressed upon further evaluation for these dosages.

**Bergese et al**[92] demonstrated efficacy of triple regimen anti-emetic therapy with palonosetron, dexamethasone and promethazine in patients undergoing craniotomy and also mentioned about less risk of QT prolongation on ECG in palonosetron combined anti-emetic regimen. Forty participants were given triple dose regimen containing 0.075 mg palonosetron, 10 mg dexamethasone and 25 mg promethazine. Patients were assessed post-operatively every 24 hours for 5 days for PONV symptoms. Incidence of PONV after 24 hrs of surgery was 30% (nausea incidence was 30% and emesis incidence was 7.5%). Overall incidence of PONV was 30% and complete response was seen in 70% in whom no nausea or vomiting has been observed from day1 to day5. As per Author's opinion, in combination anti-emetic regimen palonosetron is effective in preventing PONV without additional cardiac risk of side effects. (No QT prolongation)

**Kim and associates**[93] conducted prospective study in 109 non smoking females posted for planned laparoscopic surgery. After randomization by using computerized random number tables patient were assigned into three groups. All three groups received either ondansetron 4mg or palonosetron 0.075 mg or ramosetron 0.3mg. Primary efficacy parameters were assessed by using variables like number of PONV episodes, severity of nausea and number of times rescue medication used. Overall PONV incidence was found low in palonosetron based group (22.2%, 11.1%, 5.6%) in comparison to other two active treatment groups. (Ondansetron 77%, 48.6%, 28.6% and ramosetron 60.5%, 28.9%, 18.4%) Need of rescue anti-emetic was reduced in palonosetron arm ($P<0.001$). By Kaplan Meier analysis method palonosetron ranked first antiemetic followed by ramosetron and ondansetron.

**Chattopadhyay and collegues**[94] have inferred in a study where 109 women participated in a randomized study. Patients were allocated into two groups where first group received palonosetron (0.075mg) and second group received ramosetron (0.3mg) immediately after the birth of the baby. Participants were blinded to the procedures and investigator was also unaware about the fact that which therapeutic regimen was received to either group. Complete response in first 2 hrs of medication was 85% in palonosetron group and 83.3% in ramosetron group. After 2-24 hrs of medication, incidence of CR in palonosetron group was 70.9% and 53.7% in ramosetron group which was statistically significant. ($p<0.05$) After extrapolation of data, author remarked that palonosetron is better prophylactic agent than ramosetron in prevention of delayed PONV.

**Lorusso et al**[95] demonstrated that single dose combination therapy of palonosetron and dexamethasone is effective in controlling CINV in patients receiving multi day based chemotherapy (MD-CT). This prospective uncontrolled trial was planned in oncology OPD of Vito Fazzi Hospital in Italy. Patients were given 0.25 mg of palonosetron along with 20 mg of dexamethasone half an hour prior to induction of chemotherapy. All patients were asked to keep record in diary from day 1 to day 7. Complete response, complete control (complete response but mild nausea) and food intake amount per week were assessed. Out of enrolled 50 patients, 80% showed CR and 78% showed CC. From first to last chemotherapy cycles CR was observed in 76 to 88% and CC was seen in 62 to 88%of individuals. Patients with CR showed more food intake per week than non complete responders and the difference was

statistically significant. ($p<0.0001$) Final concluding remark from author mentioned that palonosetron with single dose was capable of preventing CINV in all scheduled chemotherapy cycles.

**Morganroth and associates**[96] have assessed safety of single dose of palonosetron towards cardiovascular related side effect (QT prolongation) in phase I trial. It was double dummy and parallel arm study in healthy participants where moxifloxacin was given as positive control. After initial evaluation participants were allocated into five groups. First group received placebo in oral as well as IV form, second group received 0.25 mg of IV palonosetron with oral placebo, third group received 0.75 mg of IV palonosetron (three fold higher than previous group) with oral placebo, fourth group received 2.25 mg of IV palonosetron (three fold higher than previous group) with oral placebo and last group received IV placebo with 400 mg of oral moxifloxacin. The study showed no prolongation of QT interval with confidence interval (CI) of 10 ms. Author concluded that palonosetron did not show any adverse effect on cardiovascular system even with increase in dose. On the other hand $5HT_3$ antagonists like ondansetron and dolasetron reported prolonged QT interval in increasing dose.

**Charbit and collegues**[97] assessed safety of ondansetron, droperidol in a small prospective study on a 16 healthy volunteers. After dividing into two equal sex

groups, participants received either ondansetron or droperidol in first group and combination of ondansetron and droperidol or placebo in second group. The QTc interval was assessed in all groups. As compared placebo group, ondansetron as well as droperidol showed prolonged QTc.

Prolonged QTc interval was also observed in a group who received combination therapy with ondansetron and droperidol. Author concluded that ondansetron or droperidol or their combination had higher risk of cardiovascular adverse effect in term of QTc prolongation.

To demonstrate anti-emetic efficacy it is better to conduct study in high risk group as these groups will be more benefitted from the intervention than normal individuals. Many studies have been conducted to evaluate safety and efficacy of anti-emetics in a specific groups undergoing particular type of surgery. We cannot make generalization because these findings in one group of population who underwent particular type of surgery may not be applicable to other type of surgery. There are insufficient data available on participant of all age groups and all post operative surgeries under general anaesthesia. To bridge this gap we conducted study to assess safety and efficacy of palonosetron against ondansetron on population covering all eligible post operative candidates undergoing general anaesthesia irrespective their type of surgery.

# 4. **MATERIALS AND METHODS**

# MATERIALS AND METHODS

The study was initiated after getting approval from the Institutional Ethical committee. Approval letter dated 21.01.2015.

**Study Design**: double blinded randomized controlled study.

**Study period**: January2015 to February 2016.

**Source of Data**: All eligible patients of ASA grade I category undergoing surgical intervention under general anaesthesia in Karpaga Vinayaga Institute of Medical Sciences were enrolled.

**Sample Size**: sample size was calculated with 5% ($p<0.05$) level of significance and a power of study at 80%. (β error 20%). Sample size required for our study was 50 in each group but 8 more samples in each group were added to improve accuracy of study results.

**Inclusion Criteria:**

1. Patients of either sex between age group 15-60 yrs with ASA grade I status
2. Patient willing to give written informed consent

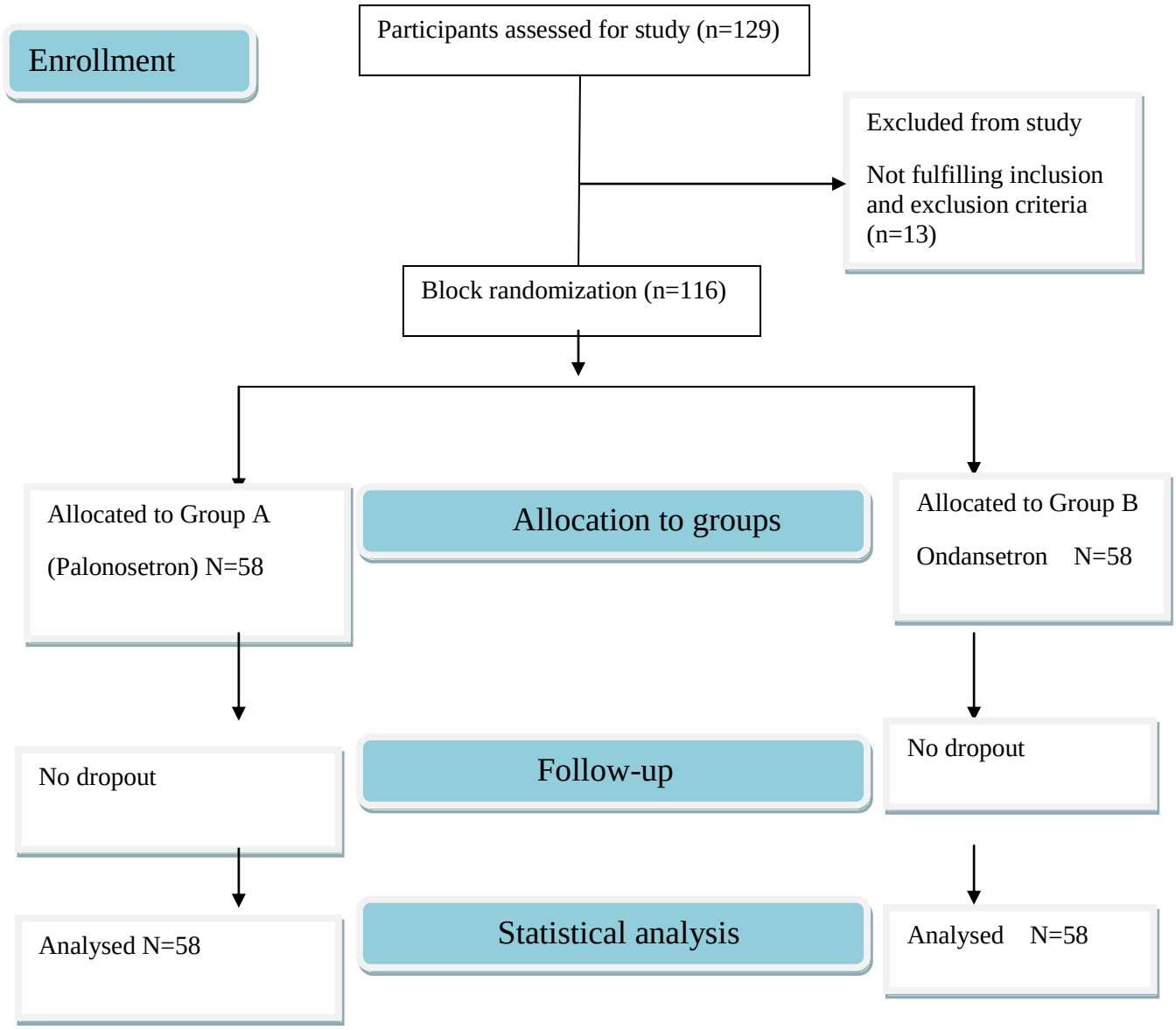
**Exclusion Criteria:**

1. Pregnancy
2. Patients with diagnosed case of Acid Peptic Disease
3. Patient with history of nausea and vomiting pre-operatively
4. Patient taking anti-emetics or steroids
5. Patient having major organ involvement like liver, kidney, heart, brain and lungs
6. Chronic alcoholic
7. Patient with known hypersensitivity to any of the study trial drug
8. Patient participated in other study trial
9. Patient with history of motion sickness
10. Patients of Malignancy

**Subject enrollment:**

A written informed consent was obtained from all participants in each group prior to surgery. Meticulous care was taken in obtaining demographic data, details of previous illness and retrieving details like past history of motion sickness or PONV.

**CONSORT diagram of patient distribution:**




116 out of 129 patients were recruited for the study based upon inclusion and exclusion criteria and routine investigations like Hb %, TLC, FBSL, PPBSL, BUL, S. Creatinine, Chest X-ray and ECG were recorded.

Patients were randomly assigned into two equal groups.

**Group A:** received palonosetron 0.075 mg intravenously.

**Group B:** received ondansetron 8 mg intravenously.

Block randomization method was used for assigning equal groups. Four letter blocks were prepared as: AABB, ABAB, ABBA, BAAB, BABA, BBAA and patients were allocated accordingly. For example, if randomly selected block would be BAAB then first patient would go to group B, second and third patient would go to group A and fourth patient would go to group B. In this way there was equal distribution of subjects in each group.

Before induction of anaesthesia vitals like pulse, respiratory rate, systolic and diastolic blood pressure, temperature and oxygen saturation ($SPO_2$) were recorded. A covered envelope was provided to anaesthetist where name of drug group was mentioned. (Obtained from block randomization) Accordingly either palonosetron or ondansetron was administered 10 minutes before anaesthesia. After premedication with fentanyl 2µg/kg[14] and glycopyrrolate[14] 5µg/kg, patients were induced with IV propofol 2mg/kg and intubated with succinyl choline[14] and muscle relaxation was achieved by vecuronium bromide 0.08mg/kg. Patients were reversed back from general anaesthesia with neostigmine 0.05mg/kg and glycopyrolate 0.2 mg. All vital parameters like pulse, BP, RR, Temperature, $SPO_2$ and ECG were monitored intra operatively and post operatively at 0, 6,12,24,48 hrs.

Patients were questioned by trained staff or on duty CRRI by using validated questionnaire for assessment of safety and efficacy. Efficacy was evaluated by complete response,[80,98] (no episode of nausea or vomiting and no use of rescue medication) severity of nausea,[80, 98] use of rescue medication, and overall satisfaction score by 5 point Likert scale within 48 hrs of surgery[98]. Nausea severity was measured by Verbal Rating Scale and patients were graded into: no nausea 0, mild nausea 1-3, moderate nausea 4-6 and severe nausea 7-10. Those who had developed severe nausea or vomiting, rescue antiemetic IV metoclopramide (10mg) was administered.

Safety was evaluated for presence of rash, itching or hypotension or any serious adverse event during and after surgery. Cardiovascular safety was assessed by comparing pre and post-operative ECG by assessing QTc interval.

**Statistical analysis:**

**Mean, standard deviations** and **proportions** were calculated among the groups. Data was entered into excel spread sheet and analysed by using SPSS software. Statistical analysis was done by **Chi-square test** and **Student t-test.** P value less than 0.05 was considered as statistically significant.

# 5. OBSERVATIONS AND RESULTS

## OBSERVATIONS AND RESULTS

**Table1: Distribution of subjects according to age**

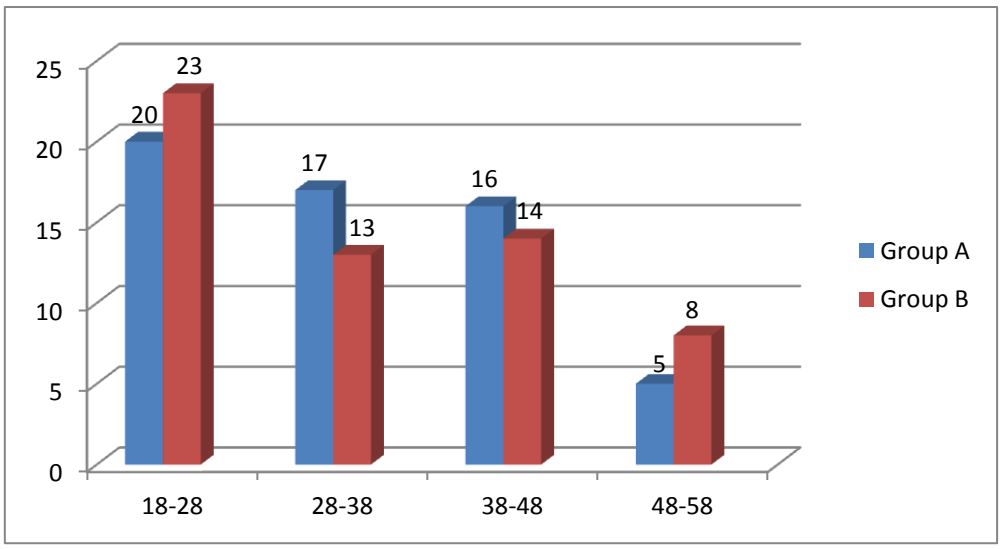
| Age Group | Group A N (%) | Group B N (%) | Total N (%) |
|---|---|---|---|
| 18-28 | 20 | 23 | 43 (37.07) |
| 28-38 | 17 | 13 | 30 (25.86) |
| 38-48 | 16 | 14 | 30 (25.86) |
| 48-58 | 05 | 08 | 13 (11.21) |
| Total | 58 | 58 | 116 (100) |
| Mean age | 33.93 ±10.32 | 34.86±11.43 | * P> 0.05 |

* (p>0.05 not significant)

In the above table it was observed that mean age among Group A and Group B were 33.93± 10.32 and 34.86 ± 11.43 years respectively.

This difference was not statistically significant. (p>0.05)

**Figure 1: Age wise distribution of subjects**




Large numbers of subjects observed in younger age group (18-28years) while small numbers of participants were present in elder age group. (48-58years)

**Table 2: Demographic data**

| Parameters | Group A | Group B | P value |
|---|---|---|---|
| Mean age | 33.93± 10.31 | 34.86 ± 11.43 | 0.46 |
| Mean height | 152.95 ± 6.81 | 153.02± 6.38 | 0.06 |
| Mean weight | 54.93 ± 9.84 | 54.83 ± 8.72 | 0.06 |
| Mean BMI | 23.54±2.56 | 23.25±2.45 | 0.8 |

Mean age observed in both groups were 33.93 and 34.86 respectively. Average height and weight in Group A and Group B were 152.95, 153.02 cms and 54.93 and 54.83 kg.

**Figure 2: Mean Age among the study groups**

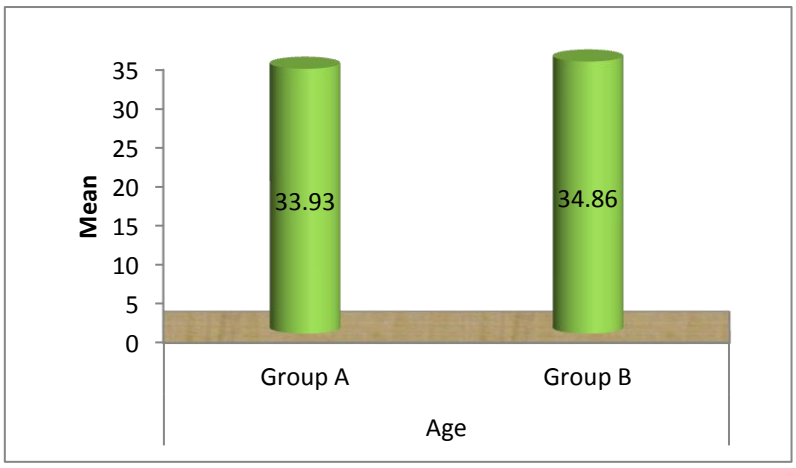
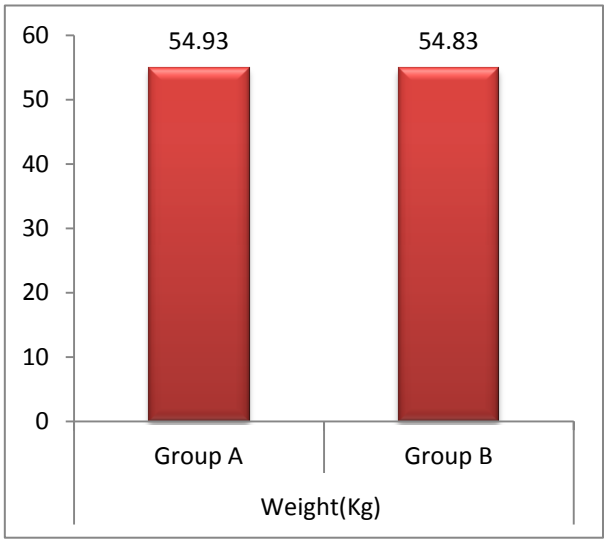



**Figure 3: Mean weight and height among the study Groups**



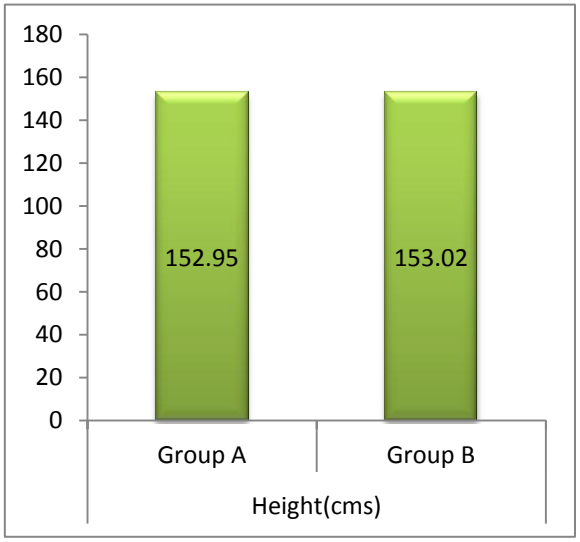



**Table 3: Distribution of subjects according to sex**

| Sex | Group A<br>N (%) | Group B<br>N (%) | Total<br>N (%) |
|---|---|---|---|
| Male | 27 ( 23.27) | 39 (33.62) | 66 (56.90) |
| | | | |
| Female | 31 (26.73) | 19 (16.38) | 50 (43.10) |
| | | | |
| Total | 58 (50) | 58 (50) | 116 (100) |

In our study 66 (56.90%) were males and 50 (43.10%) were females. The distribution of men and women among both the groups were nearly similar and there was no statistically significant difference.

**Figure 4: Distribution of sex (%) among both study groups**

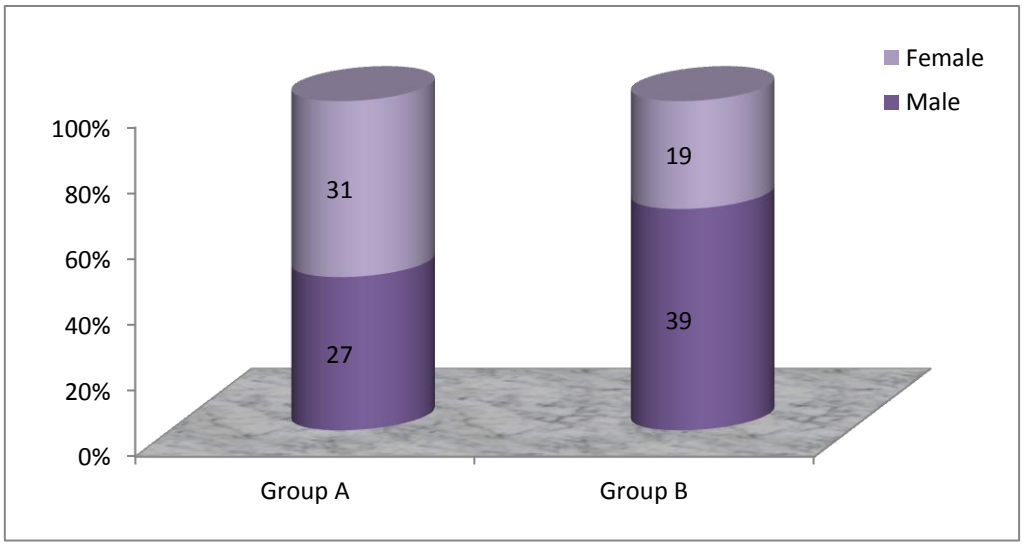


**Table 4: Risk factors among study groups:**

| Risk factor | Group A | Group B | P value |
|---|---|---|---|
| Female Gender | 31/58 (53%) | 19/58(33%) | 0.02 |
| Non smokers | 52/58 (89%) | 49/58 (84%) | 0.4 |
| Duration of surgery > 2 hrs | 7/8(88%) | 13/20 (65%) | 0.23 |

In group A, female patients were 20% more as compared to group B. In both groups non smokers were having almost equal percentage. In group A, surgical time was prolonged for more than 2 hours in 88% of subjects which was higher than group B (65%).

**Figure 5: Risk factors among group A and group B**

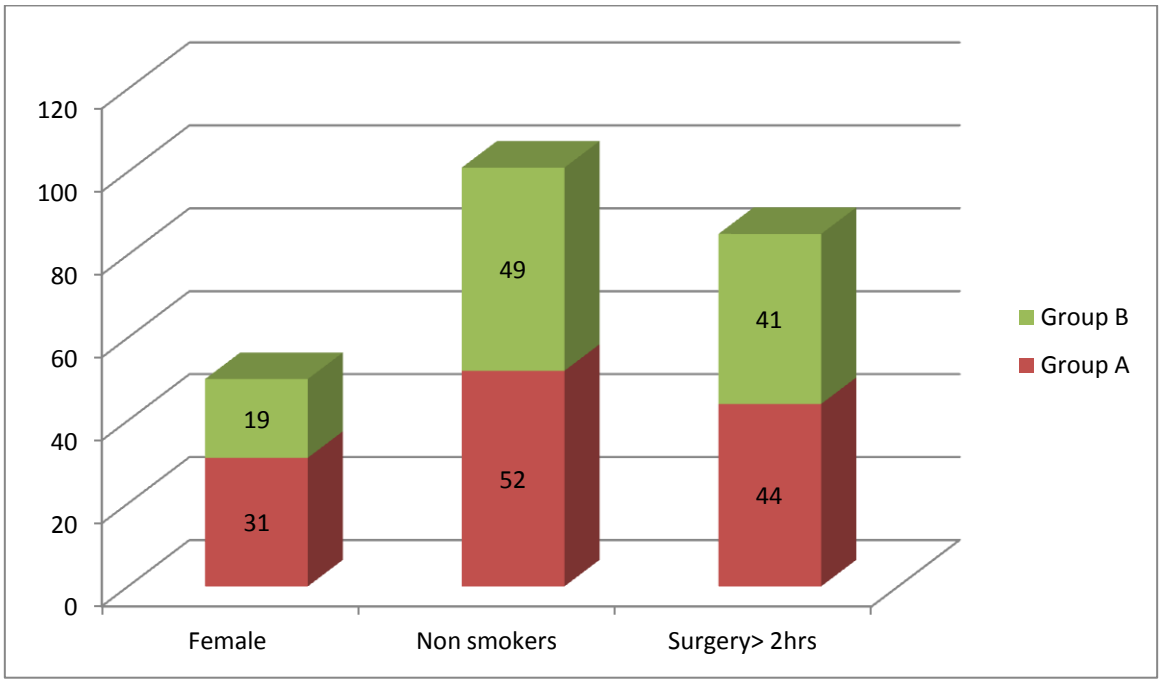


**Table 5: Mean and SD of pulse among the study groups**

| Pulse rate / min | Group | Mean | SD |
|---|---|---|---|
| Pre-op | Group A | 78.91 | 6.809 |
| | Group B | 81.05 | 9.212 |
| Pre-ind | Group A | 83.07 | 10.244 |
| | Group B | 85.22 | 11.278 |
| Intra-op | Group A | 82.98 | 8.904 |
| | Group B | 86 | 13.54 |
| Post-op (0) | Group A | 80.95 | 11.075 |
| | Group B | 79.48 | 11.509 |
| Post-op (6) | Group A | 80.83 | 9.156 |
| | Group B | 79.57 | 9.599 |
| Post-op (12) | Group A | 80.81 | 9.802 |
| | Group B | 80.1 | 10.767 |
| Post-op (24) | Group A | 81 | 10.333 |
| | Group B | 79.83 | 9.217 |
| Post-op (48) | Group A | 79.83 | 9.552 |
| | Group B | 79.19 | 8.642 |

**Table 6: Mean and SD of systolic BP among the study groups**

| Systolic BP (mmHg) | Group | Mean | SD |
|---|---|---|---|
| Pre-op | Group A | 115.62 | 9.525 |
| | Group B | 115.55 | 10.212 |
| Pre-ind | Group A | 116.34 | 7.67 |
| | Group B | 117.03 | 12.001 |
| Intra-op | Group A | 117.31 | 10.705 |
| | Group B | 116.45 | 12.151 |
| Post-op (0) | Group A | 120.17 | 13.566 |
| | Group B | 121.28 | 13.976 |
| Post-op (6) | Group A | 118.97 | 13.103 |
| | Group B | 117.86 | 9.099 |
| Post-op (12) | Group A | 116.9 | 8.779 |
| | Group B | 118.24 | 10.794 |
| Post-op (24) | Group A | 117.86 | 9.38 |
| | Group B | 117.93 | 8.385 |
| Post-op (48) | Group A | 118.66 | 9.473 |
| | Group B | 118.28 | 9.525 |

**Table 7: Mean and SD of diastolic BP among the study groups**

| Diastolic BP (mmHg) | Group | Mean | SD |
|---|---|---|---|
| Pre-op | Group A | 75.86 | 7.234 |
| | Group B | 75.52 | 7.411 |
| Pre-ind | Group A | 75.41 | 6.733 |
| | Group B | 75.69 | 6.916 |
| Intra-op | Group A | 75.93 | 9.485 |
| | Group B | 76.34 | 8.062 |
| Post-op (0) | Group A | 76.31 | 9.228 |
| | Group B | 76.17 | 9.094 |
| Post-op (6) | Group A | 75.83 | 8.396 |
| | Group B | 74.38 | 7.845 |
| Post-op (12) | Group A | 76.74 | 7.01 |
| | Group B | 75.72 | 6.429 |
| Post-op (24) | Group A | 74.59 | 7.876 |
| | Group B | 74.24 | 6.511 |
| Post-op (48) | Group A | 74.21 | 7.62 |
| | Group B | 74.41 | 5.968 |

**Table 8: Mean and SD of RR among the study groups**

| RR (cycles/min) | Group | Mean | SD |
|---|---|---|---|
| Pre-op | Group A | 18.95 | 2.502 |
| | Group B | 18.14 | 2.893 |
| Pre-ind | Group A | 18.78 | 2.492 |
| | Group B | 17.95 | 2.658 |
| Intra-op | Group A | 13.28 | 1.387 |
| | Group B | 12.62 | 0.933 |
| Post-op (0) | Group A | 19.69 | 2.624 |
| | Group B | 19.55 | 2.226 |
| Post-op (6) | Group A | 19.28 | 2.726 |
| | Group B | 18.62 | 2.491 |
| Post-op (12) | Group A | 18.93 | 2.316 |
| | Group B | 18.33 | 2.438 |
| Post-op (24) | Group A | 18.34 | 2.213 |
| | Group B | 18.09 | 2.187 |
| Post-op (48) | Group A | 18 | 2.184 |
| | Group B | 17.47 | 1.958 |

**Table 9: Mean and SD of temperature among the study groups**

| Temperature ($^0$F) | Group | Mean | SD |
|---|---|---|---|
| Pre-op | Group A | 98.16 | 0.325 |
| | Group B | 98.18 | 0.277 |
| Pre-ind | Group A | 98.12 | 0.297 |
| | Group B | 98.25 | 0.292 |
| Intra-op | Group A | 98.12 | 0.302 |
| | Group B | 98.2 | 0.353 |
| Post-op (0) | Group A | 98.34 | 0.289 |
| | Group B | 98.36 | 0.361 |
| Post-op (6) | Group A | 98.35 | 0.516 |
| | Group B | 96.7 | 12.122 |
| Post-op (12) | Group A | 98.24 | 0.363 |
| | Group B | 98.19 | 0.333 |
| Post-op (24) | Group A | 98.19 | 0.247 |
| | Group B | 98.08 | 0.207 |
| Post-op (48) | Group A | 98.17 | 0.271 |
| | Group B | 98.13 | 0.246 |

**Table 10: Mean and SD of $SPO_2$ among the study groups**

| **$SPO_2$ (%)** | **Group** | **Mean** | **SD** |
|---|---|---|---|
| Pre-op | Group A | 98.93 | 0.413 |
| | Group B | 98.95 | 0.223 |
| Pre-ind | Group A | 99.33 | 0.758 |
| | Group B | 99.17 | 0.679 |
| Intra-op | Group A | 99.29 | 0.795 |
| | Group B | 99.26 | 0.715 |
| Post-op (0) | Group A | 98.78 | 1.325 |
| | Group B | 98.9 | 0.968 |
| Post-op (6) | Group A | 99.03 | 1.27 |
| | Group B | 98.9 | 1.087 |
| Post-op (12) | Group A | 99.02 | 1.147 |
| | Group B | 99.12 | 0.88 |
| Post-op (24) | Group A | 98.76 | 1.418 |
| | Group B | 99.05 | 0.847 |
| Post-op (48) | Group A | 99 | 1.009 |
| | Group B | 99.21 | 0.744 |

There was no difference in mean vital statistics in both the groups during pre-operative, pre-induction, intra-operative and post-operative period.

**Figure 6: Trend of pulse rate (before and after surgery)**

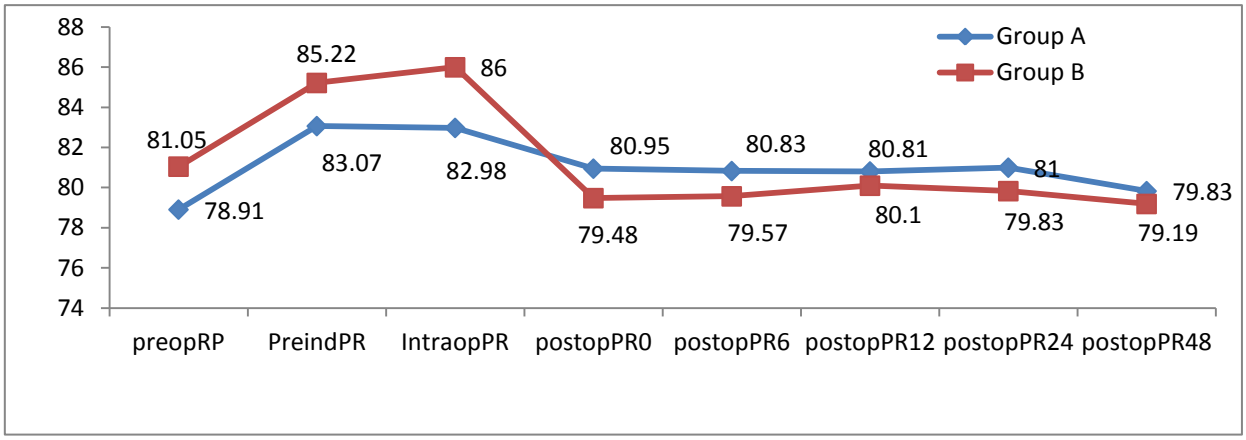
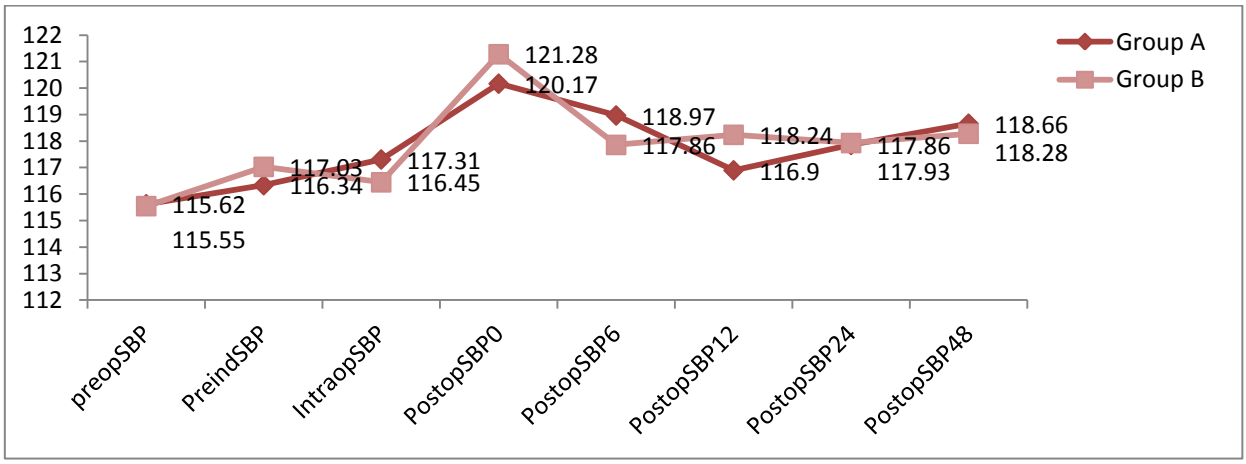



**Figure 7: Blood pressure trend (before and after surgery)**



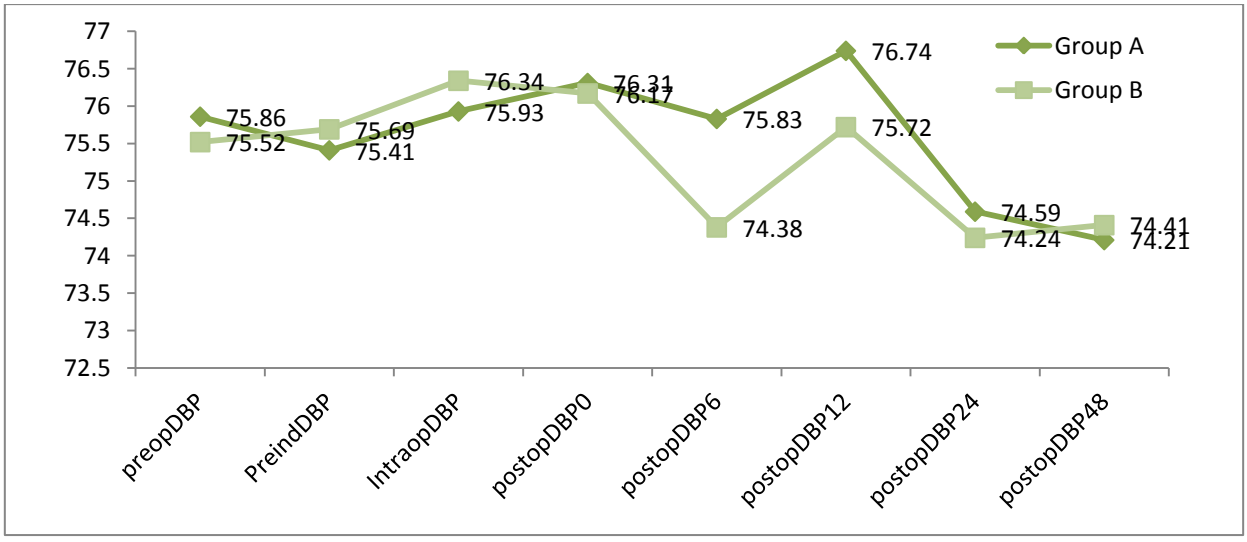
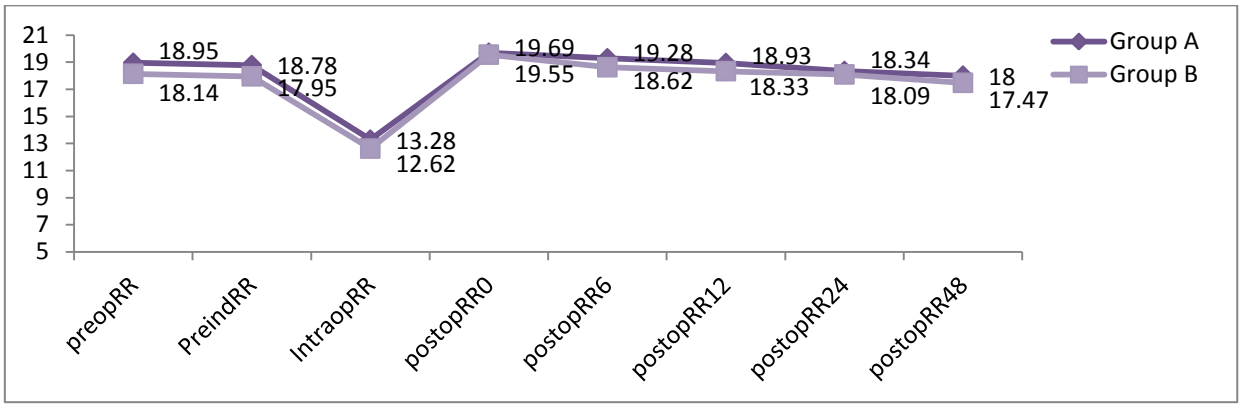



**Figure 8: Pre, intra and post-op RR trend**




Intra-operative dip in RR was due to elective ventilation where RR was set around 12-14/min.

**Figure 9: Pre, intra and post-op temp. trend**

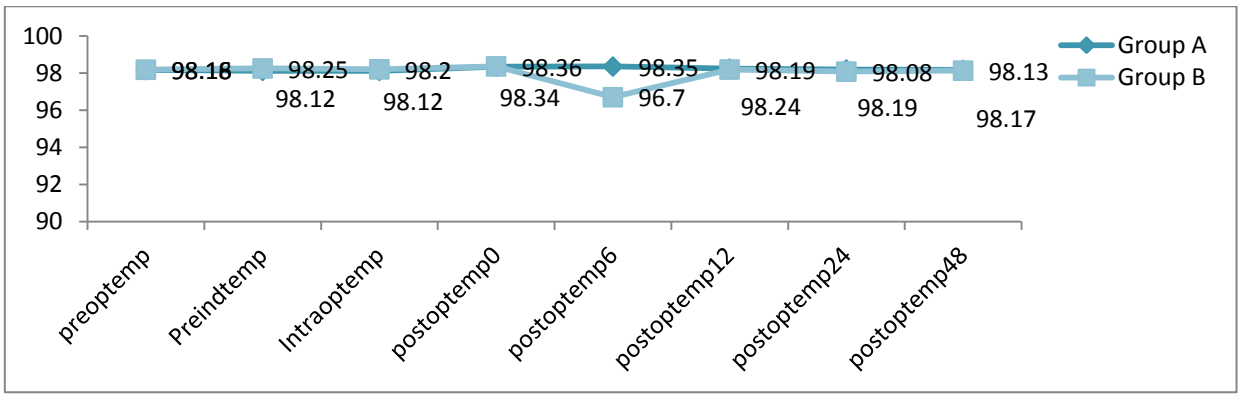



**Figure 10: Pre, intra and post-op $SPO_2$ trend**

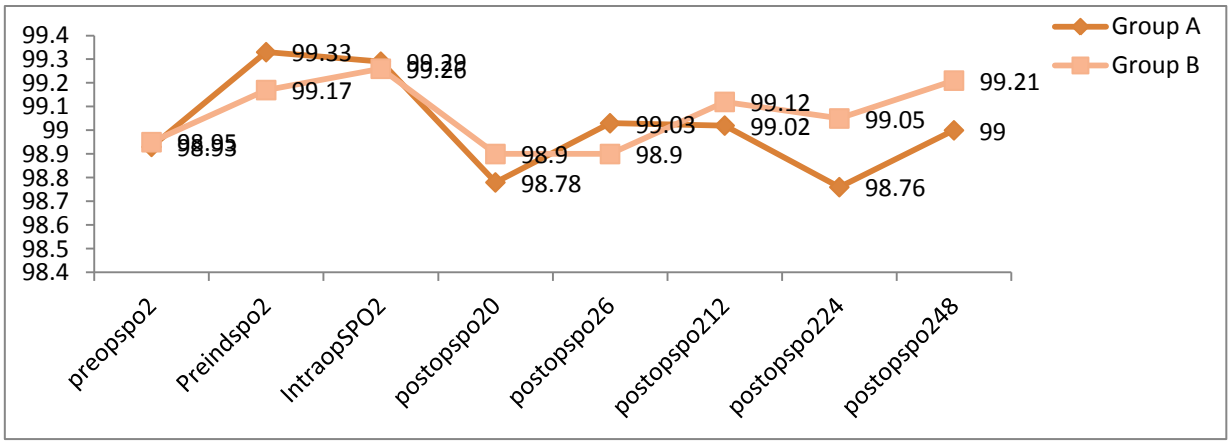
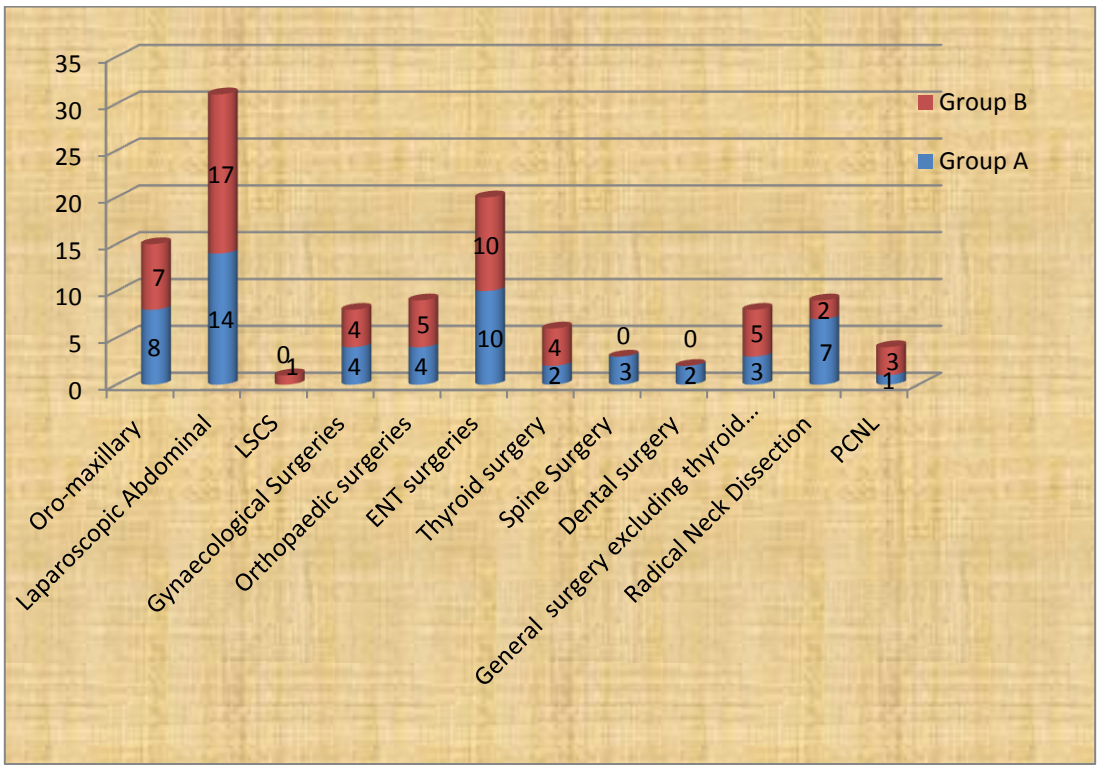


**Table 11: Distribution of various surgeries in study groups**

| Type of surgery | Group A | Group B | Chi square test | P value |
|---|---|---|---|---|
| Oro-maxillary | 08/58 (14%) | 07/58 (12%) | 0.07 | 0.7 |
| Laparoscopic Abdominal | 14/58 (25%) | 17/58 (29%) | 0.39 | 0.5 |
| LSCS | nil | 01/58 (2%) | | |
| Gynaecological Surgeries | 04/58 (7%) | 04/58 (7%) | | |
| Orthopaedic surgeries | 04/58 (7%) | 05/58 (9%) | 0.12 | 0.7 |
| ENT surgeries | 10/58 (17%) | 10/58 (17%) | | |
| Thyroid surgery | 02/58 (3%) | 04/58 (7%) | 0.7 | 0.4 |
| Spine Surgery | 03/58 (5%) | nil | | |
| Dental surgery | 02/58 (3%) | nil | | |
| General surgery excluding thyroid and laparoscopic procedures | 03/58 (5%) | 05/58 (9%) | 0.54 | 0.4 |
| Radical Neck Dissection | 07/58 (12%) | 02/58 (3%) | 3.01 | 0.08 |
| PCNL | 01/58 (2%) | 03/58 (5%) | 1.04 | 0.3 |
| Total | 58/58 | 58/58 | | |

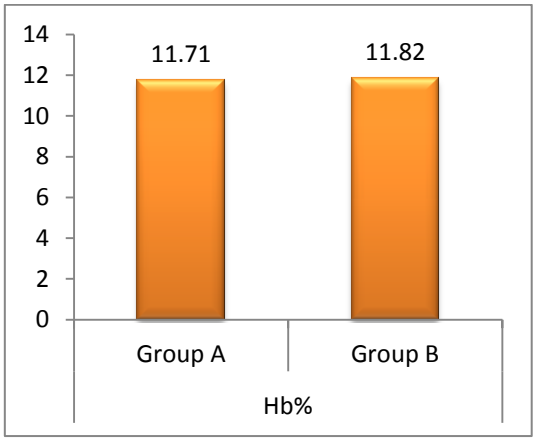
In both the groups, laparoscopic surgeries were higher in number and ENT surgeries were equal in each group.

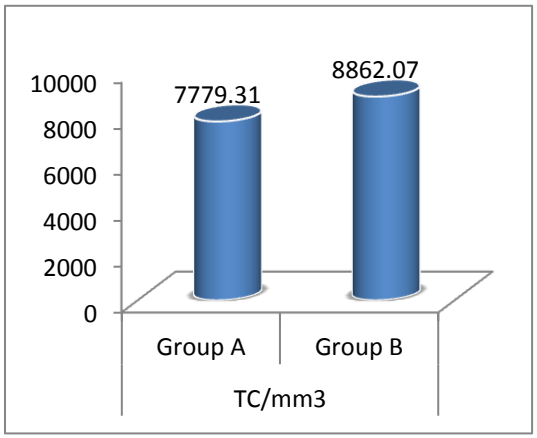
**Figure 11: Types of surgeries performed among the study groups**

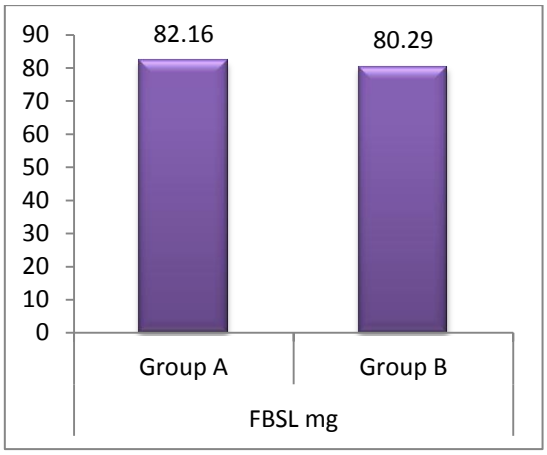


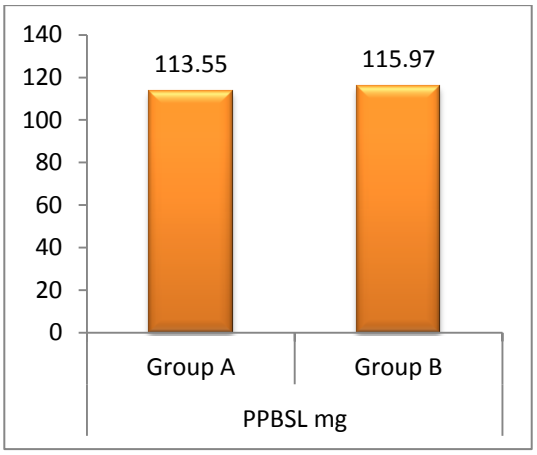

Abdominal laparoscopic surgeries were the most common type of surgery (25% and 29%) in our study. In both groups, ENT surgeries were equal in number (10, 17%). Oro-maxillary and radical neck dissection surgeries were more in group A as compared to group B. Least common surgeries were LSCS (nil) in group A and spine and dental surgeries (nil) in group B.

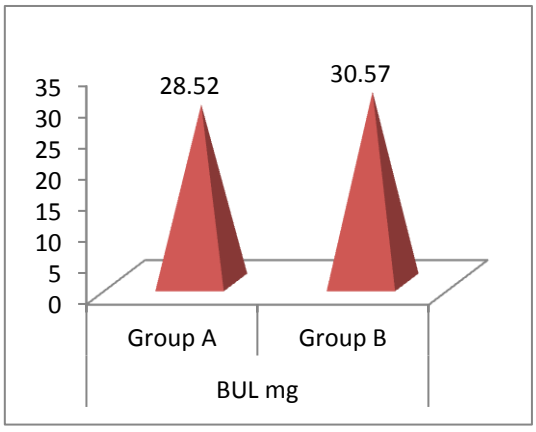
**Figure 12: comparison of investigations among study groups**

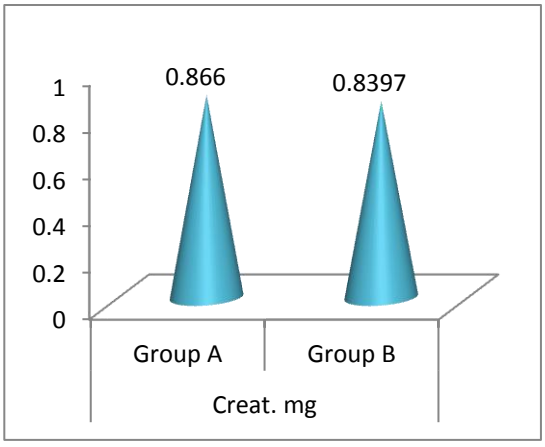



Mean HB%, TLC values, Blood sugar values and renal parameters did not show any significant difference among the groups.

**Table12: EFFICACY PARAMETERS**

| **Efficacy parameters** | **Group A (n=58)** | **Group B (n=58)** | **P value** |
|---|---|---|---|
| **1.Complete response** | 50 | 38 | 0.009* |
| **2.Use of rescue medication** | 8 | 20 | 0.009* |
| **3.Gratification score** | | | |
| DG | 2 | 9 | |
| NGNDG | 8 | 22 | |
| GR | 43 | 26 | 0.0001* |
| HGR | 5 | 1 | |
| **4. Severity of nausea** | | | |
| Nil | 50 | 38 | 0.03* |
| Mild | 4 | 12 | |
| Moderate | 4 | 08 | |

Efficacy of palonosetron was assessed by CR, number of time rescue medication used, overall gratification and nausea severity score by VRS showed statistically significance.

**Figure13: Nausea severity assessed by VRS**

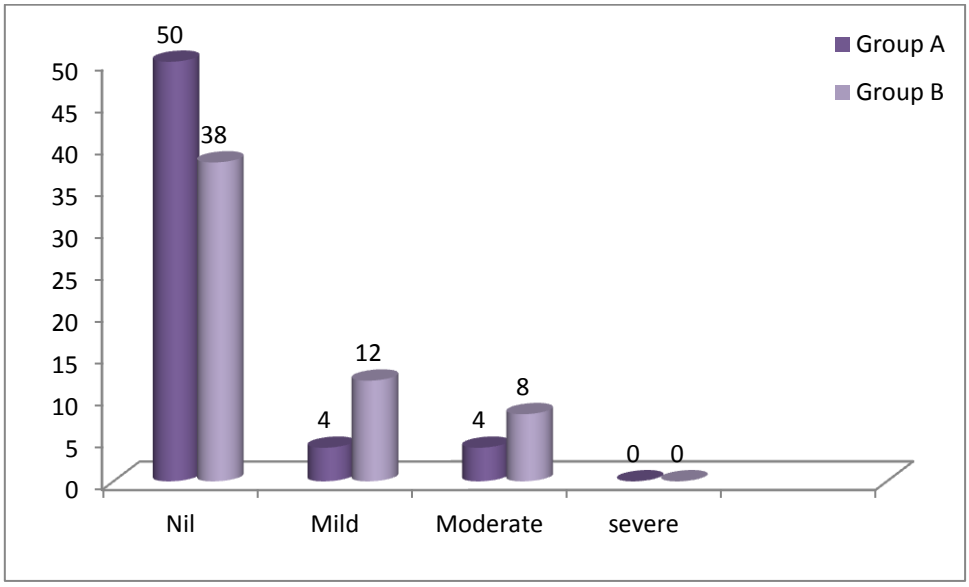



**Figure14: Gratification score assessed by 5 point Likert scale**

GS2: disgratified, GS3:neither gratified not dis-gratified, GS4:gratified and GS5:highly gratified.

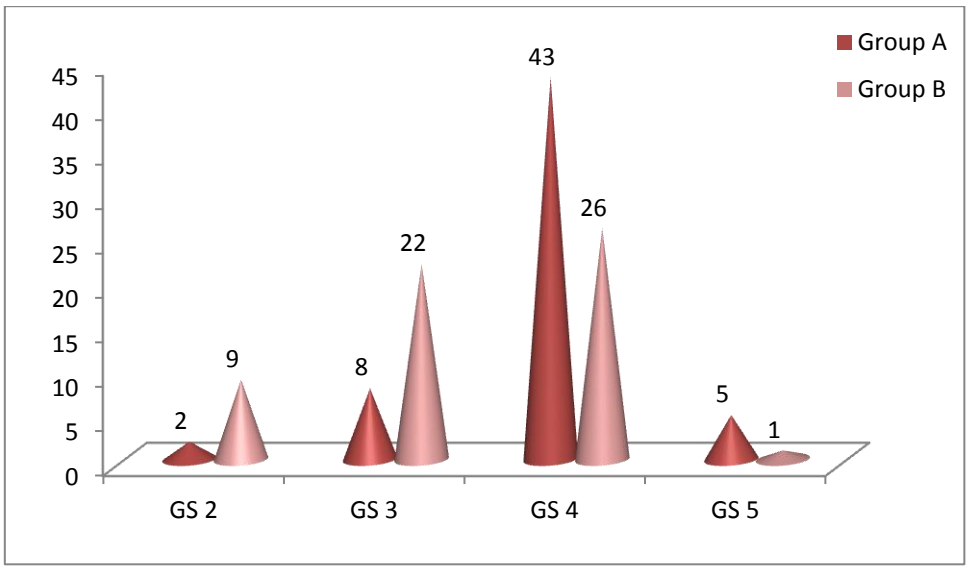


**Figure 15: Use of rescue medications in group A and B**

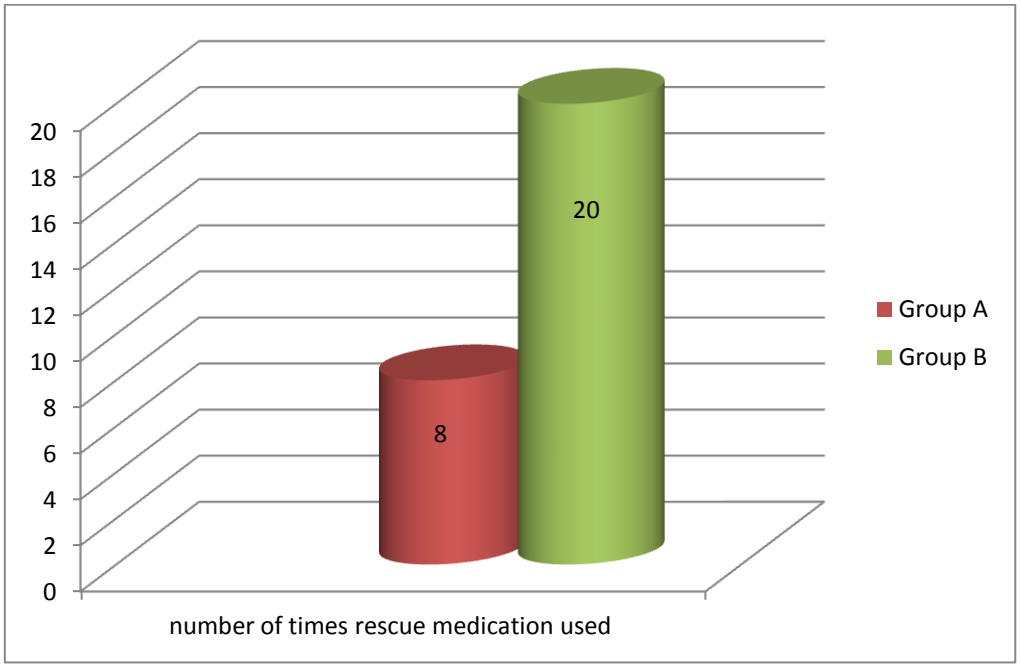
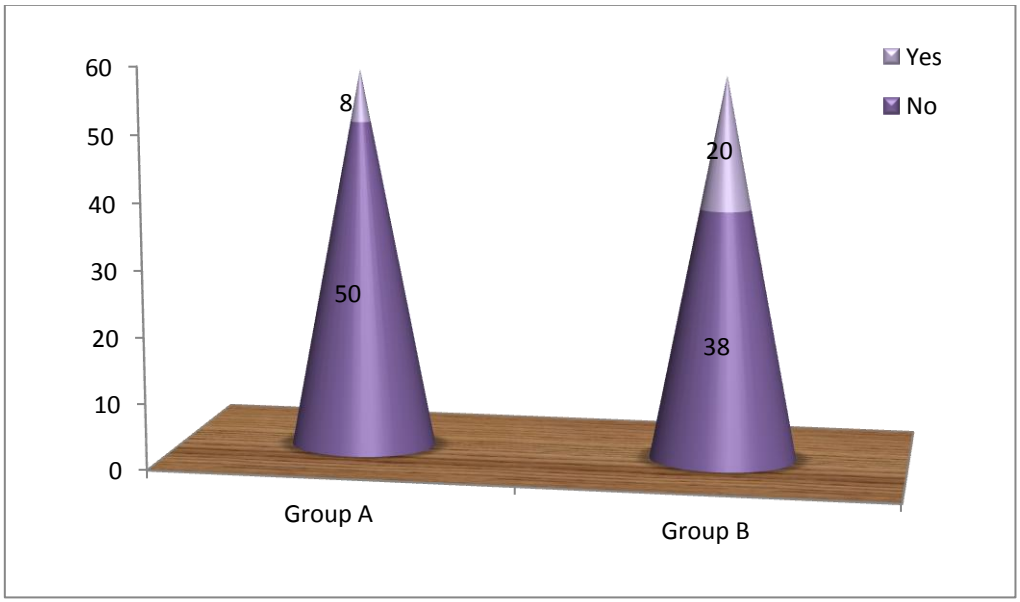



**Figure 16: Episodes PONV within first 48 hrs of surgery**

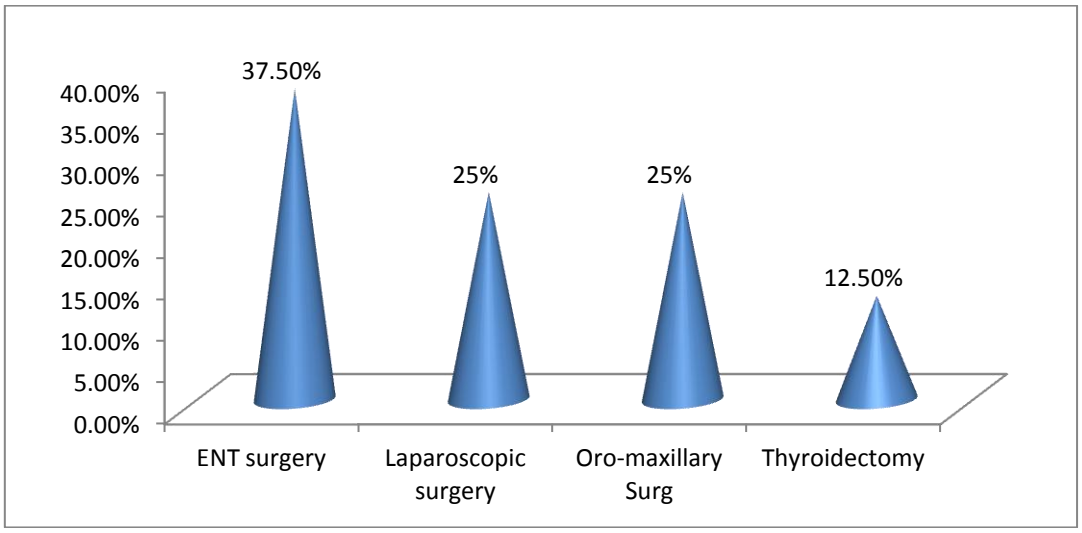



In group A, 8 had PONV while in group B, 20 had PONV.

**Table 13: Incidence of PONV (%) in various surgeries in Palonosetron group**

| Type of surgery | Percentage |
|---|---|
| ENT surgery | 37.50% |
| Laparoscopic surgery | 25% |
| Oro-maxillary Surgery | 25% |
| Thyroidectomy | 12.50% |

**Figure 17: Incidence of PONV in different types of surgeries in palonosetron group**



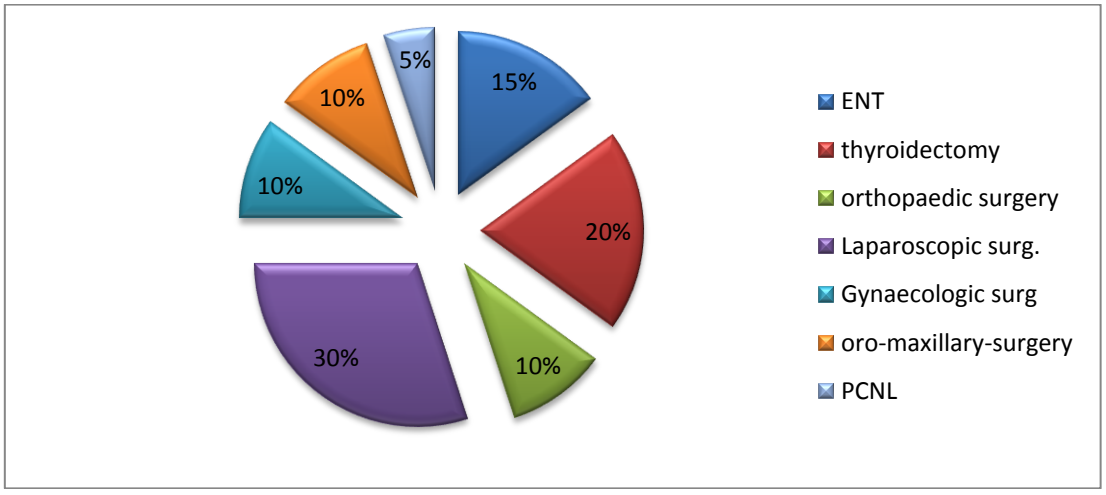

Maximum episodes of PONV has been observed in ENT surgeries in group A. Laparoscopic and Oro-maxillary surgeries were having equal number of PONV episodes.

Minimal incidence of PONV was seen in thyroid surgeries.

**Table 14: Incidence of PONV (%) in various surgeries in ondansetron group**

| Type of surgery | Percentage |
|---|---|
| ENT | 15% |
| Thyroidectomy | 20% |
| Orthopaedic surgery | 10% |
| Laparoscopic surgery | 30% |
| Gynaecologic surgery | 10% |
| Oro-maxillary-surgery | 10% |
| PCNL | 5% |

**Figure 18: PONV percentage in various surgeries in ondansetron group**

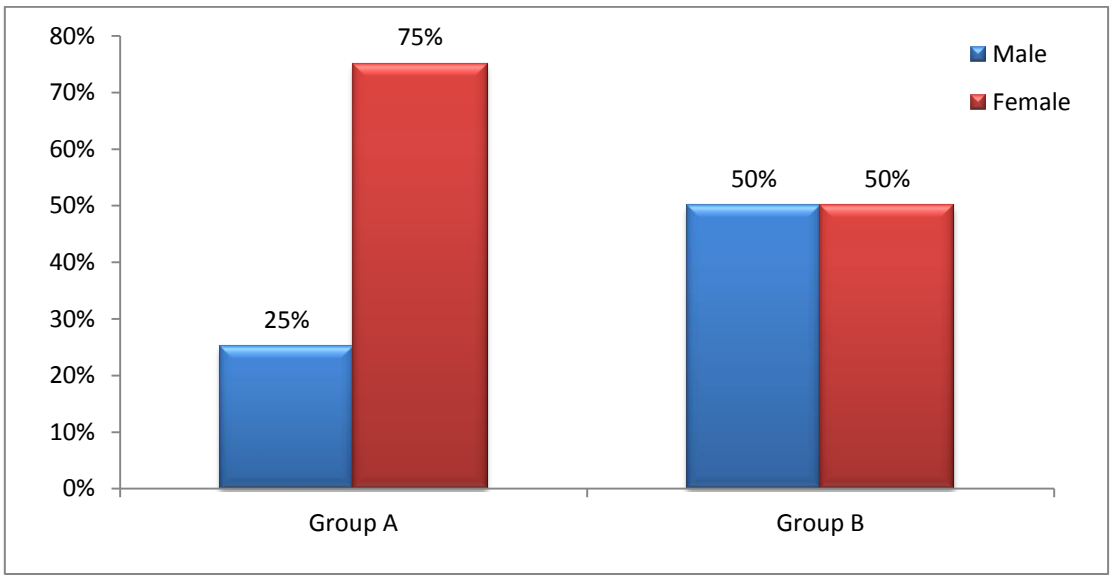



Maximum incidence of PONV in group B was seen in laparoscopic surgeries followed by thyroid surgeries. Incidence of PONV in ENT surgeries in group B was 15%. Least incidence was seen in percutaneous nephrolithotomy (PCNL).

**Table 15: Distribution of gender in PONV patients:**

| Gender | Group A (%) | Group B (%) |
|---|---|---|
| Male | 25 % | 50 % |
| Female | 75 % | 50 % |

**Figure 19: PONV incidence among males and females in study groups**



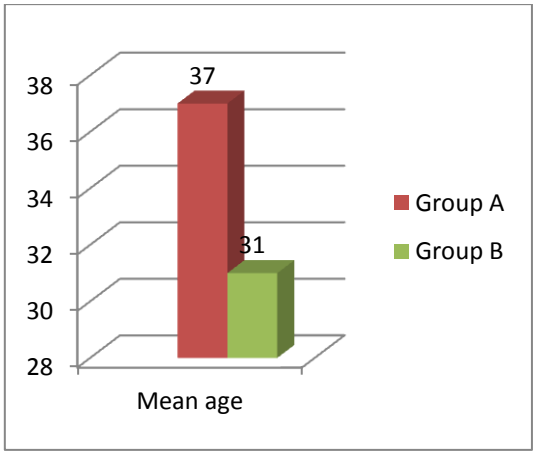

In group A, incidence of PONV was higher in females as compared to males (3:1) but was equal (1:1) in group B.

**Table16: Incidence of PONV in acute phase and late phase**

| Group | PONV 0-6 hrs | PONV 6-12 hrs | PONV 12-24 hrs | PONV 24-48 hrs | Total |
|---|---|---|---|---|---|
| Group A | 0 | 0 | 2/8 (25%) | 6/8(75%) | 8/8 |
| Group B | 0 | 12 (60%) | 7 (35%) | 1 (5%) | 20/20 |

In early phase (0-24hrs) PONV incidence in group A was less (25%) as compared to group B(95%) but in late phase PONV incidence was high.

**Figure 20: Mean age and BMI in PONV patients in study groups**



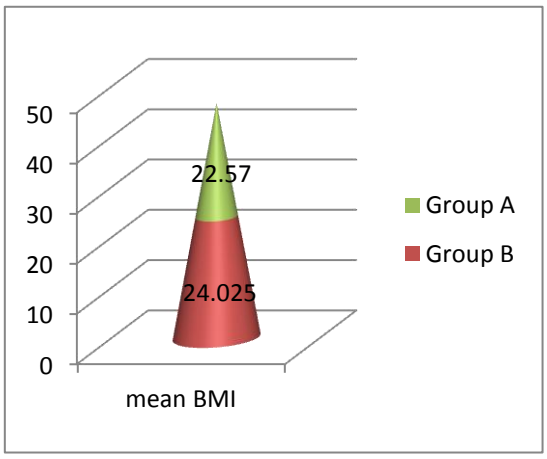
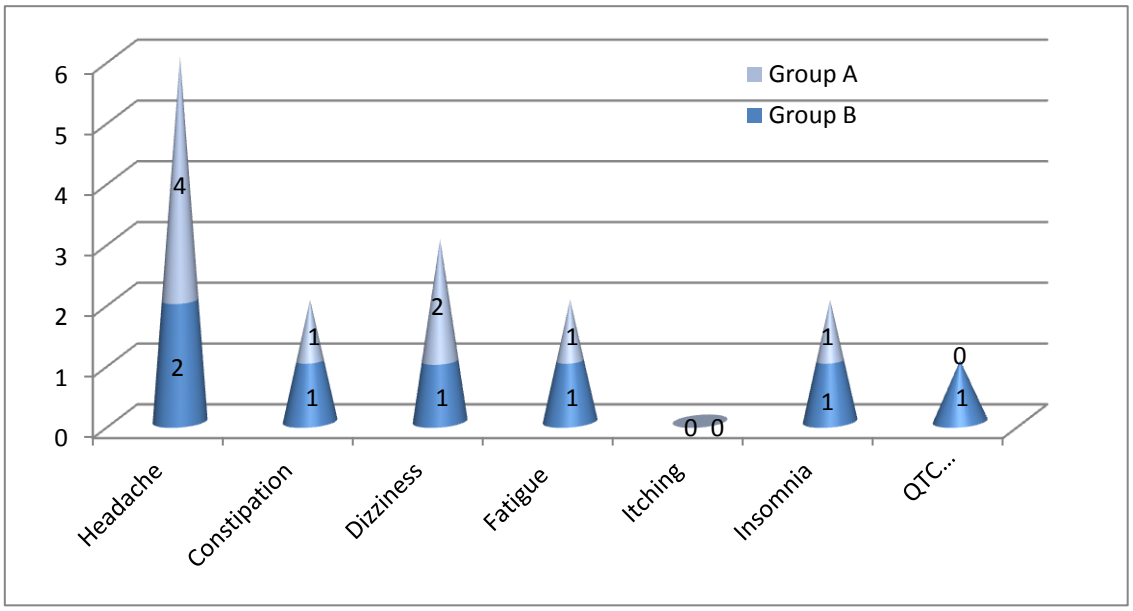



**Table 17: Safety parameters**

| Adverse effects | Group A | Group B |
|---|---|---|
| Headache | 2 | 4 |
| Constipation | 1 | 1 |
| Dizziness | 1 | 2 |
| Fatigue | 1 | 1 |
| Itching | 0 | 0 |
| Insomnia | 1 | 1 |
| $QT_C$ prolongation | 0 | 1 |
| | | |

**Figure 21: Adverse effects among the study groups:**




Both the groups did not show any serious adverse event. Most common side effect was headache in both groups and least common side effect was rash or itching. QTc prolongation was seen in ondansetron group in single patient while none in palonosetron receivers.

# 6. DISCUSSION:

## DISCUSSION

This study was undertaken to assess safety and efficacy of palonosetron versus ondansetron. Two groups with equal number of participants were chosen and total 116 participants were recruited in the study.

Mean age among group A and group B were 33.93and 34.86years respectively and does not show any statistical significance. In younger age group (18-28) maximum numbers of subjects were observed and in elder age group (48-58) minimum numbers of subjects were observed. Among 116 participants recruited, 56.9 % were male and 43.1 % were female. Sex distributions among both the groups were same with no statistical difference.

Mean body weight, height and BMI in group A were 54.93 kg, 152.95 cm and 23.54 $kg/m^2$ respectively. In another group B, mean weight, height and BMI were 54.83 kg, 153.02 cm and 23.25 $kg/m^2$. There were no statistically significant differences among the groups in relation to demographic parameters.

Vital parameters like pulse, systolic and diastolic BP, RR, temperature and $SPO_2$ were assessed pre-operatively, before induction, during surgery and post-operatively after 6,12,24 and 48 hours. It was observed that there were no significant differences in mean vital parameters.

Mean pulse rate was slightly high during pre-operative and induction period which may be due to initial anxiety of the patient just before undergoing surgery. Rise in mean systolic BP during intra-operative session was due to

increased sympathetic activity and during post-operative period was due to pain. Small dip in mean RR was because of artificial ventilation provided during general anaesthesia at the rate of 12-14 breaths/min.

The most commonly performed surgeries in both the groups were laparoscopic abdominal surgery followed by ENT and Oro-maxillary surgeries. In ENT category, common surgeries were septo-plasty and tonsillectomy while in Oro-maxillary category common surgeries were ORIF (open reduction and internal fixation) mandible and radical neck dissection. There was no statistical significance between group A and group B in relation to types of surgery.

Efficacy parameters were assessed by complete response, number of rescue anti-emetics used, nausea severity and overall satisfaction score.

Complete response was evaluated as no nausea, vomiting and no need of rescue anti-emetics. Out of 116 patients, 88 were complete responders among which 50 (86%) were from palonosetron group and 38(65%) were from ondansetron group. The difference of numerical value of 12 among the groups was highly significant. Similar results were seen in a study published by Musso[99] and colleagues which was prospective study conducted on different types of cancer patients. It showed 80% CR for CINV in palonosetron group and 60% in ondansetron group. Mattiuzzi et al[89] also demonstrated higher CR in palonosetron arm versus ondansetron arm. The study conducted by Chattopadhyay[94] and associates where PONV was assessed in post caesarean delivery. In the same study, CR was observed in 85% of subjects using

palonosetron and 83% of subjects using ramosetron. In another study for prevention of CINV, Schwartzberg and colleagues[100] stated overall CR 51% in palonosetron group and 40% in ondansetron, dolasetron or granisetron group. Our study demonstrated higher CR rates compared to previous study. This may be due to recruitment of subjects with less number of high risk population in our study.

In our study, number of times rescue medications used in palonosetron group and ondansetron group were 8 and 20 respectively. In ondansetron group, more number of patients required rescue anti-emetics as compared to palonosetron group and the difference was statistically significant. Sharma and colleagues[85] study also showed higher (20%) use of rescue medication in ondansetron group as compared to palonosetron group (4%). Kim and associates[87] found less use of rescue anti-emetics in palonosetron group than ondansetron or ramosetron group.

Out of 116 patients, only 28 had nausea among which 8 belonged to palonosetron group and 20 belonged to ondansetron group. Of 8 patients from palonosetron receivers, 4 had mild nausea and remainder had moderate nausea while in ondansetron group, 12 had mild nausea and rest had moderate nausea. None had severe nausea in both the groups. Severity of nausea among the group was statistically significant. Similar results were observed by Bajwa[80] et al study where 6.66% had nausea and 3.33% had vomiting in palonosetron group while 20% observed nausea and 13.33% observed vomiting in ondansetron group and the difference was statistically significant.

Schwartzberg[100] and associates demonstrated no significant difference between palonosetron and other $5HT_3$ antagonists during early post-chemotherapy period but significant difference was observed in delayed chemotherapy period.

PONV episodes during first 48 hrs were 8 (13.76%) in palonosetron group and 20 (34.4%) in ondansetron group which was highly significant. Consistent results were also observed in previous study conducted by Kim[93] and associates where PONV incidence in palonosetron group was 22.2% and 77% in ondansetron group. Lower values observed in our study were due to patient related and surgery related factors. Higher incidence was because of recruitment of more high risk predictors of PONV in other study.

Overall satisfaction score was assessed by 5 point Likert score. In palonosetron group, gratified participants were 43, highly gratified were 5, 8 were of neutral opinion and 2 were disgratified. In ondansetron group, 26 were gratified, 22 were neutral, one was highly gratified and 9 were disgratified. Overall gratification score (82% vs 46%) with anti-emetic drugs showed significant difference between the groups. An analogous results were observed by Mansour[86] study. In a three different groups receiving palonosetron or saline or metoclopramide along with dexamethasone had total satisfaction score 88%, 48% and 62% respectively.

In our study, patients from palonosetron group had higher CR, lesser nausea, lesser vomiting and higher satisfaction score as compared to ondansetron

group. Even though both drugs belong to same structural group, palonosetron was much superior in controlling PONV. Few studies conducted[73, 78, 82, 85, 88, 89,

[98] among two groups have showed domination of palonosetron as anti-emetic agent. Palonosetron has ranked one[93] in anti-emetic property than other $5HT_3$ antagonists like ramosetron and granisetron. Even with combination chemotherapy[85] palonosetron appears to be effective in controlling PONV.

In spite higher number of females in our study group, PONV incidence was (14%) as compared to ondansetron group (34.48%). Palonosetron proved its utility not only in normal patients but also in high risk individuals[73,75,79,81] in controlling episodes of PONV. Superior efficacy of palonosetron could be due to its higher receptor affinity[74,75] due to allosteric site[74] and longer half life[12,73]. Palonosetron was not only effective in reducing overall incidence of PONV but in controlling PONV episodes during early post-operative period (0-24hrs). This cardinal finding has more value when previous study[101] has been demonstrated efficacy of other $5HT_3$ antagonist to palonosetron in decreasing early episodes of PONV. From above mentioned findings we can conclude that palonosetron is also equally competent to other 5 $HT_3$ antagonist in controlling early phase PONV.

Pre-operative, intra-operative and post-operative vital parameters were compared in both the groups showed not much significance among the groups. Fewer exceptions were pre-induction temperature, intra-operative RR and post-operative temperature where p value was statistically significant. As temperature and RR can be affected by various external factors like infection, underlying pathology, effect of anaesthetic agents, this statistical difference among two groups do not carries any significance.

Various clinical trials had been supporting about safety[96, 102] of palonosetron. In our study palonosetron was well tolerated and was equally safe as ondansetron because both group had mild and lesser side effects. Side effects in both the groups were similar to previous studies. The common side effects observed were headache, constipation, fatigue and insomnia. Most common side effect in both group was headache. Mattiuzzi et al[89] demonstrated most frequent adverse effect as headache and constipation. A study carried out by Sadaba et al[83] also stated headache, constipation and diarrhoea as frequent adverse events. No one from either group developed rash or itching or diarrhoea. A single participant had QT prolongation in ondansetron group but no one had it from palonosetron group. Very few studies[96] have demonstrated cardiac safety of palonosetron with increasing dose. In our study, no effect was observed on electrocardiogram measured by QT prolongation. Mean QTc for palonosetron group before and after surgery was 0.391 and 0.396 ms while mean QTc for ondansetron group before and after surgery was 0.393 and 0.396 ms respectively. Very few studies[97, 103] have showed risk of QT prolongation and development of ventricular tachycardia while using ondansetron. As in ondansetron group, only one patient had QT prolongation and not much difference in mean QTc among both the groups, cardiac repolarisation measured by QTc interval cannot be generalised to all ondansetron population. Superiority of palonosetron in relation to cardiac safety cannot be concluded

with above inadequate data. To prove cardiac safety of palonosetron over ondansetron more number of subjects will be required. Hence we can draw inference that palonosetron is not superior to ondansetron in terms of safety but

equally safe as far as side effects are concerned. There is definite scope to explore cardiac safety profile of palonosetron over ondansetron in large sample size population to affirm higher safety of palonosetron.

In our study, there was no loss of follow-up as patients were monitored from 0-48 hrs after surgery with regular intervals. Also no deaths were observed in either group.

Our study has few limitations…

First, non-inclusion of placebo group to evaluate baseline incidence but withholding antiemetic therapy in post-operative patients would be like denying treatment to them.

Second, propofol containing regimen used for induction of anaesthesia may interfere with incidence of PONV.

Third, Patient satisfaction score cannot be considered as end point because subjective feeling may show wide variation in groups.

# 7. SUMMARY

## SUMMARY

The present double blinded, randomized controlled study was carried out to evaluate efficacy and safety of palonosetron against ondansetron in post-operative patients undergoing General Anaesthesia.

A total 116 patients were recruited in the study after fulfilling inclusion and exclusion criteria. After block randomization subjects were allocated in two different groups. Group A was given IV palonosetron 75 µg and group B was given IV ondansetron 8 mg before induction of anaesthesia. All patients were followed up intra-operatively and post-operatively.

The study revealed the following findings:

The mean age among group A and group B patients were 33.93± 10.32 and 34.86 ± 11.43 years respectively.

The numbers of subjects in age groups 18-28 years were more in both groups (20 and 23 respectively)

Among 116 participants 66 were male and 50 were female.

The mean weight, height and BMI in group A and group B were 54.93±9.84 kg, 152.95±6.81 cm 23.54± 2.56 kg/$m^2$ and 54.83±8.72 kg, 153.02±6.38 cm, 23.25± 2.45 kg/$m^2$respectively.

Vital parameters recorded before induction, during and after surgery showed no statistical significance with few exceptions.

Efficacy parameters were evaluated by CR, nausea severity, use of rescue medication and overall satisfaction score. For all efficacy parameters statistical values were highly significant.

Safety parameters were assessed by comparing episodes of adverse drug events and cardiac safety was evaluated by measuring QTc interval from post-operative ECGs. There was no significant difference in adverse events among the groups. Although QTc prolongation in one subject was seen in ondansetron group was not considered significant due to small sample size.

From statistical data analysis, the present study inferred that second generation palonosetron is more effective and equally safe to ondansetron in preventing PONV in post-surgical patients undergoing general anaesthesia.

As our study could not able to prove better safety of palonosetron due to less number of adverse effects, further research is suggested to assess safety of palonosetron with larger sample size population.

# 8. CONCLUSION

# CONCLUSION

Thus from the current study we conclude that…

1. Palonosetron was more efficacious than ondansetron in controlling PONV in a post-surgical patients undergoing general anaesthesia.

2. In addition, palonosetron was also effective in reducing PONV in first 24 hours of post-operative period. Overall satisfaction was high in palonosetron receivers than patients whom ondansetron was given.

3. Palonosetron was found equally safe as Ondansetron.

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# 10. ANNEXURES

## List of abbreviations

(Annexure I)

1. PONV: Post operative nausea vomiting
2. CINV: chemotherapy induced nausea vomiting
3. ECG: Electrocardiogram
4. CR complete response
5. CC: complete control
6. MD-CT : Multi day based chemotherapy
7. I.V: Intravenous
8. CI: Confidence interval
9. PCA: Patient controlled analgesia
10. Sc : Subcutaneous
11. Ms : Millisecond
12. PR: Pulse rate
13. RR: Respiratory rate
14. BP: Blood pressure
15. $SPO_2$ : Oxygen saturation
16. Pre-op: Pre-operative
17. Pre-ind: Pre-induction
18. Intra-op: Intra-operative
19. Post-op : Post- operative
20. AUC: Area under curve
21. ASA : American Society of Anaesthesiologists

22. AML : Acute Myeloid Leukaemia
23. OPD : Out Patient Department
24. QTc : Corrected QT interval
25. TLC : Total leukocyte count
26. BUL : Blood urea level
27. F BSL : Fasting Blood sugar level
28. PP BSL: Post prandial Blood sugar level
29. cms : centimetres
30. SD : Standard deviation
31. GS : Gratification score
32. ORIF : Open reduction and internal fixation

**Informed consent document**

**Subject Information sheet**

(Annexure II A)

You are invited to participate in this study titled "to study efficacy and safety of intravenous palonosetron against ondansetron in post surgical patients undergoing general anaesthesia."

**Study Purpose:**

The purpose of this study is to find out whether there is difference in safety and efficacy of Intravenous palonosetron versus intravenous ondansetron in patients undergoing surgery under general anaesthesia.

**Study Details:**

- Along with you total 100 patients will be included in this study.
- You will be enrolled only after giving your voluntary consent.
- This study involves administration of either injection palonosetron or ondansetron before anaesthesia as well as collection of 5 ml of blood from vein by expert for routine baseline investigations like complete blood count, Fasting and post prandial BSL, Blood urea, serum creatinine, X-ray Chest and ECG.

- After 4 hrs of surgery ECG will be taken once again. You will be asked questions from the formatted questionnaire and you will be requested to answer this in the format mentioned in proforma.

**Benefit of participating in the study**: By participation in this study you will be prevented from most troublesome symptom like Post operative nausea vomiting (PONV).

**Risks involved in participation of this study:** As these antiemetic agents have adverse effect on heart, administration of this drug may lead to fast and irregular rhythm of heart. If any unwanted side effects occur, it will be treated free of cost and your health will be safe guarded.

**Rights:** participation in this study is purely voluntary. If you do not want to participate you can withdraw from study at any time.

**Confidentiality**: your participation will be kept confidential. The investigators and other authorized personnel will only have access to the data. The information will be used for publication and further research without revealing your identity.

**Subject consent form**

(Annexure II B)

I, the undersigned confirmed that..

- ✓ I have read and understood the information about the study titled "to study efficacy and safety of intravenous palonosetron against ondansetron in post surgical patients undergoing general anaesthesia" as provided in information sheet.
- ✓ I have been given opportunity to ask questions about the project and my participation.
- ✓ I understand that I can withdraw myself from study at any time without giving any reason.
- ✓ Procedures regarding confidentiality have been very well explained to me.
- ✓ The use of data for publication, research sharing and archiving has been explained to me.
- ✓ I voluntarily agree to participate in the study research.
- ✓ I along with the researcher agree to sign and date this informed consent form.

Signature Signature

Name of the participant: Name of the Researcher:

Date: Date:

**Investigator's Declaration**

(Annexure II C)

I have accurately read the information sheet for the study titled "to study efficacy and safety of intravenous palonosetron against ondansetron in post surgical patients undergoing general anaesthesia" to the potential participant and to the best of my knowledge participant understands that following will be done.

1. Injection of palonosetron or ondansetron will be given prior to anaesthesia.
2. About 5 ml blood will be aspirated for routine investigations mentioned in information sheet.
3. Chest X ray will be taken before surgery.
4. ECG will be taken before surgery and after 4 hrs of surgery.
5. In case of unexpected events, reactions treatment will be given free of cost.

I confirm that participant was given as opportunity to ask questions related to study and all questions asked have been answered correctly to the best of my knowledge. I confirmed that individual has not been pressurised to give consent rather consent is obtained freely and voluntarily. A copy of this ICF has been provided to the participant.

Date: Signature of the researcher taking consent

(Name of the researcher taking consent: )

## Ethical clearance document

(Annexure III)

***INSTITUTIONAL ETHICAL COMMITTEE***

**KARPAGA VINAYAGA INSTITUTE OF MEDICAL SCIENCES & RESEARCH CENTRE**

**MADURANTHAGAM-603 308.**

21.01.2015

**CERTIFICATE FOR APPROVAL**

The Institutional Ethical Committee of Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Maduranthagam reviewed and discussed the application for approval **"TO STUDY EFFICACY AND SAFETY OF INTRAVENOUS PALONOSETRON AGAINST ONDANSETRON IN POST SURGICAL PATIENTS UNDERGOING GENERAL ANAESTHESIA"** by **Dr. SUNIL VISHWASRAO,** Post Graduate Student, Department of Pharmacology, Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Maduranthagam.

The proposal is **APPROVED**

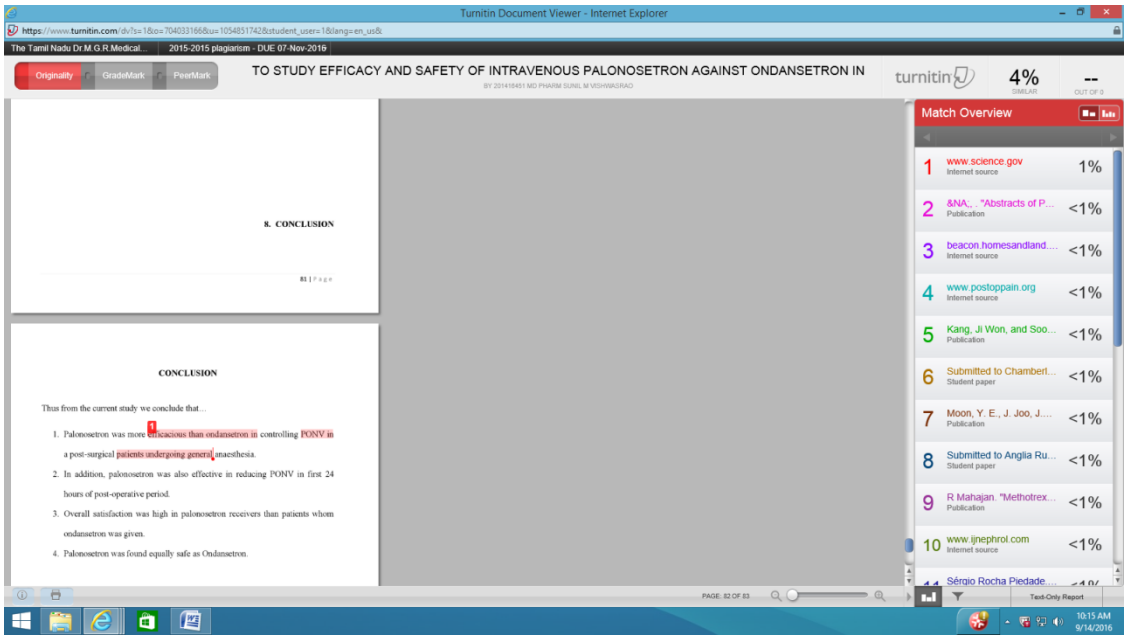
The Institutional Ethics Committee expects to be informed about the progress of the study, and Adverse Drug Reaction occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

KARPAGA VINAYAGA INSTITUTE OF MEDICAL SCIENCES & RESEARCH CENTRE
21 JAN 2015

**CHAIRPERSON**

# Plagiarism certificate

(Annexure IV)



**PROFORMA**

(Annexure V)

**Name:**

**Age:** **Sex:**

**Address:** **Operation performed:**

**H/O Medical illness**: Like DM, HT, Asthma, Heart disease, IHD

**LMP:**

H/o Alcoholism, h/o ongoing steroids, h/o ongoing anti-emetics, h/o nausea vomiting, h/o APD

**Before entering OT:**

P: BP: RR: Temp: $SPO_2$:

**Systemic Examination**:

CVS:

RS:

CNS:

PA:

**Before Induction In OT:**

Vitals: P: BP: RR: Temp:

$SPO_2$: ECG Monitor:

**Intra-operative parameters**:

Vitals: P: BP: RR: Temp:

$SPO_2$: ECG Monitor: Any adverse event if any:

**Post- operative Parameters:**

| Parameters | Pulse | BP | RR | Temp. | $SPO_2$ |
|---|---|---|---|---|---|
| 0 hrs | | | | | |
| 6 hrs | | | | | |
| 12 hrs | | | | | |
| 24 hrs | | | | | |
| 48 hrs | | | | | |

ECG at 4 hrs

**Questionnaire** (To be asked post operatively)

1) Have you vomited? Yes / No

2) Do you have nausea? Yes/No

3) How severe is nausea? (Mild/ Moderate/ Severe by VRS)

4) Do you have rash/itching?

5) Does patient receive rescue anti-emetic? if yes how many times?

6) Patient gratification score with 5 point Likert scale (strongly disgratified, disgratified, neither gratified nor disgratified, gratified, strongly gratified)

7) Does patient has any other adverse event?

8) Time of first episode after how many hours of surgery?

**Investigations :**

**CBC:**

**Chest X-Ray (PA):**

**ECG:**

**Renal Parameters: BUL and Serum Creatinine**

**Diabetic Profile: BSL: (F) (PP)**

**Urine (R)**

## Data

(Annexure VI)

## Group A

| Sr No | IP | Age | Sex | Ht(cms) | Wt(Kg) | BMI | ECG - pre-op | QTc 4 hrs |
|---|---|---|---|---|---|---|---|---|
| 1 | 1408140010 | 23 | M | 160 | 62 | 24.2 | 0.4 | 0.42 |
| 2 | 1408140014 | 35 | F | 158 | 55 | 22 | 0.4 | 0.42 |
| 3 | 809140015 | 40 | F | 149 | 52 | 23.4 | 0.4 | 0.43 |
| 4 | 809140043 | 35 | F | 152 | 56 | 24.2 | 0.42 | 0.44 |
| 5 | 2509140003 | 25 | M | 150 | 56 | 24.9 | 0.4 | 0.41 |
| 6 | 2509140009 | 22 | F | 156 | 50 | 20.5 | 0.4 | 0.4 |
| 7 | 2510140011 | 40 | F | 155 | 55 | 22.9 | 0.4 | 0.42 |
| 8 | 2510140012 | 45 | F | 150 | 44 | 19.6 | 0.4 | 0.41 |
| 9 | 1211140002 | 30 | F | 154 | 42 | 17.7 | 0.38 | 0.38 |
| 10 | 1211140006 | 58 | F | 151 | 49 | 21.5 | 0.4 | 0.41 |
| 11 | 302150045 | 37 | F | 155 | 56 | 23.3 | 0.4 | 0.4 |
| 12 | 902150012 | 46 | F | 147 | 49 | 22.7 | 0.4 | 0.41 |
| 13 | 1102150050 | 20 | F | 140 | 35 | 17.9 | 0.41 | 0.42 |
| 14 | 1602150017 | 35 | F | 152 | 59 | 25.5 | 0.39 | 0.39 |
| 15 | 1802150056 | 24 | M | 148 | 43 | 19.6 | 0.39 | 0.4 |
| 16 | 2802150008 | 20 | F | 152 | 59 | 25.5 | 0.38 | 0.38 |
| 17 | 903150011 | 21 | M | 144 | 44 | 21.2 | 0.39 | 0.39 |
| 18 | 903150014 | 21 | M | 160 | 60 | 23.4 | 0.39 | 0.39 |
| 19 | 903150017 | 29 | F | 145 | 48 | 22.8 | 0.38 | 0.4 |
| 20 | 903150021 | 36 | M | 159 | 69 | 27.3 | 0.38 | 0.4 |
| 21 | 1003150043 | 29 | M | 158 | 67 | 26.8 | 0.38 | 0.39 |
| 22 | 1003150045 | 34 | F | 137 | 71 | 37.8 | 0.4 | 0.4 |
| 23 | 1504150014 | 49 | F | 154 | 60 | 25.3 | 0.4 | 0.41 |
| 24 | 1504150015 | 38 | F | 156 | 60 | 24.7 | 0.38 | 0.39 |
| 25 | 2004150198 | 21 | M | 168 | 72 | 25.5 | 0.38 | 0.39 |
| 26 | 2304150016 | 40 | F | 150 | 59 | 26.2 | 0.39 | 0.4 |
| 27 | 2704150006 | 24 | M | 155 | 49 | 20.4 | 0.39 | 0.4 |
| 28 | 2704150024 | 24 | F | 140 | 39 | 19.9 | 0.39 | 0.41 |
| 29 | 305150010 | 39 | M | 159 | 62 | 24.5 | 0.39 | 0.39 |
| 30 | 505150049 | 52 | F | 139 | 62 | 32.1 | 0.38 | 0.38 |
| 31 | 605150001 | 27 | M | 149 | 49 | 22.1 | 0.4 | 0.4 |
| 32 | 605150054 | 20 | F | 153 | 55 | 23.5 | 0.4 | 0.41 |
| 33 | 2905150046 | 35 | M | 163 | 68 | 25.6 | 0.39 | 0.4 |
| 34 | 106150047 | 38 | F | 145 | 39 | 18.5 | 0.39 | 0.39 |
| 35 | 306150013 | 39 | F | 140 | 39 | 19.9 | 0.38 | 0.39 |
| 36 | 806150099 | 21 | M | 151 | 47 | 20.6 | 0.39 | 0.38 |
| 37 | 1006150005 | 40 | M | 158 | 66 | 26.4 | 0.38 | 0.4 |
| 38 | 1106150054 | 30 | M | 160 | 67 | 26.2 | 0.4 | 0.4 |

| Sr No | IP | Age | Sex | Ht(cms) | Wt(Kg) | BMI | ECG - | QTc |
|---|---|---|---|---|---|---|---|---|
| 39 | 1506150001 | 20 | M | 157 | 56 | 22.7 | 0.4 | 0.4 |
| 40 | 2406150038 | 25 | F | 149 | 42 | 18.9 | 0.4 | 0.38 |
| 41 | 2506150021 | 38 | F | 148 | 54 | 24.7 | 0.39 | 0.4 |
| 42 | 607150040 | 46 | F | 156 | 52 | 21.4 | 0.39 | 0.42 |
| 43 | 907150048 | 45 | F | 150 | 52 | 23.1 | 0.39 | 0.4 |
| 44 | 1507150037 | 40 | F | 148 | 42 | 19.2 | 0.38 | 0.4 |
| 45 | 1507150039 | 23 | M | 159 | 49 | 19.4 | 0.39 | 0.39 |
| 46 | 1507150040 | 32 | M | 156 | 71 | 29.2 | 0.4 | 0.4 |
| 47 | 2807150047 | 21 | M | 159 | 63 | 24.9 | 0.4 | 0.39 |
| 48 | 208150014 | 39 | M | 148 | 44 | 20.1 | 0.38 | 0.38 |
| 49 | 508150027 | 39 | M | 168 | 72 | 25.5 | 0.38 | 0.4 |
| 50 | 508150042 | 33 | F | 158 | 57 | 22.8 | 0.39 | 0.39 |
| 51 | 1808150030 | 25 | M | 162 | 70 | 26.7 | 0.36 | 0.36 |
| 52 | 1509150061 | 45 | F | 153 | 47 | 20.1 | 0.38 | 0.4 |
| 53 | 1410150063 | 23 | M | 156 | 61 | 25.1 | 0.38 | 0.41 |
| 54 | 211150050 | 40 | M | 147 | 48 | 22.2 | 0.39 | 0.39 |
| 55 | 411150030 | 26 | M | 160 | 68 | 26.6 | 0.4 | 0.4 |
| 56 | 1412150012 | 47 | M | 159 | 63 | 24.9 | 0.4 | 0.38 |
| 57 | 1801160029 | 55 | F | 149 | 42 | 27.9 | 0.38 | 0.38 |
| 58 | 2401160009 | 30 | M | 157 | 59 | 23.9 | 0.39 | 0.39 |

| Sr No | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| 1 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 2 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 3 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 4 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 5 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 6 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 7 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 8 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 9 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 10 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 11 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 12 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 13 | 1 | 1 | 2 | 0 | 2 | 2 | 0 | 24 hrs |
| 14 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |

| Sr No | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---|---|---|---|---|---|---|---|---|
| 15 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 16 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 17 | 1 | 1 | 2 | 0 | 1 | 2 | 0 | 24 hrs |
| 18 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 19 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | |
| 20 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 21 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | |
| 22 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | |
| 23 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 24 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 25 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 26 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 27 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 28 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 29 | 1 | 1 | 2 | 0 | 1 | 3 | 0 | 24 hrs |
| 30 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 31 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 32 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 33 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 34 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 35 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | |
| 36 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 37 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 38 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 39 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 40 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | |
| 41 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 42 | 1 | 1 | 2 | 0 | 1 | 3 | 0 | 12 hrs |
| 43 | 1 | 1 | 1 | 0 | 1 | 3 | 0 | 24 hrs |
| 44 | 0 | 1 | 1 | 0 | 1 | 3 | 0 | 24 hrs |
| 45 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 46 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 47 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 48 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 49 | 1 | 1 | 1 | 0 | 1 | 3 | 0 | 12 hrs |
| 50 | 0 | 1 | 1 | 0 | 1 | 3 | 0 | 24 hrs |
| 51 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 52 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 53 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 54 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 55 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 56 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 57 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 58 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |

## Group B

| Sr.No. | IP | Age | Sex | Ht (cms) | Wt.(Kg) | BMI | ECG - | QTc |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Pre-op | 4 hrs |
| 1 | 309140012 | 24 | M | 150 | 54 | 24 | 0.39 | 0.39 |
| 2 | 809140012 | 40 | F | 139 | 44 | 22.8 | 0.4 | 0.4 |
| 3 | 909140001 | 42 | F | 152 | 58 | 25.1 | 0.4 | 0.4 |
| 4 | 1909140002 | 32 | M | 140 | 44 | 22.4 | 0.39 | 0.39 |
| 5 | 2509140007 | 48 | F | 148 | 65 | 29.7 | 0.38 | 0.4 |
| 6 | 1410140019 | 22 | M | 140 | 63 | 32.1 | 0.38 | 0.4 |
| 7 | 2310140010 | 40 | F | 152 | 50 | 21.6 | 0.39 | 0.4 |
| 8 | 2310140012 | 47 | F | 152 | 60 | 26 | 0.4 | 0.39 |
| 9 | 1012140004 | 43 | M | 155 | 52 | 21.6 | 0.4 | 0.4 |
| 10 | 1012140008 | 30 | M | 155 | 55 | 22.9 | 0.4 | 0.39 |
| 11 | 1102150005 | 26 | M | 156 | 64 | 26.3 | 0.38 | 0.4 |
| 12 | 1102150045 | 20 | M | 152 | 64 | 27.7 | 0.39 | 0.4 |
| 13 | 1602150002 | 46 | M | 156 | 55 | 22.6 | 0.38 | 0.39 |
| 14 | 1802150016 | 45 | M | 140 | 40 | 20.4 | 0.39 | 0.4 |
| 15 | 2502150051 | 58 | F | 150 | 50 | 22.2 | 0.4 | 0.4 |
| 16 | 2802150004 | 48 | M | 155 | 69 | 24.6 | 0.4 | 0.39 |
| 17 | 103150008 | 24 | M | 155 | 52 | 21.6 | 0.4 | 0.4 |
| 18 | 703150012 | 28 | F | 146 | 40 | 18.8 | 0.38 | 0.39 |
| 19 | 903150022 | 28 | M | 156 | 62 | 25.5 | 0.38 | 0.4 |
| 20 | 903150033 | 25 | M | 163 | 61 | 23 | 0.39 | 0.4 |
| 21 | 1703150006 | 34 | M | 152 | 55 | 23.8 | 0.39 | 0.39 |
| 22 | 2503150080 | 30 | M | 152 | 42 | 18.2 | 0.41 | 0.39 |
| 23 | 1504150001 | 34 | M | 160 | 65 | 25.4 | 0.4 | 0.4 |
| 24 | 1504150018 | 55 | F | 147 | 49 | 22.7 | 0.4 | 0.4 |
| 25 | 1504150019 | 21 | M | 153 | 58 | 24.8 | 0.39 | 0.4 |
| 26 | 2304150002 | 26 | M | 146 | 43 | 20.2 | 0.39 | 0.4 |
| 27 | 2604150010 | 50 | F | 152 | 48 | 20.8 | 0.4 | 0.4 |
| 28 | 2704150021 | 36 | M | 156 | 55 | 22.6 | 0.4 | 0.38 |
| 29 | 2804150003 | 24 | M | 155 | 66 | 27.5 | 0.39 | 0.39 |
| 30 | 605150064 | 23 | F | 142 | 41 | 20.3 | 0.4 | 0.4 |
| 31 | 705150003 | 27 | M | 156 | 57 | 23.4 | 0.4 | 0.4 |
| 32 | 705150063 | 47 | M | 155 | 63 | 26.2 | 0.39 | 0.39 |
| 33 | 2305150008 | 24 | M | 150 | 52 | 23.1 | 0.39 | 0.4 |
| 34 | 2905150039 | 25 | M | 160 | 70 | 27.3 | 0.4 | 0.4 |
| 35 | 106150048 | 47 | M | 166 | 67 | 24.3 | 0.4 | 0.4 |
| 36 | 106150049 | 58 | M | 159 | 60 | 23.7 | 0.4 | 0.4 |
| 37 | 806150067 | 30 | F | 147 | 48 | 22.2 | 0.4 | 0.4 |
| 38 | 1006150013 | 43 | F | 149 | 45 | 20.3 | 0.39 | 0.4 |
| 39 | 1006150037 | 21 | M | 159 | 58 | 22.9 | 0.39 | 0.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 40 | 1806150055 | 34 | M | 162 | 60 | 22.9 | 0.39 | 0.39 |
| 41 | 2506150046 | 28 | F | 156 | 50 | 20.5 | 0.39 | 0.4 |
| 42 | 2506150052 | 30 | M | 156 | 48 | 19.7 | 0.4 | 0.4 |
| 43 | 707150044 | 35 | M | 155 | 59 | 24.6 | 0.4 | 0.4 |
| 44 | 1307150001 | 50 | M | 155 | 59 | 24.6 | 0.4 | 0.4 |
| 45 | 2007150030 | 24 | F | 148 | 52 | 23.7 | 0.39 | 0.4 |
| 46 | 2807150039 | 30 | M | 160 | 69 | 27 | 0.39 | 0.39 |
| 47 | 2907150031 | 29 | F | 152 | 44 | 19 | 0.39 | 0.4 |
| 48 | 508150024 | 39 | M | 152 | 48 | 20.8 | 0.39 | 0.4 |
| 49 | 1208150049 | 49 | F | 159 | 54 | 21.4 | 0.4 | 0.39 |
| 50 | 1308150065 | 21 | M | 148 | 49 | 22.4 | 0.4 | 0.4 |
| 51 | 1409150029 | 23 | F | 144 | 49 | 23.6 | 0.4 | 0.4 |
| 52 | 2309150066 | 58 | F | 149 | 42 | 18.9 | 0.39 | 0.39 |
| 53 | 2909150063 | 26 | M | 159 | 60 | 23.7 | 0.39 | 0.4 |
| 54 | 3010150034 | 24 | F | 148 | 42 | 19.2 | 0.39 | 0.4 |
| 55 | 812150015 | 44 | M | 165 | 70 | 25.7 | 0.38 | 0.39 |
| 56 | 912150047 | 56 | M | 158 | 66 | 26.4 | 0.39 | 0.4 |
| 57 | 2301160046 | 20 | M | 166 | 67 | 24.3 | 0.4 | 0.4 |
| 58 | 2801160048 | 31 | F | 155 | 48 | 20 | 0.4 | 0.39 |

| Sr No. | Q 1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| 1 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 2 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 3 | 1 | 1 | 2 | 0 | 2 | 2 | 0 | 6 hrs |
| 4 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 5 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 6 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 7 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 8 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 9 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 10 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 11 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 12 | 1 | 1 | 2 | 0 | 1 | 3 | 0 | 6 hrs |
| 13 | 1 | 1 | 1 | 0 | 1 | 2 | 0 | 6 hrs |
| 14 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 15 | 1 | 1 | 2 | 0 | 1 | 2 | 0 | 12 hrs |
| 16 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 17 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 18 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 19 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 20 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 21 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 22 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 23 | 1 | 1 | 1 | 0 | 1 | 2 | 0 | 6 hrs |
| 24 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 25 | 1 | 1 | 2 | 0 | 2 | 2 | 0 | 12 hrs |
| 26 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 27 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 28 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 29 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 30 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 31 | 1 | 1 | 2 | 0 | 1 | 2 | 0 | 6 hrs |
| 32 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 33 | 1 | 1 | 1 | 0 | 1 | 3 | 0 | 6 hrs |
| 34 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 35 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | |
| 36 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 37 | 1 | 1 | 1 | 0 | 1 | 2 | 0 | 12 hrs |
| 38 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 39 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |

| Sr No. | Q 1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---|---|---|---|---|---|---|---|---|
| 40 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 41 | 1 | 1 | 1 | 0 | 1 | 2 | 0 | 6 hrs |
| 42 | 1 | 1 | 1 | 0 | 1 | 3 | 0 | 12hrs |
| 43 | 1 | 1 | 1 | 0 | 1 | 2 | 0 | 6 hrs |
| 44 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 45 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 46 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 47 | 0 | 1 | 1 | 0 | 1 | 4 | 0 | 12 hrs |
| 48 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 49 | 1 | 1 | 1 | 0 | 1 | 3 | 0 | 6 hrs |
| 50 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 51 | 1 | 1 | 1 | 0 | 2 | 3 | 0 | 6 hrs |
| 52 | 0 | 1 | 2 | 0 | 1 | 3 | 0 | 24 hrs |
| 53 | 1 | 1 | 2 | 0 | 1 | 3 | 0 | 12 hrs |
| 54 | 1 | 1 | 2 | 0 | 2 | 3 | 0 | 6 hrs |
| 55 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 56 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | |
| 57 | 1 | 1 | 1 | 0 | 1 | 3 | 0 | 6 hrs |
| 58 | 1 | 1 | 1 | 0 | 1 | 3 | 0 | 12 hrs |