COMPARISON OF THE EFFICACY OF ONDANSETRON AND APREPITANT FOR THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING – A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL IN PATIENTS UNDERGOING MASTECTOMY/ THYROIDECTOMY

This dissertation is in partial fulfilment of the requirement for the M.D. Degree (branch X) Anaesthesiology examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be conducted in April 2013.

CERTIFICATE

This is to certify that the dissertation entitled "**comparing the efficacy of aprepitant and ondansetron for the prevention of postoperative nausea and vomiting – a double blinded randomized control trial in patients undergoing mastectomy / thyroidectomy** " is a bonafide original work of Dr. Salome Jeyabalan, towards the M.D. Branch X

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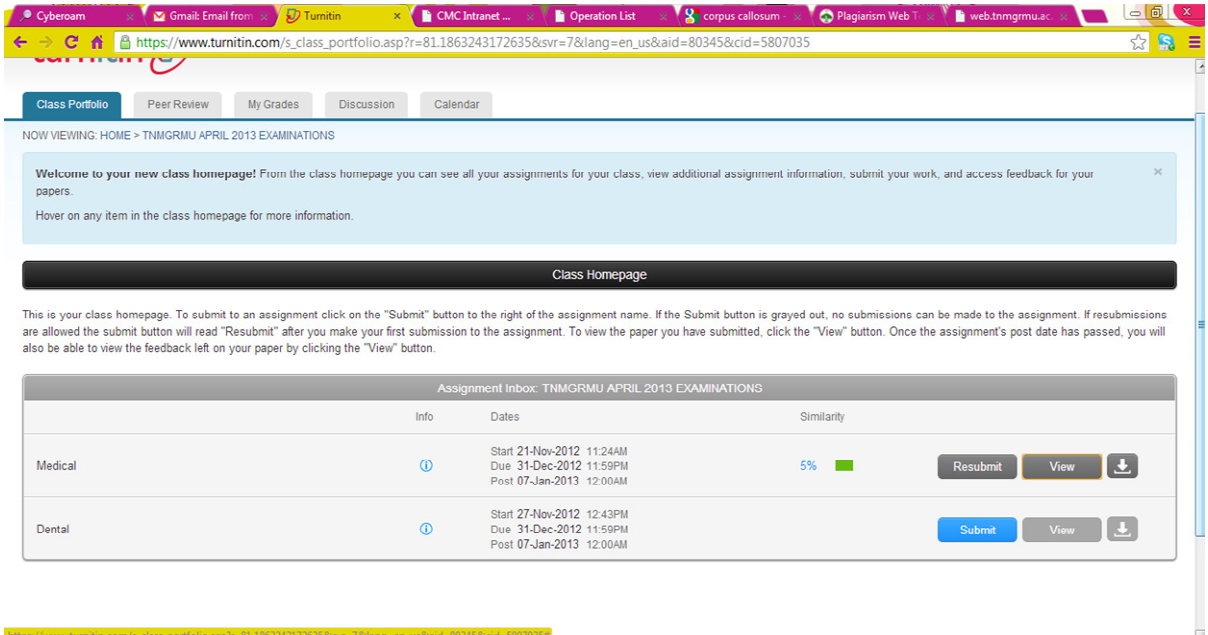
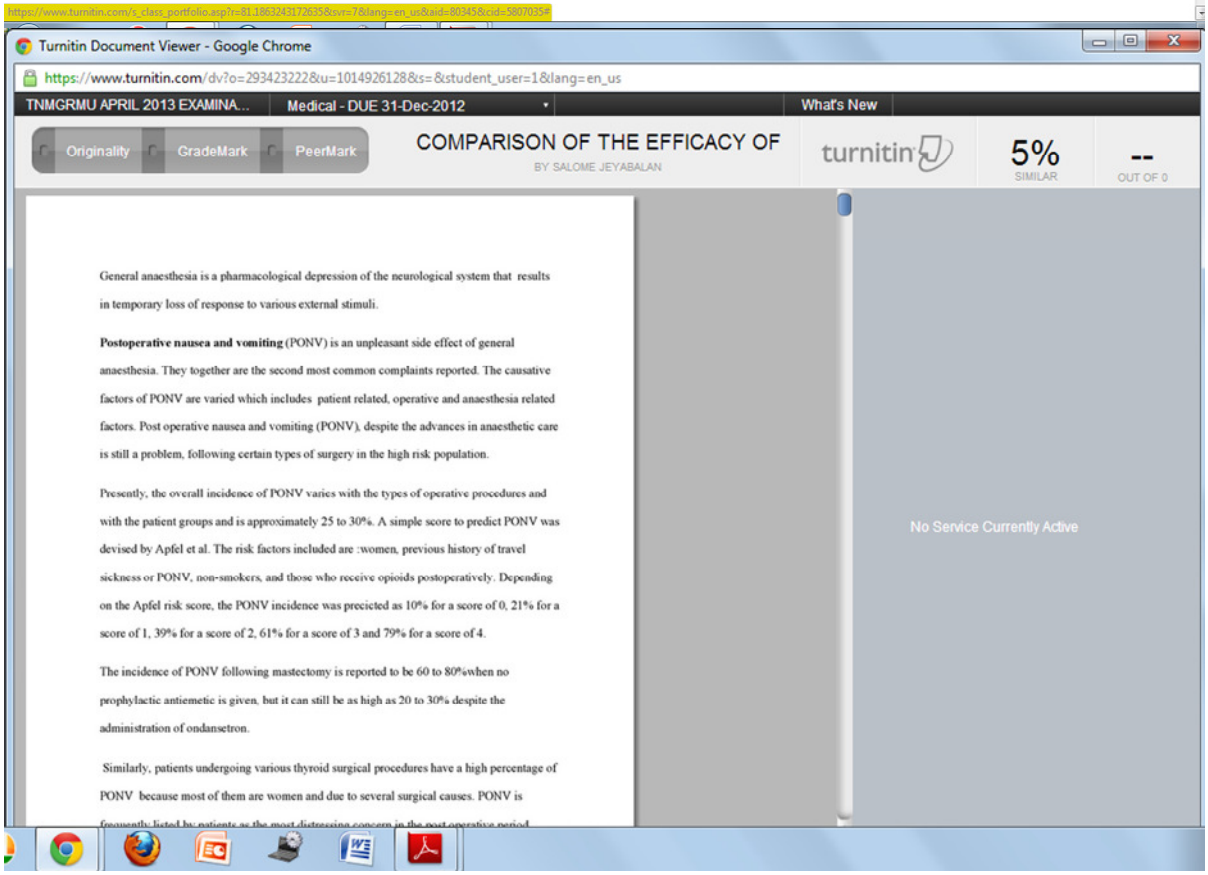
ANTI PLAGIARISM CERTIFICATION





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CONTENTS

AIM

The aim of this study is to compare the efficacy of ondansetron and aprepitant in the prevention of postoperative nausea and vomiting in women undergoing mastectomy and thyroidectomy.

OBJECTIVES

- To compare the antiemetic efficacy of ondansetron and aprepitant in the prevention of postoperative vomiting in female patients undergoing mastectomy / thyroidectomy.

- To evaluate the severity of postoperative nausea, number of episodes of vomiting, timing of the first vomiting episode and use of rescue antiemetics in thyroidectomy and mastectomy patients receiving ondansetron or aprepitant as antiemetic.

- To assess if the patients satisfaction in the management of postoperative nausea and vomiting improves with this intervention.

INTRODUCTION

General anaesthesia is a pharmacological depression of the neurological system that results in temporary loss of response to various external stimuli.

Postoperative nausea and vomiting (PONV) is an unpleasant side effect of general anaesthesia. They together are the second most common complaints reported. The causative factors of PONV are varied which includes patient related, operative and anaesthesia related factors. Post operative nausea and vomiting (PONV), despite the advances in anaesthetic care is still a problem, following certain types of surgery in the high risk population.

Presently, the overall incidence of PONV varies with the types of operative procedures and with the patient groups and is approximately 25 to 30%. A simple score to predict PONV was devised by Apfel et al. The risk factors included are : women, previous history of travel sickness or PONV, non-smokers, and those who receive opioids postoperatively

Depending on the Apfel risk score, the PONV incidence was precicted as 10% for a score of 0, 21% for a score of 1, 39% for a score of 2, 61% for a score of 3 and 79% for a score of 4.

The incidence of PONV following mastectomy is reported to be 60 to 80%when no prophylactic antiemetic is given, but it can still be as high as 20 to 30% despite the administration of ondansetron.

Similarly, patients undergoing various thyroid surgical procedures have a high percentage of PONV because most of them are women and due to several surgical causes. PONV is frequently listed by patients as the most distressing concern in the post operative period, sometimes even exceeding the pain of surgery. The growing awareness to improve patient satisfaction has prompted to strive for a post operative period free of nausea and vomiting.

Aprepitant belongs to the class of Neurokinin 1 receptor antagonist. It is highly selective for neurokinin receptors and its half life is long.. It is demonstrated to be effective against emesis induced by opioids and chemotherapeutic drugs. In patients having open abdominal surgical procedures and craniotomy, studies have shown that aprepitant had more antiemetic effect than ondansetron in preventing vomiting in the postoperative period. This study was an effort to compare the antiemetic efficacy of ondansetron and aprepitant in women undergoing mastectomy and thyroidectomy.

REVIEW OF LITERATURE

NAUSEA AND VOMITING

Nausea and vomiting are protective reflexes that occur as defence mechanisms against the intake of harmful substances. In fact, vomiting was a recognised effective treatment tool in older civilization(1).

Nausea is an uncomforable feeling which leads to a tendency to vomit.

Retching is an effort to vomit which is not under voluntary control, but these efforts do not cause does not cause expulsion of stomach contents through the oral cavity.

During vomiting, motor changes occur in the muscles of the abdomen and respiration and is coordinated by the brain stem (1).

Phases of vomiting (2)

Retching phase

The abdominal muscles undergo a few coordinated contractions together with the diaphragm and inspiratory muscles.

Expulsive phase

During this phase glottis closes, contraction occurs in the abdominal muscles, diaphragm, oesophagus and relaxation occurs at the sphincter which is present the junction of the oesophagus and stomach. This leads to evacuation of the stomach contents that is aided by a backward contraction of the upper oesophagus and decreases in tone of the diaphragmatic portion that encircles the oesophagus and this aids in the process of vomiting(3).

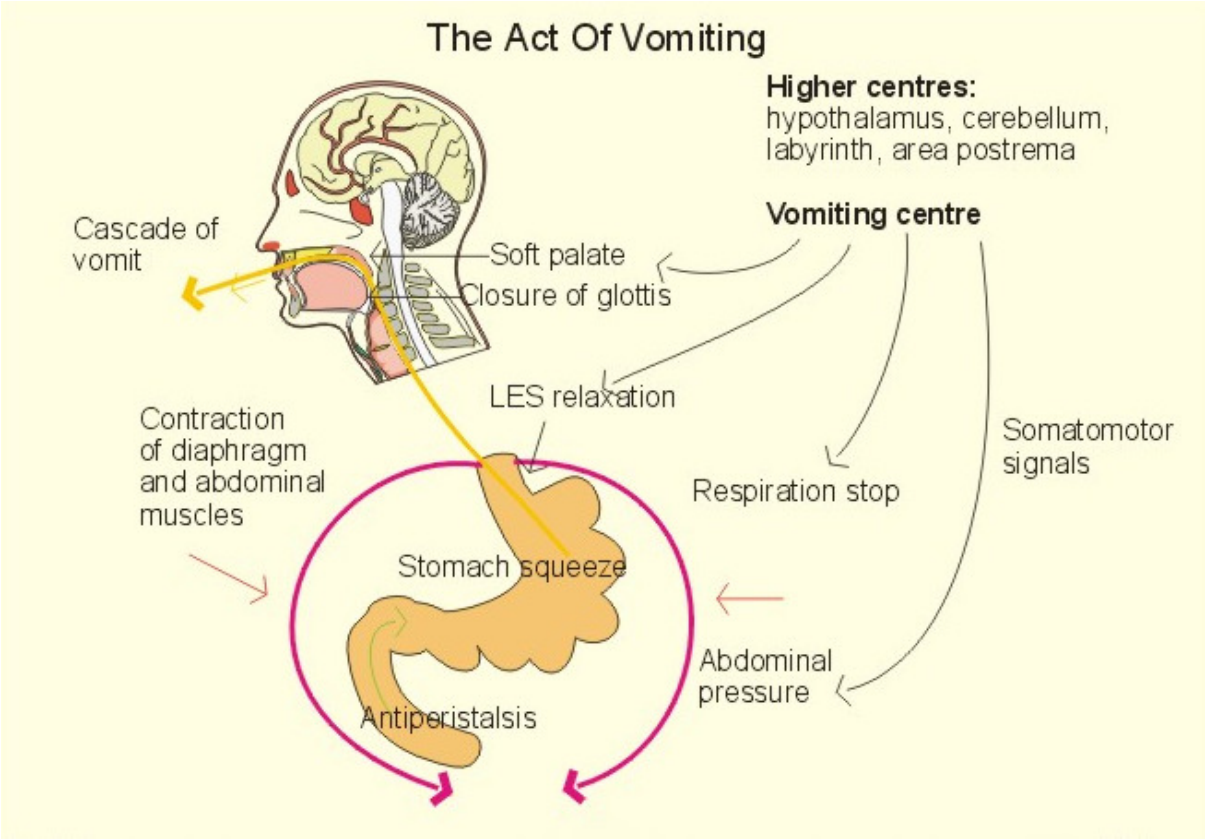


Fig 1: THE ACT OF VOMITING (4)

Vomiting is a uncomfortable act that occur with many procedures. Vomiting is a major problem during recovery from various operations , in cytotoxic anticancer chemotherapy and in situations involving motion and vestibular disturbances(5).

VOMITING AND ASPIRATION

Under normal circumstances, the protective reflexes such as gag and cough reflex prevents aspiration of gastric contents thereby preventing aspiration pneumonia or asphyxiation. However these protective reflexes are compromised in certain situations like alcohol influence or under anaesthesia where vomiting can be dangerous(6).

During anaesthesia, depression of airway reflexes places patients at increased risk of for intra operative pulmonary aspiration or for aspiration during the recovery period. Pulmonary consequences from perioperative aspiration fall into 3 categories- particle related, acid related and bacterial contamination.

Particle related – Acute airway obstruction can cause immediate death due to arterial hypoxemia of asphyxiation. Immediate intervention requires prompt removal of aspirated matter, oxygenation of the patient and tracheal intubation to prevent further aspiration.

Acid related – The ill effects of acid aspiration occurs in two phases. Immediate direct tissue injury occurs initially and subsequently followed by an inflammatory response. A chemical burn occurs within a few seconds from the central airways to the alveoli. Within a few hours, desquamation of the superficial cell layer with complete loss of ciliated and non ciliated cells occurs. After three days, regeneration is seen and complete recovery occurs in 7 days.

The alveolar type 2 cells are very sensitive to hydrochloric acid and degenerate within 4 hours of acid exposure. An increase in lysophosphatidyl choline occurs within 4 hours after

acid aspiration and leads to an increase in alveolar permeability and increase in lung water. This leads to an increase in ventilation-perfusion mismatching, decrease in lung compliance and increase in the alveolar arterial oxygen tension difference.

The second phase includes acid mediated induction and release of pro-inflammatory cytokines like tumour necrosis factor alpha and interleukin-8. These will in turn trigger the expression of adhesion molecules on the endothelium thus promoting a neutrophilic inflammatory response.

The morbidity increases directly with the volume and inversely with the pH of the acid aspirate. In severe cases, epithelial degeneration, interstitial and alveolar oedema and hemorrhage into the alveolar spaces rapidly progresses to ARDS with high permeability pulmonary oedema.

Destruction of pneumocytes, decreased surfactant activity, hyaline membrane formation and emphysematous changes can follow, leading to V/Q mismatching and reduced compliance. Destruction of the microvasculature increases pulmonary vascular resistance and dead space ventilation. Thus gastric aspiration combines a particulate injury causing foreign body reaction and focal inflammatory changes and a diffuse acid damage. Both together contribute to increase alveolar capillary leak.

Bacteria related- the gastric contents are not sterile and mixed with aerobic-anaerobic bacteria resulting in pneumonia. Gram negative and ventilator acquired pneumonias many of which are caused by aspiration of oropharyngeal secretions and gastric contents are significant determinants of death in post operative pneumonia(5).

MENDELSON'S SYNDROME

Mendelson's syndrome or aspiration pneumonitis was first described in obstetrical cases by Curtis Lister Mendelson who was a practising obstetrician in New York. In his classic paper, he explains about the lung manifestations in obstetric patients caused by aspirating the stomach contents. Typically there is history of vomiting after inhalational anaesthesia, either intraoperatively or in the early postoperative period. Within a few hours of aspiration, there is sudden onset of dyspnea, cyanosis, tachycardia and shock. Examination reveals generalised adventitious breath sounds and bronchospasm, but no localised signs of lung disease.

The presentation simulates pulmonary oedema with extensive ronchi and rales in both lungs. Tachycardia and tachypnea are common findings. In extreme cases, gross pulmonary oedema may supervene and can even have rapid deteriorating course leading to death from cardiac failure. Chest X ray reveals soft patchy mottling throughout the lung fields. Mendelson showed that acid content of the stomach was responsible for the asthma like syndrome(7).

POST OPERATIVE NAUSEA AND VOMITING- PONV

It is the uncomfortable feeling of nausea or the act of vomiting that occurs during the first postoperative day(8).

Predisposing factors for vomiting / regurgitation and aspiration(6).

1. Emergency surgeries
2. Light plane of anaesthesia / unexplained response to stimulation
3. Upper or lower GI pathology- acute or chronic
4. Obese patients
5. Premedication with opioids
6. Impaired conscious level due to neurological disease or sedation
7. Patient position- lithotomy
8. Difficult airway or difficult intubation
9. Gastrointestinal reflux disease
10. Hiatus hernia

NEUROCIRCUITRY INVOLVED IN EMESIS

The centre of vomiting in the CNS co-ordinates this complicated act of emesis. This centre is an ill defined area located in the lateral medullary reticulum, proximal to the fourth ventricle of the cerebrum. The chemoreceptor trigger zone is situated close to the medullary structure calles as area postrema. Dopamine, histamine, muscarinic and opioid receptors are included in the chemoreceptor trigger zone (8).

Vomiting can be triggered bynumerous signals. The vomiting centre receives inputs from the vestibular system, cerebellum, solitary tract nucleus, higher cortical centres, glossopharyngeal nerve and the vagus nerve.

These inputs induce areas involved in the causation of emesis. Another signal to the vomiting centre is from the chemoreceptor trigger zone that is situated in the medullary area which is outside the cerebrospinal fluid-blood barrier. This highly vascularised structure detects vomiting causing substances in the blood and cerebrospinal fluid. In addition Serotonin is released by the enterochromaffin cells of the gastrointestinal tract which bind to 5-HT_3 receptors. This causes the afferent neurons of the vagus nerve in the stomach and intestine to be stimulated which conduct impulses that reach the area postrema in the brain stem.

Neurons from the area postrema send impulses to the nucleus of the solitary tract. The vestibular, limbic and gastrointestinal systems also send impulses to the nucleus of the solitary tract.. Efferent neurons from the nucleus of the solitary tract reach the ambiguous nucleus located in the dorsal medulla, the anterior respiratory group and the posterior motor nucleus of the vagus. Thus, the main structures included in the act of vomiting are scattered in the lower half of the brainstem. These structures are located in the Bolzinger area which is located in the brain stem and is involved in co-ordination of respiratory rhyth and are called as the central area involved in the generation of vomiting.

The receptors involved in the transmission of nausea and vomiting impulses include serotonergic (5HT3), dopaminergic (D2), histaminergic (H1), cholinergic (muscarinic) and

neurokinin (NK1) systems(9). Post operative nausea and vomiting is due to various factors that can be triggered by several receptors at central or peripheral areas.

RISKS INVOLVED

A number of anaesthesia-related, patient-specific and procedure-related reasons are implicated in the occurrence of PONV(11).

NON ANAESTHETIC CAUSES

-PATIENT RELATED

-SURGERY RELATED

ANAESTHESIA RELATED FACTORS

-PREMEDICATION

-ANAESTHETIC TECHNIQUES

-GENERAL ANAESTHETIC AGENTS

-REVERSAL AGENTS

POST OPERATIVE FACTORS

-PAIN

-ORAL INTAKE

-AMBULATION

-OPIOIDS

NON-ANAESTHETIC FACTORS

PATIENT RELATED FACTORS

Many patient related causes have been recognised which affect the occurrence of emesis in the postoperative period.

This includes patient's age, history of PONV, gender, phase of the menstrual cycle, history of motion sickness, preoperative anxiety, history of morning sickness, co-existing medical conditions, non-smoking, degree of dehydration, associated medical conditions and metabolic abnormalities like uremia, diabetes mellitus, raised intra cranial pressure, acid peptic disease, electrolyte imbalances and exposure to emetogenic drugs like digoxin, ergometrine(2,12,13).

AGE

In adults, as age increases there are a decreasing incidence of PONV. Age decreases the chances of PONV by 13% for every 10 years increase(14,15). In children the incidence of

PONV increases with age, reports of PONV being relatively low in less than 3 years of age. Reduced autonomic reflexes with increasing age may be an underlying mechanism(11,16,17).

HISTORY OF PONV, TRAVEL SICKNESS & MORNING SICKNESS.

The PONV occurrence increases by 3 fold in individuals who had increased vomiting in the postoperative period during the previous operations (2, 15, 18–20). In one study, the author has reported an increasing occurrence of PONV in individuals who had previously experienced morning sickness(21).

GENDER

The incidence of PONV is approximately 3 times more common in women. (2,20,22–24). However, this gender difference is not seen in patients beyond the 8^{th} decade of life and in the preadolescent age group. This suggests that the higher occurrence of emesis in female patients may be due to changes in the amount of serum gonadotropin or other hormones during their menstrual cycle.

In a recent systematic review by Apfel et al, female gender was found to be the strongest overall predictor of PONV. The exact mechanism causing women to experience greater vomiting postoperatively is not clear(11).

PHASE OF THE MENSRUAL CYCLE

Post operative nausea and vomiting seems to increase around the time of menarche (25) and is decreased around the time of menopause(26). In post operative nausea and vomiting, the stage of menstrual cycle may also alter the occurrence of nausea and vomiting in the postoperative period(27).

Earlier trials have demonstrated a greater occurrence of nausea and vomiting postoperatively in women during the first 8 days of their menstrual cycle. The exact mechanism of this greater occurrence of PONV is unknown. The postulated explanation is that, the changing concentrations of FSH or oestrogen, or both, seem to sensitize the vomiting centre or chemoreceptor zone or both(28).

Honkavaara et al suggested that the incidence of PONV is higher during the luteal phase or the periovulatory period(29). Beattie et al reported a four -fold increase in the occurrence of nausea and vomiting in the postoperative period in female patients during menstruation (27).

The incidence of PONV also increases if the menstrual cycles are irregular(30). In a later study done by Gratz et al, no relationship was found between the stage of the menstrual cycle and the incidence of emesis(31). Similarly a systematic review disproved that the 1 to 7 days of the menstrual cycle increases the susceptibility to PONV(11,32). A recent systematic

review of prospective studies to identify independent predictors of PONV found insufficient evidence for menstrual cycle as a risk factor in the incidence of PONV(11).

OBESITY

A positive correlation between obesity and higher incidence of post operative nausea and vomiting is known to exist(33). The explanation given to this relationship is that fat causes accumulation of volatile anaesthetics and they continue to enter the blood stream from there even after discontinuing the administration of inhaled anaesthetics(2,19). Other likely explanations are an increased incidence of gastro-oesophageal reflux disease and larger residual gastric volume.

Obese individuals have a higher incidence of airway difficulties and gastric insufflation occurs in an attempt to maintain adequate airway during bag mask ventilation(2).However, some studies found no correlation between body habitus and post operative nausea and vomiting(14,20).

NON-SMOKERS

The occurrence of PONV is found to be greater in non-smokers compared to smokers. Smoking seems to have a protective effect against the incidence of post operative nausea and

vomiting(2,12). Smoking habit seems to reduce the likelihood of the incidence of PONV by one third(14, 15, 34).

The exact underlying mechanism behind the anti-emetic effect of smoking is not known so far. One postulation is that long term contact with cigarette smoke which contains polycyclic aromatic hydrocarbons causes induction of CYP2E1 of the cytochrome P450 enzymes which are responsible for first pass (phase 1) metabolism of volatile anaesthetics(16, 17, 35). However, since only a limited fraction of inhaled anaesthetics get metabolised (0.02% of desflurane, 0.2% of isoflurane) it seems unlikely that liver enzyme induction accounts for such a large difference in the nausea and vomiting that occurs between individuals who smoke and those who do not smoke (11).

Brattwall et al, suggested similar effect from regular sniffing of tobacco. This observation suggests that some substance in tobacco is responsible for the previously described effect of PONV reduction among smokers(36).

PREOPERATIVE ANXIETY

Preoperative anxiety is predicted as a risk factor for post operative nausea and vomiting. Preoperative anxiety is a common component of undergoing a surgery. There is a higher occurrence of nausea and vomiting in the postoperative period in such anxious individuals.

(37). Increased level of catecholamines in such patients is suggested to be a contributing factor. Other reason postulated is the excessive air swallowing seen in anxious patients, which increases the gastric volume(2).

SURGICAL FACTORS

OPERATIVE PROCEDURE

After general anaesthesia, the occurrence of nausea and vomiting in the postoperative period, is found to be high after certain types of surgeries namely laparoscopic surgeries, gynaecological surgeries, breast surgeries, thyroid surgeries, middle ear procedures, orchidopexy and strabismus surgery(2, 38- 42).

PONV can be caused by many factors including gender, age, history of motion sickness, obesity, surgical procedure, anaesthetic technique, vagal afferent stimulation during manipulation of the gut, increased middle ear pressure due to the use of nitrous oxide and traction of the extra ocular muscle which stimulates the oculogastric reflex(9, 40-44).

THYROID SURGERY

The main reason for the increased incidence of nausea and vomiting in patients undergoing thyroid surgery is entirely not known. Since most patients undergoing thyroid procedures are

middle aged women, it is suggested as one of the main reasons. Another reason may be due to stimulation of the tenth cranial nerve during surgical handling of the neck.

PONV causes adverse consequences in post thyriodectomy patients, because vomiting can result in oozing from the operated area. This oozing if worsens, can cause tracheal compression and can cause quick onset obstruction of the airway. This may require endotracheal intubation and re-exploration of the operated area. Hence it is appropriate that PONV prevention instead of treating it after PONV has occured(40–43).

BREAST SURGERY

Approximately 60 % of patients undergoing breast surgery experience emesis in the postoperative period(44–46). More than 60 % of patients undergoing mastectomy along with axillary lymph node dissection experience nausea and vomiting in the postoperative period when they do not receive antiemetic medication(46,47) and about 10 to 50 % of them have emesis in spite of receiving one or two component prophylaxis for PONV(45,48,49). Women undergoing surgeries on the breast by themselves are at increased risk, since being female is an important predictor for a higher incidence of PONV (15,20).

The causes of increased emesis following anaesthesia for various surgical procedures of the breast is not clear. It is dependent on multiple factors which include obesity, age, operative

procedure, history of motion sickness and/or previous PONV, phase of menstrual cycle, anaesthetic technique, postoperative pain and psychological factors.

The causes in many emetic syndromes comprise estrogen. In the breast tissue, hormones influence the various receptors present. A clear association between PR positive breast cancer in postmenopausal women and trend towards greater estrogen concentration was found. (50). The higher estrogen levels in the serum of post menopausal women has been correlated to the cancer of breast tissue. In female patients aged more than 50 years, the postoperative emesis is correlated with the presence of estrogen receptors(44).

In premenopausal women, due to the cyclical variation of hormonal levels, the changes in the ovary due to chemotherapeutic agents and the presence of various receptors influence the occurrence of nausea and vomiting in the postoperative period.

DURATION OF SURGERY

Duration of general anaesthesia greater than 4 hours is known to have increased emesis in the postoperative period(32,51). This increased incidence is explained as being due to the use of parenterally administered drugs and volatile agents. Since patients are administered these lipid soluble agents for a long time, they experience greater emesis in the postoperative period.(2).

ANAESTHESIA RELATED FACTORS

PREMEDICATION

Opioids when given as premedication can stimulate the CNS opioid receptors and increase the incidence of PONV(2). They can directly stimulate the area postrema causing PONV. Opioids decrease the gastrointestinal motility thereby prolonging the gastric emptying time. Opioids sensitise the regions in the vestibular area to movement thus predisposing to PONV(2,19,34). Atropine or scopalamine concurrently administered as premedication with opioids decreases the incidence of emesis after opioid administration(2).

Benzodiazepines like midazolam and lorazepam used as premedication decreases the PONV incidence by decreasing the plasma catecholamine levels(52,53).

ANAESTHETIC TECHNIQUES AND AGENTS

The occurrence of nausea and vomiting in the postoperative period is affected by the type of anaesthetic administered. Emesis is less after neuraxial blockade provided complications like decreased blood pressure and high sympathetic inhibition are prevented, as emetogenic agents such as volatile anaesthetics and opioids are not used. Since anaesthesiologists often

use a combination of drugs during an anaesthetic, it is difficult to point out an individual drug as the cause of PONV and it is more of a combined effect of the drugs used(2,19).

GENERAL ANAESTHESIA

VOLATILE ANAESTHETIC AGENTS

Older anaesthetic agents like cyclopropane and diethyl ether were associated with emesis of approximately 80 %. This high occurrence of emesis was related to the greater levels of endogenous catecholamines associated with these older anaesthetic agents. They caused more emesis compared to the potent volatile anaesthetics used in current practice(2,12,18,19).

The occurrence of emesis after exposure to the currently used volatile agents is the same(2,16,19).Thus the use of volatile agent itself is a high risk factor for the incidence of PONV(11,16,54–57). In fact, inhalational anaesthetic agents are implicated as the greatest risk for the occurrence of emesis postoperatively(11).

NITROUS OXIDE

Nitrous oxide has anaesthetic characteristics but it causes greater emesis in the postoperative period.(58). Several mechanisms have been suggested as contributing factors in increasing

the postoperative emesis associated with nitrous oxide. a) increase in middle ear pressure by diffusion and stimulates the vestibular apparatus(58,59). b) transfer of nitrous oxide into the bowel causing gaseous distension. c) stimulation of dopamine receptors in the CTZ d) action on the receptors that are sensitive to opioids(58,60,61).

The incidence of emesis in the postoperative period, increases with increasing concentrations of nitrous oxide(58). Thus omitting nitrous oxide contributes to decreasing nausea and vomiting when followed as part of other strategies to decrease its occurence(58,60,62,63).

INTRAVENOUS ANAESTHETIC AGENTS

Ketamine when used for induction and / or maintanence of anaesthesia causes a higher incidence of PONV compared to patients receiving barbiturates. The release of endogenous catecholamines may cause this emetic effect(2).

Propofol is an anaesthetic solution administered intravenously. These days it is used not only for inducing anaesthesia but also for maintaining anaesthesia because it has a fast onset and recovery profile and low incidence of PONV(64).

Several studies have proved that total intravenous anaesthesia with propofol alone is associated with less emesis compared to other techniques. (65,66). Propofol is also known to

have antiemetic properties. This is attributed to its central antiseratoninergic action(2,67). Propofol induction is known to cause less emesis after surgery compared to thiopentone(68).

A balanced anaesthetic technique using opioid-nitrous oxide-relaxant causes greater emesis in comparison with total intravenous anaesthesia. This increase in the incidence of emesis is attributed to the use of opioid-nitrous oxide combination which has a direct action on the chemoreceptor trigger zone(2,18,19,34).

REVERSAL AGENTS

Use of anticholinesterase agents for the reversal of muscle relaxation may cause emesis postoperatively. This occurred only when neostigmine was used in doses higher than 2.5 mg(2,63,69).The muscarinic effect of these drugs cause movement of the gut which adds to the occurrence of postoperative emesis. This minor effect is decreased when anticholinergic is used along with neostigmine(2).

REGIONAL ANAESTHESIA

In central neuraxial blockade techniques such as spinal and epidural, the occurrence of nausea and vomiting is approximately 10 to 20%(18). This incidence is higher compared to local

anaesthetic inhibition of impulse conduction in the peripheral nerve because neuraxial anaesthesia is associated with sympathetic inhibition which contributes to the fall in blood pressure which induces emesis (2). In one study it was observed that the nausea and vomiting in these patients is reduced by administering 100% oxygen, suggesting that hypoxemia at the vomiting centre was the stimulus for vomiting(70).

Several aetiological factors contribute to the occurrence of emesis in obstetric cases. The factors include fall in blood pressure,compression of great vessels, strong vagal stimulation due to handling of the viscera during surgery and various drugs used intraoperatively such as opiates and uterotonics such as oxytocin and particularly ergometrine. Most postoperative analgesia regimens include opiates which contribute to PONV(71).

Intrathecal or epidural administration of opioids increases the incidence of PONV than when local anaesthetics are used alone. This emetogenic effect of intrathecal opioid is attributed to its rostral spread to the vomiting centre and the CTZ. The agents with higher lipid solubility have less rostral spread than the less soluble agents such as morphine(2).

POSTOPERATIVE FACTORS

PAIN

Pain in the postoperative period is found to significantly contribute to nausea and vomiting. This is supported by the fact that regional nerve blocks when used for postoperative analgesia

significantly reduces the incidence of PONV(72,73). It is also reported that pain relief is associated with the relief of nausea. The incidence of PONV in association with pain is especially higher with pelvic or visceral pain(74).

AMBULATION

Changes in position like sitting up or transport to the post anaesthesia care unit can cause sudden movement that can precipitate vomiting in patients who have received opioids, due to sensitisation of the vestibular system(34). Afferent impulses sent from the vestibular apparatus reach the chemoreceptor trigger zone via the histamininergic and the cholinergic fibres and may cause emesis following ambulation in the postoperative period(75).

ORAL INTAKE

Traditionally it is believed that following all abdominal surgeries, there is inhibition of GIT activity for a short period. This clinical phenomenon has been proposed to be caused by excessive sympathetic tone, stimulation of nerve fibres and the neurochemical substances that cause inhibition of GIT. So it was believed that if patient starts orally soon after surgery, it can cause emesis and aspiration,wound dehiscence and anastamotic leakage. However a Cochrane review done in 2009 reported an greater occurrence of nausea but the occurrence of vomiting or paralytic ileus after early intiation of oral or enteral feeding was not different(76).

OPIOIDS

Opioid compounds, irrespective of the route of administration cause emesis as common side effects in the postoperative period(2,19,34). Opioid analgesia primarily involves central receptors in the brain stem and in the rostral anterior cingulate cortex. However peripheral opioid activity at the gut receptors inhibits acetylcholine release from the mesenteric nerves which causes reduction of gut motility and tone. This leads to delayed gastric emptying and this triggers nausea and vomiting through a serotonergic signalling pathway(11).

COMPLICATIONS OF PONV

PATIENT RELATED

Although postoperative nausea and vomiting is usually self limiting, it decreases patient comfort and satisfaction(11,12). Many studies involving high risk populations have clearly shown an increase in patient satisfaction with prophylactic antiemetic regimens when compared to placebo with rescue antiemetic in the post anaesthesia care unit(77,78).

MEDICAL

PONV causes interruption of oral drug therapy, nutrition, diet which can lead to dehydration, electrolyte imbalances like hypochloremia, hyponatremia, hypokalemia, metabolic alkalosis, increased postoperative pain and orthostatic hypotension(2,8,17,18).

SURGICAL

PONV leads to several surgical complications like venous hypertension, bleeding, hematoma formation, disruption of surgical anastamosis, grafts, flaps, wound dehiscence and haemorrhage, hematoma formation, increased intracranial and intraocular pressures, aspiration pneumonia and oesophageal tears or rupture, the most severe complications being rare(2,8,17,18).

ANAESTHESIA RELATED

Approximately 20 % of patients have emesis in the post anaesthesia care unit(8,14,33,83). Aspiration of gastric contents can occur in patients who are under the effect of residual anaesthetic(2,18,19).

ECONOMIC BURDEN

PONV and its resulting complications increase unexpected hospital admission in day care surgeries, nursing care time, delay discharge from the post anaesthesia care unit, increase the length of hospital stay, thus imposing an economic burden on the hospital resources and delaying return to work(2,8,11,18).

PREDICTION OF PONV

Patient related factors like age, gender, non-smoking status, past history of motion sickness or PONV and duration of anaesthesia are used to obtain a risk score for PONV(20).

APFEL'S RISK SCORE

In a study by Apfel et el, it was concluded that women, patients with previous emetic experiences postop, travel sickness, individuals who do not smoke and administration of opioid medications after surgery were predictive of PONV.

The occurrence of emesis in the postoperative period was predicted as 10% for an Apfel score of 0, 21% for a score of 1, 39% for a score of 2, 61% for a score of 3 and 79% for a

score of 4(79,80). An Apfel's risk score of 2-3 for PONV indicates high risk and a score of more than 3 is considered very high risk(79).

Another risk identification for objective assessment of nausea and vomiting suggested by Koivuranta et all included women, patients who experienced emesis postoperatively during previous surgeries, travel sickness, increased time of operation and non smoking. The predicted incidence of PONV with the presence of 0 to 5 of these factors is 17%, 18%, 42%, 54%, 74% and 87%(11,34).

A review of 22 studies done earlier was conducted recently to assess how prone the individuals are to the occurrence of nausea and vomiting in the postoperative period. In that female gender was found to be the strongest patient specific predictor, followed by those who experienced emesis during previous operations, travel sickness, individuals who do not smoke and younger age.

The strongest anaesthesia related predictor was the use of volatile anaesthetics and then the length of the procedure and use of opioids after surgery were implicated. There was insufficient or no support for numerous beliefs like surgery type, phase of the menstrual cycle and preoperative fasting status(11).

This risk stratification helps to avoid the potential side effects and the expense of prophylactic antiemetics in low risk population(10,32).

PREVENTION AND TREATMENT STRATEGIES FOR PONV.

A detailed preanaesthetic history and evaluation will help to identify those individuals who will benefit from PONV prophylaxis and enable to plan specific PONV management suitable for the patient. The occurrence of nausea and vomiting postoperatively has decreased to 30 % presently when compared to the use of older inhalational agents(14). However the occurrence is about 80% in certain high risk populations.

Preventive antiemetics should be administered for patients with moderate to high risk of PONV, or if PONV occurrence would delay their recovery, compromise their surgery or has medical consequences and cause unwarranted hospital admission(74).

As no single antiemetic can completely prevent or treat PONV, recently the focus on PONV management has been on using different agents which have different sites of action and the adoption of multiple management strategies to handle this issue. This maximises the clinical efficacy thereby minimising the side effects(10,38).

Various modalities for PONV management can be classified as

- Pharmacological
- Non pharmacological

PHARMACOLOGICAL

Receptors causing transmission of impulses leading to emesis include cholinergic (muscarinic), dopaminergic (D_2), serotonergic (5-HT_3), histaminergic (H_1) and neurokinin (NK 1) systems. To cause disruptionoif sequential neural transmission of emesis, the potential targets for the antiemetic drugs are the receptors involved(2,8,9,11).

PHENOTHIAZINES

Phenothiazines are some of the commonly employed antiemetics worldwide. They exert a t D_2 dopamine inhibitory action on the chemoreceptor trigger zone with some anticholinergic and antihistaminic effect. The aliphatic phenothiazines like chlorpromazine and promethezine have lower effect in preventing nausea and vomiting and causing more sedation than prochlorperazine and perphenazine. Also, the heterocyclic ones have higher incidence of extrapyramidal symptoms than the aliphatic phenothiazines(2,38).

Presently, the use of phenothiazines has fallen out of favour in view of their high incidence of adverse effects such as restlessness, sedation, dizziness, diarrhoea, agitation, central nervous system depression and rarely extrapyramidal symptoms, hypotension, supraventricular tachycardia and neuroleptic syndrome(8,38). They are currently not recommended as the first line management of PONV.

BUTYROPHENONES

Butyrophenones like droperidol and haloperidol have similar antiemetic and pharmacological effectiveness as the phenothiazines. They have stronger D_2 receptor antagonism on the area postrema and chemoreceptor trigger zone(2). Their alpha blocking action contributes to their sedation and extrapyramidal side effects, although the latter are rare due to the low dose used to treat PONV(38). The clinical efficacy of injection droperidol 0.625 -1.25 mg given intravenously before the end of surgery has been well established(82).

Until recently it has been used widely as a cost effective antiemetic in the management of nausea and vomiting in the postoperative period. The IMPACT trail found that droperidol is equally efficacious as ondansetron and dexamethasone in the management of nausea and vomiting in the postoperative period(83).

A meta analysis by Leslie and Gan found out that droperidol can safely be used in combination with 5 HT_3 antagonists and that they are generally well tolerated and have comparable safety profiles(84). However in 2001, a black box warning was issued for droperidol by the FDA citing reports of severe cardiac arrhythmias like torsades de pointes and rare cases of sudden cardiac death associated with the use of droperidol(85). Although since then the use of droperidol has declined precipitously, many anaesthesia providers still believe that the warning was not justified and that it still remains a effective, safe and economical antiemetic(85–87).

Neverthless , the warning, along with the recommendations by the FDA that all elective surgery patients receiving droperidol should have continous electrocardiographic monitoring for 2 to 3 hours following administration has limited its use.

Haloperidol primarily used as an antipsychotic, has weak antiemetic properties though has a faster onset of antiemetic action and a longer half life because it has less affinity than droperidol for the D_2 receptors in the chemoreceptor trigger zone and area postrema(38,88).

BENZAMINES

The most popular antiemetic in this class of drugs is metoclopramide which is a procainamide derivative and has both central and peripheral antiemetic action. It blocks the D_2 receptors centrally at the medullary vomiting centre and peripherally in the bowel(38,88).

This promotes intestinal motility and enhances emptying thus making it useful in cases of delayed emptying caused by opioids(2,38,88–90). The common side effects of metoclopromide are extrapyramidal symptoms and sedation. Intravenous administration sometimes causes hypotension and rarely, supraventricular tachycardia(2,88).

In a previous systematic review it was concluded that metoclopramide 10 mg did not have any clinically meaningful effect in the prevention of PONV(91). Here it should be noted that this analysis involved various studies with questioned validity done by the author Yoshitaka

Fujii(92,93). The current guidelines for the prevention of PONV by the Society of ambulatory anaesthesia does not include metoclopramide in the management of nausea and vomiting in the postoperative period(94).

A recent quantitative systematic review was conducted to study the activity of systemic metoclopramide in the management of nausea and vomiting in the postoperative period in individuals having various operations. This concluded that metoclopramide in a dose of 10 mg given intravenously is good in preventing emesis. Hence it is an acceptable substitute to other agents employed in the management of nausea and vomiting(95).

CHOLINERGIC ANTAGONISTS

The anticholinergics are among the oldest antiemetic agents used. Both scopolamine (hyoscine) and atropine inhibits cholinergic receptorslocated in the pons and cerebrum (96). Compounds with selective M_3 and M_5 muscarinic inhibitory activity possess greater action against motion sickness(2,88,97).

Atropine and scopolamine, being tertiary amines cross the blood CSF barrier and has effect in emesis postop and in travel sickness. However, compared to scopolamine, atropine has weaker antiemetic properties (38,88) and because of its cardiovascular effects it is generally not used as an antiemetic in the postoperative period(98). Scopolamine inhibits transmission from the vestibular system to the cntral structures involved in vomiting(88,97).

The common side effects of the use of anticholinergics are dry mouth, sedation, memory loss, mydriasis, disorientation, confusion, blurred vision, urinary retention and hallucinations(2,88).

Most studies on the use of scopolamine in PONV have investigated transdermal scopolamine (TDS) patch designed to release 1.5 mg over a 3 day period. White et al compared preoperative TDS patch 1.5 mg and ondansetron 4mg or droperidol 1.25 mg given during the end of operation and found that preoperative TDS patch was as effective as ondansetron or droperidol in the management of early and late PONV(104). The high occurrence of anticholinergic side effects of scopolamine limits its use as a stand alone antiemetic agent.

It may be better to use scopolamine in addition to the routinely used antiemetic agents. In a study by Sah, he concluded that when preoperative TDS patch was combined with intraoperative ondansetron, there was a marked decrease in the nausea in the first postop day when compared to those who received a placebo patch and ondansetron only(99). The incidence of anticholinergic side effects was not statistically significant with TDS patch, suggesting that scopolamine may be a safe and effective adjunct in PONV management especially when used in combination with ondansetron(106).

ANTIHISTAMINES

The antihistamines such as diphenhydramine, dimnehydrinate, cyclizine, promethzine and doxylamine exert antiemetic properties by blocking the histamine H_1 receptors in the nucleus tractus solitarius, at the vomiting centre and the vestibular system with little or no direct effect at the chemoreceptor trigger zone(2,88,100). These compounds are particularly useful in the prophylaxis and treatment of emesis following middle ear surgery, vertigo and motion sickness(2,88).

The common side effects of antihistamines are excessive sleep , dimness of vision, dryness of mouth and urinary stasis and are due to their anticholinergic activity. Although antihistamines are readily available and inexpensive, their use in the management of PONV has not been well studied so far.

In the prevention and treatment of PONV and motion sickness, cyclizine and promethazine have equal efficacy. The most common disadvantage of cyclizine is the excess sedation. In a placebo controlled trial comparing the efficacy of ondansetron and cyclizine intravenously in daycare gynaecological laparoscopic surgeries , it was found that both ondansetron and cyclizine were comparable in causing a reduction in the occurrence of moderate to severe nausea and vomiting postoperatively. Also, the need for administration of rescue drug was lower in the cyclizine group(101).

In a meta analysis of 18 controlled trials done by Kranke et al, they reported that the use of dimenhydrinate in the dose of 1mg/kg as prophylaxis, decreases nausea and vomiting in children and in adults upto 48 hours after surgery. They concluded that dimenhydrinate is a clinically relevant inexpensive drug with antiemetic efficacy(102). However, the optimal time of administration, the dose response, benefit of repetitive doses and estimation of side effects need to be evaluated further.

Promethazine, a phenothiazine is a potent antiemetic used for the prophylaxis and treatment of motion sickness. It has both antihistaminic and anticholinergic activity with a longer duration of action, thus preferable to scopolamine. Its major drawbacks are sedation and prolonged recovery from anaesthesia(88).

SEROTONIN ANTAGONISTS

Serotonin or $5HT_3$ receptor antagonists ($5HT_3RAs$) are popularly used agents against emesis in the postoperative period. (103). Since its introduction in the early 1990s in the treatment of emesis caused by chemotherapeutic agents, serotonin receptor antagonists have become one of the cornerstones in the management of emesis particularly during the postoperative period.

Serotonin occurs in high levels in the bowel and in the central nervous system and when released, they stimulate the vagal afferent neurons or the chemoreceptor trigger zone to activate the vomiting centre(100).

The serotonin receptors are found in abundance in the CTZ and in the nucleus of the solitary tract and is highly selective for nausea and vomiting. Although there are many types of serotonin receptors, the $5HT_3$ receptor subtype appears in greatest concentration in the nucleus of the solitary tract, in the medullary vomiting area all of which have a significant action in coordinating the vomiting reflex(38,104).

The $5HT_3$ receptor antagonists include ondansetron, granisetron, dolasetron, ramosetron, tropisetron and palanosetron. They exhibit their antiemetic action on the serotonin receptor rich areas in the brain. In general, all the serotonin receptor antagonists are effective, safe, non sedative, well tolerated and similar, side effect profiles(103,105–107).

The most common side effects are dizziness, headache, constipation and diarrhoea which are of mild to moderate intensity and usually occurs short term(38,108). In view of the differing chemical structure of each drug, they exhibit slight differences in the dose response, receptor binding affinity and the duration of action(38,109).

Ondansetron, as the prototypical $5HT_3$RA, is the most widely studied among this class of drugs and the first report of its use in PONV was published in 1990. Since then several

studies have reported its efficacy and safety in the management of PONV. A Cochrane systematic review concluded that ondansetron decreases the risk of emesis by 45% compared to the placebo(110). The review found no evidence for the differing risk of PONV for groups based on the timing of administration.

Controversy exists as to whether ondansetron in doses greater than 4 mg offers any greater benefit in PONV prophylaxis(111–114). However, ondansetron 4 mg administered intravenously before the completion of surgery is the recommended dose for clinical practice and is provento be decrease emesis postoperatively(94). The major limitation is that it's half life is 4 hours and hence it is not likely to confer protection to patients after a few hours postoperatively (9). Most of the available studies suggest that $5HT_3$RAs are most effective when administered before the end of the surgical procedure(115–117). However, one study suggests that dolasteron when given during the time of induction of anaesthesia is equally effective in preventing PONV(118).

Unlike ondansetron, the other serotonin receptor antagonists have linear dose response curves with greater clinical effect being achieved with increasing doses until the maximal effective dosage is reached(119). The recommended granisetron dose for PONV prophylaxis is 0.3 to 1.5 mg I.V (94,120,121). The recommended dolasetron dose for PONV management is 12.5 mg administered I.V towards the completion of the operative procedure(94).

Though $5HT_3$ receptor antagonists have widespread use and are perceived to be well tolerated, they are associated with QTc prolongations, cardiac arrhythmias and cardiac arrest(122–124). Palonosetron, the newest $5HT_3$RA does not affect the QTc interval(125).

Recently it was found that palosetron has unique receptor binding properties. Unlike the other drugs in its class which exhibit simple bimolecular binding, palonosetron causes antagonism of the remote binding site. This results in longer antiemetic efficacy. Due to this positive receptor binding characteristics and a long half life of 40 hours, palonosetron given intravenously in the dose of 0.25 mg is proven to be effective in preventing delayed emesis induced by chemotherapeutic agents (126–128). In the management of PONV, palonosetron in a much lesser strength of 0.075 mg successfully reduces the incidence over a 72 hour period(125).

Among this class of drugs, ondansetron, granisetron and dolosetron are available as intravenous and oral preperations. In addition, ondansetron is also available as oral disintegrating tablets which are as effective as the intravenous preparations(129).

In the research of $5HT_3$ RAs, a relatively new but growing field is the pharmacogenomics. This class of drugs are metabolised by the cytochrome P450 enzyme-CYP2D6 isoform in the liver. Differences in the levels or activity of this CYP2D6 isoform have an effect on the clinical efficacy or pharmacokinetics of this drug(109).

Another study by Reuffert et al found that genetic variation in the serotonin receptor subunits, HTR3A, HTR3B were implicated with an enhancing risk of an individual developing postoperative emesis(130). Though this pharmacogenomic research is in its early stages and is of limited use in clinical practice currently, in the future it may provide greater insight into the assessment of individual patient riskfor emesis in the postoperative period.

CORTICOSTEROIDS

Dexamethasone is an effective antiemetic proven to be useful in the management of PONV. The actual mechanism of its effect is yet unknown. The reasons suggested are blockade of prostaglandins in the periphery with enhancement of serotonin inhibition in the central nervous system (8,10,15,38).

Glucocoricoids are found to exert several effects on the brain like regulation of receptor densities, neurotransmitter concentrations, neuronal configuration and signal transduction(131).

Several receptors are present in the nucleus of the solitary tract and the area postrema (131,132). Dexamethasone may also exert its antiemetic action through these nuclei. Dexamethasone, due to its cost effectiveness and its long duration of action is an attractive choice. It is used in doses of 8-10 mg I.V (8,133) for the management of PONV but there are

reports that smaller doses of 2-2.5mg are effective(79,134). Side effects are not documented with doses used in PONV management.

Dexamethasone is particularly effective when used in combination with $5HT_3$RAs as it may inhibit release of serotonin in the GIT, reduce the serotonin levels by depleting its precursor tryptophan and sensitise the $5HT_3$ receptors to other antiemetics(133). Hence dexamethasone is a valuable addition to combination therapy(83). According to Wang et al, dexamethasone was most effective when administered at the commencement of anaesthesia when compared to administering it towards the completion of the procedure. (135).

Karanicolas et al did a systematic review and meta-analysis of 17 trials and concluded that dexamethasone causes 41 % decrease in nausea, 59 % decrease in vomiting and 45 % decrease in both nausea and vomiting compared to the placebo. The incidence of headache and dizziness were found to be similar between the 2 groups. They also reported that higher doses of dexamethasone were significantly more potent than lower doses (136). This finding was consistent with an earlier study done by Elhakim et al who concluded that dexamethasone in a dose of 8 mg when combined with ondansetron provided maximal antiemetic effect(137).

However, the society for ambulatory anaesthesia recommendations for the management of postoperarive emesis administers a prophylactic dose of 4 to 5 mg of dexamethasone at induction which seems to be equally potent as ondansetron in the management of nausea and vomiting in the postoperative period(94). This recommendation is given after a through

analysis on the minimum dosage needed for effective prevention of nausea and vomiting postoperatively. (133).

NEUROKININ-1 (NK1) RECEPTOR ANTAGONISTS

Tachykinins are neuropeptides which cause contraction of smooth muscles and they share a common C-terminal sequence Phe-Xaa-Gly-leu-MetNH_2. These compounds are substance P, neurokinin A and neurokinin B. These exert their biological activity through NKI, NK2 and NK3 receptors which are G-protein coupled receptor subtypes(8,145). The NK1 receptor mediates the activity encoded by C-terminal sequence according to the Montreal nomenclature.

Substance P causes antagonism of NK1 receptor. This has an important role in emesis by acting as a ligand to the above mentioned receptors (103,138). This substance P is competitively inhibited by neurokinin-1 receptor antagonists (NK-1 RAs) and are believed to halt neurotransmission in the vomiting centre thereby curbing nausea and vomiting centrally(139). Thus it is an good technique to inhibit vomiting by administering a drug which has inhibitory action on the vomiting centre. (8). A possible contribution from peripheral sites to its action has been suggested(140). This hypothesis is yet to be confirmed(8).

In view of their action in the final potential commonroute, the NK1RAs possess a wider range of activity in preventing nausea and vomiting than $5HT_3$RAs, corticosteroids and

anticholinergics. The efficacy of this class of drugs is optimised by combining it with other different classes of antiemetics(8). Similar to serotonin receptor antagonists, aprepitant does not cause sedation, but unlike most serotonin receptor antagonists, it has a half life of 9 to 12 hours. Also, it is not associated with QTc prolongation(103,141).

Aprepitant, the first FDA approved highly selective nonpeptide NK-1RA was shown effective against opioid induced emesis and a large reduction in vomiting and nausea compared to ondansetron(138,142,143). It crosses the blood-brain barrier and exerts its antiemetic action by blocking substance P in the dorsal vagal complex and area postrema(138).

The bioavailability of aprepitant after a single oral dose is approximately 65 %. It has 95% protein binding and the mean Vdss is 70 litres in humans. It is metabolised by the liver (CYP450 3A4 enzymes). Excreted is both in the faeces and urine. Therefore co administration of aprepitant with medications that induce or inhibit this enzyme activity can cause reduced or increased blood levels of aprepitant respectively. Medications known to induce or inhibit CYP3A4 should be used with caution(144).

Aprepitant induces the activity of CYP2C9. Hence co administration of aprepitant with drugs like warfarin and tolbutamide which are metabolised by the same enzyme causes a decrease in blood levels of these drugs.

Dosage adjustment is not required for elderly, patients with renal, liver impairment. It is not studied in patients with severe liver failure and in children. When co-administered with hormonal contraceptives, their efficacy is decreased for approximately one month after using aprepitant. It is not recommended for continous chronic use since it has not been studied so far(145).

For the prevention ofemesis caused by chemotherapeutic agents, aprepitant is prescribed for 3 days which includes a $5HT_3$ antagonist and corticosteroid. The recommended dose is 125 mg orally on the first day and 80 mg once a day for the next 2 days. Injection fosaprepitant dimeglumine is a prodrug of aprepitant. It can be given IV instead of the oral preparation and given in the dose of 115 mg which equals 125 mg of the oral drug. This is adminisrered as an intravenous infusion over 15 minutes. This prodrug is converted to aprepitant in about 15 minutes(8).

From an analysis of findings from 2 RCTs with aprepitant, Diemunsch and colleagues compared 40 mg of oral aprepitant with 125 mg given within 3 hours before induction of anaesthesia and showed similar or slightly reduced effect in the latter. Hence 40 mg of aprepitant given within 3 hours prior to anaesthesia is the recommended regimen.

Side effects of aprepitant include pruritis, headache, fatigue and dizziness. Some also experience constipation and fever. No serious side effects are reported so far. (8,153).

The first clinical study of NK1RAs in the prevention emesis in the postoperative period was published in 1999(146). In a pooled analysis of clinical trials by Apfel et al, they illustrated

that aprepitant was able to reduce the incidence of emesis when compared to the commonly used antiemetics(141).

A randomized double blinded phase 3 trial was cperformed by Diemunsch et al in patients undergoing open abdominal operations comparing single dose aprepitant was better compared to ondansetron in preventing emesis in the first 2 postoperative days. (144).

In a study on patients undergoing total joint arthroplasty, Dilorio concluded that aprepitant given preoperatively decreased the severity and incidence ofemesis postoperatively, shortened the length of hospital stay and reduced the need for additional rescue antiemetics(147).

Its specific advantages include its oral preparation, easy to administer for prevention as a capsule, the availability of injection form which can possibly be used for patients who cannot tolerate orally, chances of reserving other different effective antiemetics for 2 nd line management since a different class is required in case of emesis despite prophylaxis and its longer duration of action. (148).

Earlier studies have shown that compared to monotherapy with ondansetron and other antiemetic drugs, multimodal approach is much superior in PONV management. Hence it is still not sure if aprepitant will be better than combination or multimodal treatment for prevention of emesis postoperatively(83).

Other area for NK1 RAs are rheumatoid arthritis, anxiety, schizophrenia, neural injury, stroke, migrane, pain, asthma and bowel disease (9,148). Another area of interest is in

preventing adhesions following laparoscopy by instillation of aprepitant intraperitoneally(149).

Data from various studies have confirmed theeffectiveness of NK1RAs in man in nausea and vomiting caused by chemotherapeutic agents and in the postoperative period. (150).

The investigational NK1RAs are vofopitant,. casopitant, maropitant, rolapitant, and vestipitant(8). The newer NK1 antagonists such as casopitant and rolapitant have a longer half-life of up to 120 hours but are not approved by the FDA so far(151,152). As this group of drugs are the most effective class of antiemetics available, they should be considered for patients who have a very high risk of PONV and the medical complications associated with vomiting(141).

EPHEDRINE

Ephedrine is a indirectly acting sympathomimetic drug which helps in prevention of travel sickness and postoperative emesis induced by orthostatic hypotension and fluid dehydration. Ephedrine helps to maintain the blood pressure thereby prevent the nausea associated with hypotension that can occur potoperatively(10). Rothenberg et al, concluded that the antiemetic activity of ephedrine was similar to droperidol without any centrally mediated side effects in patients undergoing outpatient laparoscopic gynaecological surgery(153).

PROPOFOL

It has been observed that patients who receive propofol for induction tend to have less postoperative nausea and vomiting(154). The antiemetic effect of propofol may be mediated by the influence of gamma-aminobutyric acid on the serotonin system the exact mechanism of which is not known. It may directly act on the neurons of the area postrema via the GABA(A) receptor to reduce their activity and depleting serotonin levels in the CSF and brain. (155).The minimum effective concentration of propofol for the prevention emesis postoperatively is 300 ng per ml(156).

A systematic review of randomised control trial by Tramer et al concluded that propofol has some beneficial effect on PONV only when used for maintenance of anaesthesia and has no beneficial effect when used only as an induction agent(66). This observation is supported by several meta-analyses which concluded that occurrence of PONV is greater in patients who receive volatile agents when compared to those who had total intravenous anaesthesia with propofol(157,158).

Since inhalational anaesthetics are major factors in nausea and vomiting soon after the completion of surgery , the most marked decrease in the occurrence of emesis due to use of TIVA with propofol is seen in the first 2 hours after the operation(138). It is not yet proven if this advantage of TIVA can extend into the late hours postoperatively(110,150).

Recent studies have suggested that total intravenous anaesthesia with propofol alone may not be an optimal strategy for the prophylaxis of PONV. In a randomized trial done by White et al, found that there were no significant differences between those patients who received dolosetron prophylaxis and those who received TIVA in the incidence of early PONV. Hence the investigators suggest that although TIVA with propofol and dolosetron may be similar in the occurrence of emesis in the early postoperative period, the effects of TIVA may be short lived in offering protection against late PONV and in day care surgeries(159).

Over the past few years, use of TIVA with propofol has become popular especially for day care surgeries(38). One of the major limiting factors for the use of TIVA continues to be the increased expense involved, as economic analyses on the use of TIVA have suggested that it is not generally cost effective for PONV prophylaxis(160–162). Nevertheless in high risk patients, TIVA with propofol is still a reasonable option especially in high risk patients.

CLONIDINE

The antiemetic effect of clonidine is considered to be multifactorial. The significant reduction in the requirements of volatile anaesthetics caused by clonidine could reduce the incidence of anaesthesia related PONV.

A considerable reduction in the sympathetic outflow caused by clonidine also contributes to the reduced incidence of PONV since catecholamine release caused by high sympathetic tone triggers nausea and vomiting. The analgesic effect contributed by clonidine can also influence the PONV incidence(163).

In a study done by Taheri et al, found that oral clonidine premedication considerably reduced the incidence of PONV in patients having day care ear surgical procedures. (164). In a double blinded randomized placebo controlled study by Mubarak et al to investigate the effect of clonidine on PONV in patients undergoing surgery for breast cancer, found that co induction with clonidine caused marked decrease in the incidence of PONV compared to placebo(163). In another study by Handa and Fujii in paediatric strabismus surgery patients they reported that oral clonidine premedication considerably enhances the antiemetic efficacy of propofol in the prevention of PONV(165). Sedation, hypotension, bradycardia and delayed recovery from anaesthesia are the possible side effects.

BENZODIAZEPINES

Benzodiazepines possess anxiolytic, sedative and anaesthetic properties. They reduce the anaesthesia and surgery related anxiety hence reducing the incidence of emesis in the postoperative period. They do not seem to have true antiemetic receptor binding properties, but decreases the anxiety related catecholamine production, thus contributing to the decrease in the incidence of PONV(53,166).

COMBINED ANTIEMETIC THERAPY

The presently available drugs against emesis are not effective as monotherapy. Since the etiology is multifactorial and involves many different receptors, antagonizing only one receptor type is not sufficient in many of the patients.

The administration of antiemetics which act on one type of receptor typically decreases the incidence of PONV by 30 % (12). Hence the concept of balanced antiemesis was introduced which involves combining antiemetics which act at various receptor types which significantly decreases the incidence of PONV(2,63,88,167).

Many different antiemetic combinations have been studied, which often includes a 5HT3 receptor antagonist with a corticosteroid or dopamine antagonist(24,168–172).

MULTIMODAL MANAGEMENT STRATEGIES

The potential for implementation of multimodal therapy in PONV prevention was first demonstrated by Scuderi et al(173). Since the causes of postoperative nausea and vomiting are multifactorial such as patient related, surgical and anaesthesia related risk factors, an approach that goes beyond the use of regular antiemetic drugs alone or in combination needs to be followed to achieve a more holistic prevention of PONV.

A multimodal management of emesis postoperatively includes medications and various strategies which start prior to surgery and continues in the intraoperative period (45). The preoperative strategies include anxiolysis with benzodiazepines(174,175), preoperative administration of dexamethasone(176,177), aprepitant(142,144) and adequate preoperative hydration(178).

The intraoperative approach commences with minimising the factors which promote the occurrence of emesis postop. This includes the use of regional anaesthesia (179), employing propofol for induction and maintanence as total intravenous anaesthesia instead of inhalational anaesthetics and nitrous oxide(173), adequate hydration with crystalloids and colloids (180,181) and use of short acting opioids intraoperatively as part of TIVA which does not increase the occurrence of emesis postop(182).

Post operatively optimal balance should be achieved between opioid use and analgesia since pain itself causes PONV and opioids given as part of the postoperative analgesia management also causes significant PONV.

The ultimate objective is to achieve good pain relief with the minimal use of opioids. NSAIDS have opioid sparing effects thus significantly reduces the incidence of PONV(183–186). Ketamine in minimal doses enables to decrease opioid use. (187) This causes a decrease in emesis postoperatively. (188). The above strategies in addition to the intraoperative use of

more that one antiemetic according to the risks of the individuals greatly reduces the occurrence of emesis postoperatively. (177).

NON PHARMACOLOGICAL TECHNIQUES

ACUPUNCTURE

Acupuncture stimulation of P6 (pericardium 6) is suggested as one of the nonpharmacological modalities of PONV management. This acupuncture point pericardium 6 (Nei guan), the sixth point on the pericardial meridian. This is situated approximately 5 cm proximal to the wrist.

The Cochrane database concluded that acupoint stimulation of P6 would prevent emesis postoperatively in 20 % of patients who have a risk of 70 % (189). The variations of traditional acupuncture such as acupressure, manual acupuncture, laser acupuncture and trancutaneous electrical acupoint stimulation reduces PONV compared to a placebo(190).

AROMATHERAPY

Aromatherapy has been tried in the management of established emesis, but presently there is insufficient evidence that it is effective. This uses the inhalation of essential oils and other

substances which includes isopropyl alcohol and peppermint oil to alleviate physical and emotional symptoms.

A Cochrane review concluded that isopropyl alcohol was more effective compared to saline placebo in PONV, but less effective than the standard antiemetic therapy. Presently there is no reliable evidence on the use of peppermint oil(191).

PATIENTS AND METHODS

This is a double blinded, randomized clinical control trial, approved by the ethics and research committee of our institution.

INCLUSION CRITERIA

ASA (American Society of Anaesthesiology) physical status 1 and 2

Female patients

Age 18 to 65 years

Scheduled for thyroidectomy / mastectomy.

EXCLUSION CRITERIA

Patients who are receiving antiemetics

Patients on steroid medication

Patients on drugs known to cause emesis currently or in the immediate past

Patients with known hypersensitivity to ondansetron or aprepitant

Pregnant and nursing mothers

A few days before the surgery, the details of the study were explained to the eligible patients and a detailed information sheet was given to them. On the day before the surgery, an informed consent was obtained from those who were willing to participate in the study.

The randomization schedule was a computer generated random sequence, done by the biostatistician who was not involved with the study. On the day of the surgery, patients were randomized to receive one of the 2 antiemetic treatments: oral aprepitant 40 mg capsule within 3 hours of the anticipated induction of anaesthesia or injection ondansetron 8 mg I.V (4 ml) towards the end of surgery and 2 more doses in the ward at 8 hourly intervals. Double blinding was done with matching placebos.

A pharmacist who was not involved in the study prepared aprepitant 40 mg capsules, placebo matching aprepitant capsules, injection ondansetron 8 mg (4 ml) vials and matching saline placebo vials.

The anaesthesia technique included optimal premedication and standard anaesthetic agents.

The patient was shifted to the post anaesthesia care unit, monitored for 1 hour and later shifted to the ward. Other antiemetic medications were prohibited prophylactically within 24 hours of surgery. Only rescue therapy was offered on patient request, persistant nausea or an emetic episode.

The type of rescue medication was left to the discretion of the post operative care provider. The duration of anaesthesia and timing of all the emetic episodes and rescue medications given post operatively were recorded.

An independent investigator unaware of the patient's randomization collected the data.

Using a verbal rating scale , patients graded nausea from 0 (no nausea) to 10 (nausea as bad as it could be) at 0-2, 2-12 and 12-24 hours after the operation.

Nausea was defined as an uncomfortable feeling that leads to a tendency to vomit.

Retching was defined as an effort to vomit which is not under voluntary control and that does not cause expulsion of stomach contents.

Vomiting was defined as a expulsion of stomach contents.

An emetic episode was described as a single retch or vomit or any number of continuous vomits or retches.

At 24 hours, patients were asked about their satisfaction with the control of nausea and vomiting using a 5 point scale.

5 – very satisfied

4 – somewhat satisfied

3 – neither satisfied or dissatisfied

2 – somewhat dissatisfied

1 – very dissatisfied

SETTING OF THE STUDY

This study was carried out in the department of Anaesthesiology, Christian Medical College and Hospital, Vellore, which is a tertiary care hospital. The subjects were selected from among those patients posted for elective surgery by the department of Endocrine surgery.

STUDY DESIGN

The two groups in this study were group 1 who received injection ondansetron and capsule placebo and group 2 who received capsule aprepitant and injection placebo. The protocol is as follows.

GROUP 1

Cap. Placebo within 1 hour preoperatively

Inj. Ondansetron 4 ml (8 mg) in the post operative period every 8 hours - 3 doses.

(1st dose was given in theatre at the end of surgery & the next 2 doses were given in the ward).

Since most of the patients included in our study had a BMI of more than 25, we administered injection ondansetron 8 mg (comparable to a dose of 0.1mg/kg).

GROUP 2

Cap. Aprepitant within 1 hour preoperatively (along with the pre medication)

Inj. Placebo 4 ml in the post operative period every 8 hours - 3 doses

(1st dose was given in theatre at the end of surgery & the next 2 doses were given in the ward).

METHOD OF RANDOMIZATION

Block randomization- a computer generated random sequence was done by biostatistician and forwarded directly to the pharmacist for preparation.

METHOD OF ALLOCATION CONCEALMENT

After approval by the institutional review board, the bulk drug Aprepitant 10 grams was purchased from Dr.Reddy's laboratories through Pharmacy and were be packaged as capsules of 40 mg each since Cap.Aprepitant in the dose of 40 mg was not available in the market. Drugs were prepared in the pharmacy special preparation lab in our institution. Double blinding was maintained with matching placebos.

BLINDING AND MASKING

Double blinded - Participant, Investigator and outcome assessor were blinded.

PRIMARY OUTCOME

Incidence of post operative vomiting.

SECONDARY OUTCOMES

Severity of post operative nausea, number of episodes of vomiting, timing of the first vomiting episode, use of rescue antiemetics.

TARGET SAMPLE SIZE AND RATIONALE

60 in each group

The required sample size to show a difference in the proportion of post operative vomiting between aprepitant and ondansetron was found to be 60 in each arm with 80% power and at 5% level of significance with an anticipated post operative nausea of 14% and 36% in the aprepitant and ondansetron respectively.

Formula:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 2PQ}{d^2}$$

P = average proportion of vomiting from both the groups

Q = 1 – P

d = difference in the two proportions

$Z_{1-\alpha/2}$ is the standard normal deviate at 5% level of significance

$Z_{1-\beta}$ is the standard normal deviate for 80% power (192)

STATISTICAL METHODS

The primary outcome in this study is the occurrence of vomiting. Chi square test was used to compare this outcome variable between the two groups to determine the statistical significance.

Similarly, the secondary outcomes in study which includes severity of postoperative nausea, number of episodes of vomiting and use of rescue antiemetics are compared between the two groups using chi-square tests.

The other parameters like the duration of anaesthesia and the timing of the first vomiting episode were compared between the two groups using Mann-Whitney non parametric test.

Data analysis was performed using the software SPSS 14.0 and Microsoft Office Excel 2007.

RESULTS

The two groups in this study are **group 1** who received injection ondansetron and capsule placebo and **group 2** who received capsule aprepitant and the placebo injection. The protocol is as follows.

GROUP 1

Cap. placebo within 1 hour preoperatively and

Inj. Ondansetron 4 ml (8 mg) in the post operative period every 8 hours - 3 doses.

(1st dose was given in theatre at the end of surgery & the next 2 doses were given in the ward).

GROUP 2

Cap.Aprepitant within 1 hour preoperatively (along with the pre medication) and

Inj.placebo 4 ml in the post operative period every 8 hours - 3 doses

(1st dose was given in theatre at the end of surgery & the next 2 doses were given in the ward).

In this study there were 62 patients in group 1 and 63 patients in group 2 making a total of 125 patients. Out of this 125 patients, 5 patients were excluded from the study after randomisation, since they required unanticipated intensive care or high dependency unit admissions or required intraoperative steroids which will influence the assessment of antiemetic efficacy.

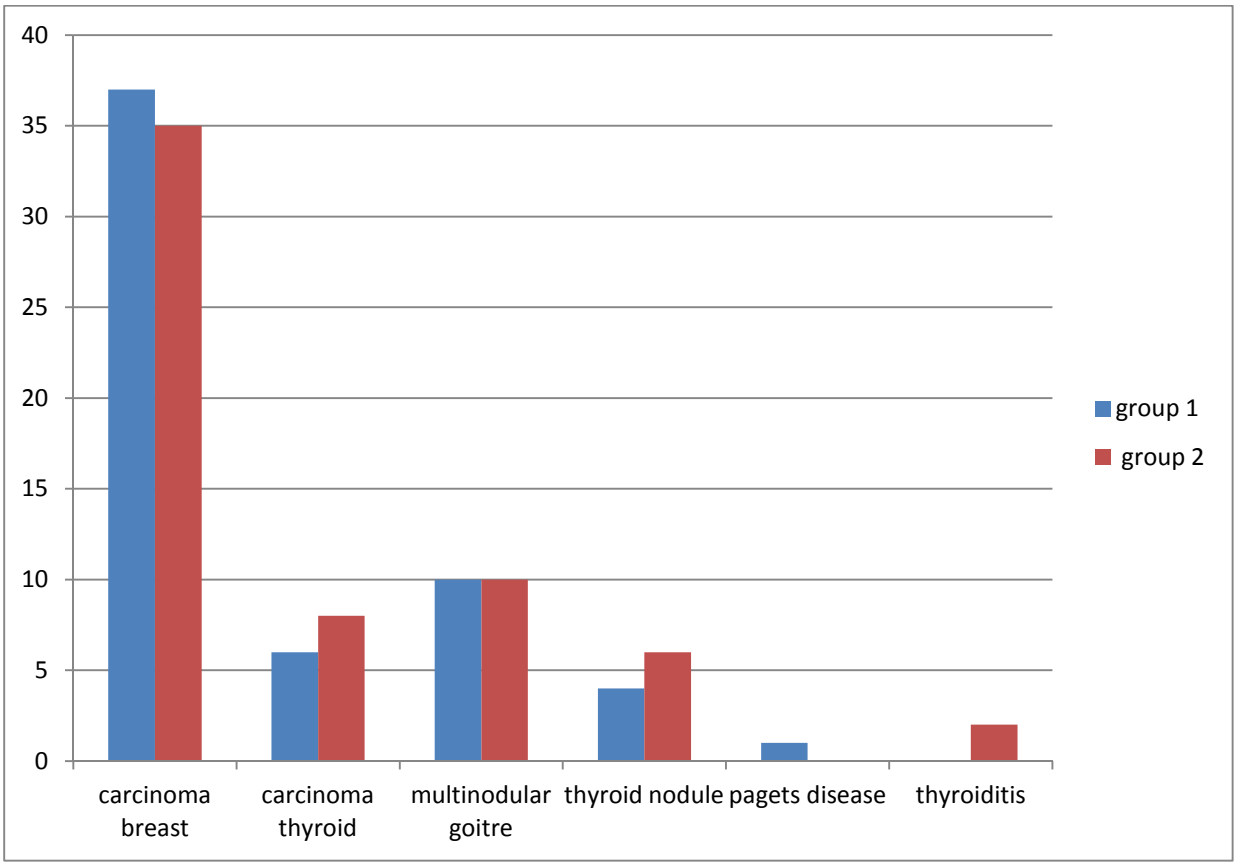
AGE DISRIBUTION AND BODY MASS INDEX

125 patients were recruited for this study, the age and BMI of the participants in both groups matched.

Age group in years	Group 1 (n=62)	Group 2 (n=63)	Total (n=125)
Less than 29	10	8	18
30 - 39	13	13	26
40 - 49	23	20	43
50 & above	16	22	38
BMI	Group 1 (n=59)	Group 2 (n=61)	Total (n=120)
Less than 25	26	27	53
25 - 29	22	22	44
30 & above	11	12	23

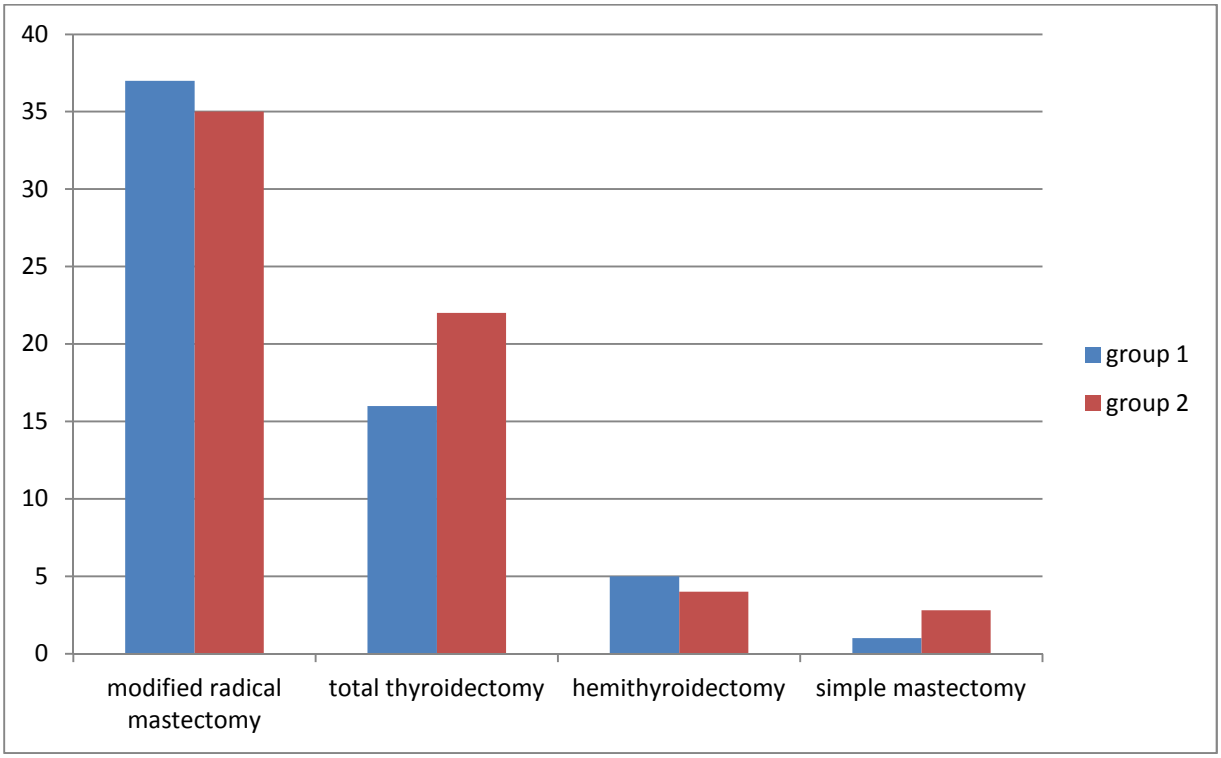
DIAGNOSIS

The distribution of diagnoses in both groups were similar, carcinoma breast being the commonest followed by various thyroid diseases.



OPERATION DONE

The commonest surgery was modified radical mastectomy 72 cases followed by total thyroidectomy 38 cases, and these were equally distributed in both groups. The graph below shows the surgical procedures undergone by the patients in group 1 and group 2



DURATION OF ANAESTHESIA

The median duration of anaesthesia was 115 minutes in group 1 and 110 minutes in group 2.

EMETIC EPISODES IN THE 24 POSTOPERATIVE HOURS

Postop hours	0 – 2		2 - 12		12 - 24	
Emetic episodes	Group 1 (n=59)	Group 2 (n=61)	Group 1 (n=59)	Group 2 (n=61)	Group 1 (n=59)	Group 2 (n=61)
0	47	52	51	52	59	58
1 – 2	11	9	6	7	0	3
> 2	1	0	2	2	0	0
P value	0.49		0.97		0.23	

In the immediate postoperative period, 79.7% in ondansetron group and 85.2% in aprepitant group were free of emesis. A smaller number 18.7% and 14.7% respectively had one emetic episode. Only one patient had more than 2 episodes of vomiting in the ondansetron group. The P value in this period is 0.49 which indicates that both ondansetron and aprepitant are equally effective in the immediate postoperative period.

In the 2 to 12 hour period postoperatively, both the groups displayed similar statistics, 86.4% in the ondansetron group and 85.2% in the aprepitant group did not have vomiting. Both groups had similar number of patients, vomiting score of 1 – 2 (grp 1n=6, grp 2 n=7) and more than 2(n=2 in both groups). The P value of 0.97 is not significant.

After 12 hours, the ondansetron group did better. Most patients in both groups were free of vomiting and 3 patients in the aprepitant group had 1-2 episodes of vomiting. The P value of 0.23 is not significant indicating that both the drugs were equally effective in the 1st postoperative day.

VERBAL RATING SCALE FOR NAUSEA IN THE 24 POSTOPERATIVE HOURS

Postop hours	0 - 2		2 - 12		12-24	
VRS for nausea	Group 1 (n=59)	Group 2 (n=61)	Group 1 (n=59)	Group 2 (n=61)	Group 1 (n=59)	Group 2 (n=61)
0	47	51	48	46	57	57
1-2	2	2	3	4	1	1
>2	10	8	8	11	1	3
P value	.84		.73		.62	

In the first 2 hours after surgery, both the groups had similar verbal rating score for nausea, 79.7% in ondansetron group and 83.6% in aprepitant group were free of nausea. 2 patients in both the groups had a score of 1-2. But a larger number, 17% in ondansetron group and 13.1% in aprepitant group had nausea score of more than 2.

In 2-12 hours of postoperative period, 81.4% in ondansetron group and 75.4% in aprepitant group did not experience nausea. Similar number of patients in both the groups(n=3 in grp 1 and n=4 in grp 2) had nausea score of 1-2.

In the 12-24 hour period, similar number of patients in both the groups were free of nausea (n=57 in both groups). Nausea score of 1-2 were also similar in both the groups (n=1). However 1 patient in ondansetron group and 3 patients in aprepitant group had a nausea score of more than 2.

The P value for both groups were not significant for nausea in the first postoperative day, with the ondansetron group doing slightly better than the aprepitant group.

PEAK NAUSEA SCORE IN THE FIRST 24 POSTOPERATIVE HOURS

Verbal rating score of postoperative nausea between 1 and 3 is rated mild and between 4 and 7 is rated moderate and more that 8 is considered severe in a scale of 0 to 10.

Peak nausea score	Group1 (n=59)	Group 2 (n=61)	Total (n=120)	P value
0	39	37	76	.406
Mild	7	14	21	
moderate	13	10	23	

Of the 120 patients, 21 of them had mild nausea and 23 had moderate nausea indicating that 38.3% of total number of cases experienced mild to moderate nausea.

TIMING OF 1ST VOMITING & USE OF RESCUE ANTIEMETIC (in hours postop)

	Timing of 1 st emesis		1 st rescue antiemetic	
	Group 1 (n=17)	Group 2 (n=18)	Group 1 (n=9)	Group 2 (n=16)
Median(hours)	01:30	02:40	01:00	02:27

In group 1, the first episode of vomiting occurred within a median duration 90 minutes postoperatively. Similarly it 160 minutes in group 2.

The average time to ask for rescue antiemetic was 60 minutes in group 1 and 147 minutes in group 2.

SATISFACTION WITH THE CONTROL OF PONV

5- very satisfied, 4- somewhat satisfied, 3- neither satisfied or dissatisfied, 2- somewhat dissatisfied, 1- very dissatisfied.

Satisfaction rating	Group 1 (n=59)	Group 2 (n=61)	Total (n=120)	P value
1	1	1	2	.676
2	3	2	5	
3	4	4	8	
4	9	16	25	
5	42	38	80	

105 patients (87.5%) inclusive of both groups were satisfied with the intervention for PONV. An equal number of 4 patients (3.3%) in both groups were non committal in their opinion. A small number comprising of 7 patients (5.8%) were dissatisfied with the PONV management. Both the groups displayed good PONV management, hence the P value of 0.676 is insignificant.

DISCUSSION

This study found that the antiemetic efficacy of $5HT_3$ antagonist, ondansetron and neurokinin-1 antagonist, aprepitant was comparable in preventing PONV in patients undergoing thyroidectomy and mastectomy.

All the 120 patients included had an Apfel's simplified risk score of 2 to 3 indicating high risk and received volatile anaesthetics, increasing the PONV incidence to 60 to 80 %. The demographic variables like age and body mass index were comparable in both groups.

Both ondansetron and aprepitant were equally efficacious in preventing emetic episodes, decrease in nausea and delayed time to ask for rescue antiemetic. The possible reasons for both these drugs to be comparable could be because aprepitant 40 mg was given as a single oral dose and injection ondansetron 8 mg was given in 3 doses, 8 hours apart, in the first post operative day.

Aprepitant has an elimination half life of 9-12 hours and hence administered once daily as compared to 5-7 hours for ondansetron. Since ondansetron was the standard antiemetic in our practice, we chose to compare it with aprepitant. Both these drugs have dissimilar half lives, hence it would be unethical to administer a single dose of ondansetron postoperatively.

The outcome in our study is not statistically significant and shows that a single oral dose of aprepitant isequally effective to injection ondansetron given eight hourly over a 24 hour period.

Though statistically not significant, the aprepitant group had a higher incidence of vomiting in the 12-24 hour period, but took longer to have the first episode of vomiting and also to receive the first dose of rescue antiemetic.

Ondansetron group though marginally fared better, had more individuals with nausea. Of the total recruits in the study , 87.5% of them were satisfied with the PONV control, 5.8% were dissatisfied and 3.3% had non committal opinion indicating that both groups were equally effective, offering good patient satisfaction.

We disagree with Diemunsch et al who studied 922 individuals who had open abdominal operationsand found that one oral dose of aprepitant 40 mg or 125 mg were more effective than a single dose of ondansetron 4 mg I.V in preventing vomiting at 24 and 48 hours after surgery(144). We also disagree with Gan et al who conducted a study with similar doses of both the drugs and concluded that aprepitant was better than ondansetron in preventing vomiting in the first 24 to 48 hours(142). We agree with both the authors above who concluded that ondansetron was not inferior to aprepitant in preventing nausea, timing of first vomiting episode and in the use of rescue antiemetics.

In a recent study by Jung et al on postoperative analgesia with fentanyl- based PCA after gynaecological laparoscopy, quoted that oral aprepitant 80 mg was more efficacious in lowering the incidence of PONV in the first 48 hours after surgery. This study also showed a trend towards a more complete response in patients who received aprepitant 125 mg group, though the difference was not statistically significant(193).

Considering its proven efficacy in preventing acute and delayed emesis caused by chemotherapeutic agents in doses of 125 mg on the first day and 80 mg each for the next 2 days, the role of doses higher than 40 mg in PONV management should be considered especially in high risk patients. We were limited to the use of oral aprepitant 40 mg as it is the approved dose by the Drug Controller General of India for PONV.

Neurotransmitter receptor systems involved in transmission of impulses causing nausea and vomiting include cholinergic (muscarinic), dopaminergic (D_2), serotonergic (5-HT_3), histaminergic (H_1) and neurokinin (NK 1) systems. Hence targeting one particular receptor may not confer complete protection against PONV. NK-1RAs may be combined with antiemetics from other classes for optimal efficacy. Thus inclusion of aprepitant to multimodal PONV therapy will have positive attributes of long half-life, lack of sedation, no QTc prolongation and effective prevention of PONV.

Though aprepitant is more expensive than the commonly used antiemetics, the traditional ones are limited in their antiemetic efficacy and their side effects. The routine use of aprepitant to prevent PONV may be expensive. It should be limited to patients at high risk of PONV such as high risk surgeries, risk of severe complications of PONV, hyper-reaction to opioids or anaesthetics, unsuccessful treatment with low-cost antiemetics or a past history of severe PONV and in multimodal antiemetic therapy.

More research is required in determining the optimal dose of neurokinin-1 receptor antagonists in PONV prophylaxis and treatment, the rescue schemes, their interaction with

other antiemetics, possible role of pharmacogenomics in the variation of individual response to PONV and their use in pregnancy, nursing mothers and in paediatric population.

LIMITATIONS

In this study, we did not include a placebo group and hence the incidence of PONV in patients who did not receive any prophylaxis was not known. However, since a high risk patient population was chosen in this study, we felt it was inappropriate to include a placebo group. The dosage of aprepitant was limited to 40 mg as recommended by the Drug controller General of India for PONV use. We did not conduct a cost effective analysis in the prophylactic use of oral aprepitant.

The rescue antiemetic was not standardised in our study. It was left to the discretion of the postoperative care giver. Hence those in the ondansetron group could have received ondansetron as rescue drug. Repeated dosing of ondansetron as rescue drug is not recommended in those already on ondansetron as prophylaxis(194), this may have influenced a small subset of patients in our study.

CONCLUSIONS

A single dose of oral aprepitant has comparable effects to injection ondansetron administered eighth hourly in preventing PONV, the severity of nausea, number of rescue antiemetics and the time to first emetic episode in the 24 hour postoperative period.

BIBLIOGRAPHY

1. Diemunsch P, Joshi GP, Brichant J-F. Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting. Br J Anaesth. 2009 Jul;103(1):7–13.

2. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. - Abstract - Europe PubMed Central [Internet]. [cited 2012 Nov 11]. Available from: http://europepmc.org/abstract/MED/1609990/reload=0;jsessionid=m9f3U9Jb9I9BdJfJ6MjT.6

3. Vomiting [Internet]. Wikipedia, the free encyclopedia. 2012 [cited 2012 Nov 11]. Available from: http://en.wikipedia.org/w/index.php?title=Vomiting&oldid=521273127

4. Google Image Result for http://www.zuniv.net/physiology/book/images/22-4.jpg [Internet]. [cited 2012 Dec 10]. Available from: http://www.google.co.in/imgres?q=3+phases+of+vomiting&start=147&um=1&hl=en&client=firefox-a&sa=N&tbo=d&rls=org.mozilla:en-US:official&channel=np&biw=1360&bih=280&tbm=isch&tbnid=0hMqH26hbCL7jM:&imgrefurl=http://www.zuniv.net/physiology/book/chapter22.html&docid=n_BEHq7fVUAhcM&imgurl=http://www.zuniv.net/physiology/book/images/22-4.jpg&w=663&h=480&ei=6X3FULqMBMLirAf_7oHABw&zoom=1&iact=hc&vpx=12&vpy=-16&dur=609&hovh=190&hovw=263&tx=166&ty=79&sig=109167227173081074255&page=12&tbnh=138&tbnw=191&ndsp=13&ved=1t:429,r:53,s:100,i:163

5. Kranke P, Eberhart LH. [Postoperative nausea and vomiting: rational algorithms for prevention and treatment based on current evidence]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2009 Apr;44(4):286–294; quiz 295.

6. Engelhardt T, Webster NR. Pulmonary aspiration of gastric contents in anaesthesia. Br J Anaesth. 1999 Sep;83(3):453–60.

7. Pre-operative fasting—60 years on from Mendelson [Internet]. [cited 2012 Nov 10]. Available from: http://ceaccp.oxfordjournals.org/content/6/6/215.full

8. McCracken G, Houston P, Lefebvre G. Guideline for the management of postoperative nausea and vomiting. J Obstet Gynaecol Can. 2008 Jul;30(7):600–7, 608–16.

9. George E, Hornuss C, Apfel CC. Neurokinin-1 and novel serotonin antagonists for postoperative and postdischarge nausea and vomiting. Curr Opin Anaesthesiol. 2010 Dec;23(6):714–21.

10. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. Anesthesiol Res Pract. 2011;2011:748031.

11. Apfel CC, Heidrich FM, Jukar-Rao S, Jalota L, Hornuss C, Whelan RP, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth. 2012 Nov;109(5):742–53.

12. Gan TJ. POstoperative nausea and vomiting—can it be eliminated? JAMA. 2002 Mar 13;287(10):1233–6.

13. Naylor RJ, Inall FC. The physiology and pharmacology of postoperative nausea and vomiting. Anaesthesia. 1994 Jan;49 Suppl:2–5.

14. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. Anesth. Analg. 1994 Jan;78(1):7–16.

15. Can Postoperative Nausea and Vomiting Be Predicted? : Anesthesiology [Internet]. [cited 2012 Nov 11]. Available from: http://journals.lww.com/anesthesiology/Fulltext/1999/07000/Can_Postoperative_Nausea_and_Vomiting_Be.18.aspx

16. Apfel CC, Stoecklein K, Lipfert P. PONV: a problem of inhalational anaesthesia? Best Pract Res Clin Anaesthesiol. 2005 Sep;19(3):485–500.

17. Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. Br J Anaesth. 1999 Jul;83(1):104–17.

18. Palazzo MG, Strunin L. Anaesthesia and emesis. I: Etiology. Can Anaesth Soc J. 1984 Mar;31(2):178–87.

19. Kenny GN. Risk factors for postoperative nausea and vomiting. Anaesthesia. 1994 Jan;49 Suppl:6–10.

20. Apfel CC, Greim CA, Haubitz I, Goepfert C, Usadel J, Sefrin P, et al. A risk score to predict the probability of postoperative vomiting in adults. Acta Anaesthesiol Scand. 1998 May;42(5):495–501.

21. Cherian VT, Smith I. Prophylactic ondansetron does not improve patient satisfaction in women using PCA after Caesarean section. Br. J. Anaesth. 2001 Sep 1;87(3):502–4.

22. Honkavaara P, Saarnivaara L, Klemola UM. Prevention of nausea and vomiting with transdermal hyoscine in adults after middle ear surgery during general anaesthesia. Br J Anaesth. 1994 Dec;73(6):763–6.

23. Honkavaara P. Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia. Br. J. Anaesth. 1996 Feb 1;76(2):316–8.

24. Rajeeva V, Bhardwaj N, Batra YK, Dhaliwal LK. Comparison of ondansetron with ondansetron and dexamethasone in prevention of PONV in diagnostic laparoscopy. Can J Anaesth. 1999 Jan;46(1):40–4.

25. Rita L, Goodarzi M, Seleny F. Effect of low dose droperidol on postoperative vomiting in children. Can Anaesth Soc J. 1981 May;28(3):259–62.

26. Forrest JB, Cahalan MK, Rehder K, Goldsmith CH, Levy WJ, Strunin L, et al. Multicenter study of general anesthesia. II. Results. Anesthesiology. 1990 Feb;72(2):262–8.

27. Menstruation Increases the Risk of Nausea and Vomiting after... : Anesthesiology [Internet]. [cited 2012 Nov 11]. Available from: http://journals.lww.com/anesthesiology/Fulltext/1993/02000/Menstruation_Increases_the_Risk_of_Nausea_and.10.aspx

28. Fujii Y, Toyooka H, Tanaka H. Prevention of postoperative nausea and vomiting in female patients during menstruation: comparison of droperidol, metoclopramide and granisetron. Br J Anaesth. 1998 Feb;80(2):248–9.

29. Honkavaara P, Lehtinen AM, Hovorka J, Korttila K. Nausea and vomiting after gynaecological laparoscopy depends upon the phase of the menstrual cycle. Can J Anaesth. 1991 Oct;38(7):876–9.

30. Harmon D, O'Connor P, Gleasa O, Gardiner J. Menstrual cycle irregularity and the incidence of nausea and vomiting after laparoscopy. Anaesthesia. 2000 Dec;55(12):1164–7.

31. Gratz I, Allen E, Afshar M, Joslyn AF, Buxbaum J, Prilliman B. The effects of the menstrual cycle on the incidence of emesis and efficacy of ondansetron. Anesth. Analg. 1996 Sep;83(3):565–9.

32. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth. Analg. 2006 Jun;102(6):1884–98.

33. Mendes MN, Monteiro R de S, Martins FAN da C. Prophylaxis of postoperative nausea and vomiting in morbidly obese patients undergoing laparoscopic gastroplasties: a comparative study among three methods. Revista Brasileira de Anestesiologia. 2009 Oct;59(5):570–6.

34. Koivuranta M, Läärä E, Snåre L, Alahuhta S. A survey of postoperative nausea and vomiting. Anaesthesia. 1997 May;52(5):443–9.

35. Murakawa M, Adachi T, Nakao S, Seo N, Shingu K, Mori K. Activation of the cortical and medullary dopaminergic systems by nitrous oxide in rats: a possible neurochemical basis for psychotropic effects and postanesthetic nausea and vomiting. Anesth. Analg. 1994 Feb;78(2):376–81.

36. Brattwall M, Warrén Stomberg M, Rawal N, Segerdahl M, Houltz E, Jakobsson J. Postoperative impact of regular tobacco use, smoking or snuffing, a prospective multi-center study. Acta Anaesthesiol Scand. 2010 Mar;54(3):321–7.

37. Atanasova M, Hinev S. [Preoperative anxiety and its influence over the postoperative nausea and vomiting]. Khirurgiia (Sofiia). 2009;(6):40–3.

38. Le TP, Gan TJ. Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. Anesthesiol Clin. 2010 Jun;28(2):225–49.

39. PONV_a_Review_of_Current_Literature__200.pdf [Internet]. [cited 2012 Nov 18]. Available from: http://facweb.northseattle.edu/cduren/North%20Seattle%20AT%20Program%202011-2012%20CJ%20Duren-

Instructor/ATEC%20008%20Clinical%20Monitoring/Bonus%20Quizzes/PONV%20Post op%20Nausea%20and%20Vomiting/PONV_a_Review_of_Current_Literature__200.pdf

40. Sonner JM, Hynson JM, Clark O, Katz JA. Nausea and vomiting following thyroid and parathyroid surgery. J Clin Anesth. 1997 Aug;9(5):398–402.

41. Kim GH, Ahn HJ, Kim H-S, Bang SR, Cho H-S, Yang M, et al. Postoperative nausea and vomiting after endoscopic thyroidectomy: total intravenous vs. balanced anesthesia. Korean J Anesthesiol. 2011 Jun;60(6):416–21.

42. Zhou H, Xu H, Zhang J, Wang W, Wang Y, Hu Z. Combination of dexamethasone and tropisetron before thyroidectomy to alleviate postoperative nausea, vomiting, and pain: randomized controlled trial. World J Surg. 2012 Jun;36(6):1217–24.

43. Moon YE, Joo J, Kim JE, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. Br J Anaesth. 2012 Mar;108(3):417–22.

44. Bakshi SG, Jibhkate B, Sareen R, Badwe R. Nausea and vomiting after breast cancer surgery, and relationship with tumor receptor status. Journal of Anesthesia. 2011 Nov 13;26(2):187–95.

45. Gärtner R, Kroman N, Callesen T, Kehlet H. Multimodal prevention of pain, nausea and vomiting after breast cancer surgery. Minerva Anestesiol. 2010 Oct;76(10):805–13.

46. Sadhasivam S, Saxena A, Kathirvel S, Kannan TR, Trikha A, Mohan V. The safety and efficacy of prophylactic ondansetron in patients undergoing modified radical mastectomy. Anesth. Analg. 1999 Dec;89(6):1340–5.

47. Oddby-Muhrbeck E, Jakobsson J, Andersson L, Askergren J. Postoperative nausea and vomiting. A comparison between intravenous and inhalation anaesthesia in breast surgery. Acta Anaesthesiol Scand. 1994 Jan;38(1):52–6.

48. Fujii Y, Tanaka H, Kawasaki T. Benefits and risks of granisetron versus ramosetron for nausea and vomiting after breast surgery: a randomized, double-blinded, placebo-controlled trial. Am J Ther. 2004 Aug;11(4):278–82.

49. Abou Zeid H, Al-Gahamdi A, Abdul-Hadi M. Dolasetron decreases postoperative nausea and vomiting after breast surgery. Breast J. 2002 Aug;8(4):216–21.

50. Kakugawa Y, Minami Y, Tateno H, Inoue H, Fujiya T. Relation of serum levels of estrogen and dehydroepiandrosterone sulfate to hormone receptor status among postmenopausal women with breast cancer. Breast Cancer. 2007;14(3):269–76.

51. Phillips BT, Wang ED, Rodman AJ, Watterson PA, Smith KL, Finical SJ, et al. Anesthesia duration as a marker for surgical complications in office-based plastic surgery. Ann Plast Surg. 2012 Oct;69(4):408–11.

52. Splinter WM, MacNeill HB, Menard EA, Rhine EJ, Roberts DJ, Gould MH. Midazolam reduces vomiting after tonsillectomy in children. Can J Anaesth. 1995 Mar;42(3):201–3.

53. Khalil SN, Berry JM, Howard G, Lawson K, Hanis C, Mazow ML, et al. The antiemetic effect of lorazepam after outpatient strabismus surgery in children. Anesthesiology. 1992 Nov;77(5):915–9.

54. Leslie JB. How can we best prevent or treat postoperative nausea and vomiting? Curr Opin Anaesthesiol. 2001 Dec;14(6):623–7.

55. Rüsch D, Becke K, Eberhart LHJ, Franck M, Hönig A, Morin AM, et al. [Postoperative nausea and vomiting (PONV) - recommendations for risk assessment, prophylaxis and therapy - results of an expert panel meeting]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2011 Mar;46(3):158–70.

56. Pompeo DA, Rossi LA. [The administration of volatile anesthetics as a factor related to nausea and vomiting in the postoperative period: integrative review of the literature]. Rev Gaucha Enferm. 2008 Mar;29(1):121–8.

57. Alghanem SM, Massad IM, Rashed EM, Abu-Ali HM, Daradkeh SS. Optimization of anesthesia antiemetic measures versus combination therapy using dexamethasone or ondansetron for the prevention of postoperative nausea and vomiting. Surg Endosc. 2010 Feb;24(2):353–8.

58. Mraovic B, Simurina T, Sonicki Z, Skitarelic N, Gan TJ. The dose-response of nitrous oxide in postoperative nausea in patients undergoing gynecologic laparoscopic surgery: a preliminary study. Anesth. Analg. 2008 Sep;107(3):818–23.

59. Majstorović BM, Radulović RB, Dukić VB, Kastratović DA, Popović NP, Gajić MM. [Effects of nitrous oxide on middle ear pressure]. Med. Pregl. 2007 Oct;60(9-10):473–8.

60. Fernández-Guisasola J, Gómez-Arnau JI, Cabrera Y, del Valle SG. Association between nitrous oxide and the incidence of postoperative nausea and vomiting in adults: a systematic review and meta-analysis. Anaesthesia. 2010 Apr;65(4):379–87.

61. Leslie K, Myles PS, Chan MTV, Paech MJ, Peyton P, Forbes A, et al. Risk factors for severe postoperative nausea and vomiting in a randomized trial of nitrous oxide-based vs nitrous oxide-free anaesthesia. Br J Anaesth. 2008 Oct;101(4):498–505.

62. Gilani SM, Sofi K. Is nitrous oxide necessary for general anaesthesia? J Ayub Med Coll Abbottabad. 2008 Dec;20(4):149–52.

63. Tramèr MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues. Acta Anaesthesiol Scand. 2001 Jan;45(1):4–13.

64. Lee DW, Lee HG, Jeong CY, Jeong SW, Lee SH. Postoperative nausea and vomiting after mastoidectomy with tympanoplasty: a comparison between TIVA with propofol-remifentanil and balanced anesthesia with sevoflurane-remifentanil. Korean J Anesthesiol. 2011 Nov;61(5):399–404.

65. Jellish WS, Leonetti JP, Murdoch JR, Fowles S. Propofol-based anesthesia as compared with standard anesthetic techniques for middle ear surgery. Otolaryngol Head Neck Surg. 1995 Feb;112(2):262–7.

66. Klockgether-Radke A, Piorek V, Crozier T, Kettler D. Nausea and vomiting after laparoscopic surgery: a comparison of propofol and thiopentone/halothane anaesthesia. Eur J Anaesthesiol. 1996 Jan;13(1):3–9.

67. Tramèr M, Moore A, McQuay H. Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. Br J Anaesth. 1997 Mar;78(3):247–55.

68. Chanvej L, Kijsirikul S, Thongsuksai P, Naheem L. Post-operative nausea and vomiting in out-patient gynecologic laparoscopy: a comparison of thiopental-nitrous oxide, propofol-nitrous oxide and total intravenous anesthesia using propofol. J Med Assoc Thai. 2001 May;84(5):697–704.

69. Tramèr MR, Fuchs-Buder T. Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. Br J Anaesth. 1999 Mar;82(3):379–86.

70. Ratra CK, Badola RP, Bhargava KP. A study of factors concerned in emesis during spinal anaesthesia. Br J Anaesth. 1972 Nov;44(11):1208–11.

71. Griffiths JD, Gyte GM, Paranjothy S, Brown HC, Broughton HK, Thomas J. Interventions for preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section. Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 1996 [cited 2012 Nov 28]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007579.pub2/abstract

72. Chatellier A, Dugué AE, Caufourier C, Maksud B, Compère JF, Bénateau H. [Inferior alveolar nerve block with ropivacaine: Effect on nausea and vomiting after mandibular osteotomy.]. Rev Stomatol Chir Maxillofac. 2012 Nov 16;

73. Cai H-D, Lin C-Z, Yu C-X, Lin X-Z. Bilateral superficial cervical plexus block reduces postoperative nausea and vomiting and early postoperative pain after thyroidectomy. J. Int. Med. Res. 2012;40(4):1390–8.

74. Chatterjee S, Rudra A, Sengupta S. Current Concepts in the Management of Postoperative Nausea and Vomiting. Anesthesiology Research and Practice. 2011;2011:1–10.

75. Postoperative Nausea and Vomiting: Its Etiology, Treatment,... : Anesthesiology [Internet]. [cited 2012 Nov 11]. Available from: http://journals.lww.com/anesthesiology/Fulltext/1992/07000/Postoperative_Nausea_and_Vomiting__Its_Etiology,.23.aspx

76. Charoenkwan K, Phillipson G, Vutyavanich T. Early versus delayed oral fluids and food for reducing complications after major abdominal gynaecologic surgery. Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 1996 [cited 2012 Nov 29]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004508.pub3/abstract

77. Sadhasivam S, Shende D, Madan R. Prophylactic ondansetron in prevention of postoperative nausea and vomiting following pediatric strabismus surgery: a dose-response study. Anesthesiology. 2000 Apr;92(4):1035–42.

78. Tang J, Watcha MF, White PF. A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. Anesth. Analg. 1996 Aug;83(2):304–13.

79. A Simplified Risk Score for Predicting Postoperative Nausea... : Anesthesiology [Internet]. [cited 2012 Nov 11]. Available from: http://journals.lww.com/anesthesiology/Fulltext/1999/09000/A_Simplified_Risk_Score_for_Predicting.22.aspx

80. Apfel CC, Roewer N, Korttila K. How to study postoperative nausea and vomiting. Acta Anaesthesiol Scand. 2002 Sep;46(8):921–8.

81. Jokinen J, Smith AF, Roewer N, Eberhart LHJ, Kranke P. Management of postoperative nausea and vomiting: how to deal with refractory PONV. Anesthesiol Clin. 2012 Sep;30(3):481–93.

82. Henzi I, Sonderegger J, Tramèr MR. Efficacy, dose-response, and adverse effects of droperidol for prevention of postoperative nausea and vomiting. Can J Anaesth. 2000 Jun;47(6):537–51.

83. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N. Engl. J. Med. 2004 Jun 10;350(24):2441–51.

84. Leslie JB, Gan TJ. Meta-analysis of the safety of 5-HT3 antagonists with dexamethasone or droperidol for prevention of PONV. Ann Pharmacother. 2006 May;40(5):856–72.

85. White PF. Droperidol: a cost-effective antiemetic for over thirty years. Anesth. Analg. 2002 Oct;95(4):789–90.

86. Habib AS, Gan TJ. The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. J Clin Anesth. 2008 Feb;20(1):35–9.

87. Dershwitz M. Droperidol: should the black box be light gray? J Clin Anesth. 2002 Dec;14(8):598–603.

88. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. Drugs. 2000 Feb;59(2):213–43.

89. Quaynor H, Raeder JC. Incidence and severity of postoperative nausea and vomiting are similar after metoclopramide 20 mg and ondansetron 8 mg given by the end of laparoscopic cholecystectomies. Acta Anaesthesiol Scand. 2002 Jan;46(1):109–13.

90. Harrington RA, Hamilton CW, Brogden RN, Linkewich JA, Romankiewicz JA, Heel RC. Metoclopramide. An updated review of its pharmacological properties and clinical use. Drugs. 1983 May;25(5):451–94.

91. Henzi I, Walder B, Tramèr MR. Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies. Br J Anaesth. 1999 Nov;83(5):761–71.

92. Carlisle JB. The analysis of 168 randomised controlled trials to test data integrity. Anaesthesia. 2012 May;67(5):521–37.

93. Pandit JJ. On statistical methods to test if sampling in trials is genuinely random. Anaesthesia. 2012 May;67(5):456–62.

94. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth. Analg. 2007 Dec;105(6):1615–1628, table of contents.

95. De Oliveira GS Jr, Castro-Alves LJ, Chang R, Yaghmour E, McCarthy RJ. Systemic metoclopramide to prevent postoperative nausea and vomiting: a meta-analysis without Fujii's studies. Br J Anaesth. 2012 Nov;109(5):688–97.

96. McCarthy BG, Peroutka SJ. Differentiation of muscarinic cholinergic receptor subtypes in human cortex and pons: implications for anti-motion sickness therapy. Aviat Space Environ Med. 1988 Jan;59(1):63–6.

97. Takeda N, Morita M, Hasegawa S, Horii A, Kubo T, Matsunaga T. Neuropharmacology of motion sickness and emesis. A review. Acta Otolaryngol Suppl. 1993;501:10–5.

98. Cameron D, Gan TJ. Management of postoperative nausea and vomiting in ambulatory surgery. Anesthesiol Clin North America. 2003 Jun;21(2):347–65.

99. Sah N, Ramesh V, Kaul B, Dalby P, Shestak K, Vallejo MC. Transdermal scopolamine patch in addition to ondansetron for postoperative nausea and vomiting prophylaxis in patients undergoing ambulatory cosmetic surgery. J Clin Anesth. 2009 Jun;21(4):249–52.

100. Scuderi PE. Pharmacology of antiemetics. Int Anesthesiol Clin. 2003;41(4):41–66.

101. Cholwill JM, Wright W, Hobbs GJ, Curran J. Comparison of ondansetron and cyclizine for prevention of nausea and vomiting after day-case gynaecological laparoscopy. Br J Anaesth. 1999 Oct;83(4):611–4.

102. Kranke P, Morin AM, Roewer N, Eberhart LHJ. Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. Acta Anaesthesiol Scand. 2002 Mar;46(3):238–44.

103. George E, Hornuss C, Apfel CC. Neurokinin-1 and novel serotonin antagonists for postoperative and postdischarge nausea and vomiting. Curr Opin Anaesthesiol. 2010 Dec;23(6):714–21.

104. Barnes NM, Hales TG, Lummis SCR, Peters JA. The 5-HT3 receptor--the relationship between structure and function. Neuropharmacology. 2009 Jan;56(1):273–84.

105. Gyermek L. 5-HT3 receptors: pharmacologic and therapeutic aspects. J Clin Pharmacol. 1995 Sep;35(9):845–55.

106. Russell D, Kenny GN. 5-HT3 antagonists in postoperative nausea and vomiting. Br J Anaesth. 1992;69(7 Suppl 1):63S–68S.

107. Loewen PS, Marra CA, Zed PJ. 5-HT3 receptor antagonists vs traditional agents for the prophylaxis of postoperative nausea and vomiting. Can J Anaesth. 2000 Oct;47(10):1008–18.

108. De Leon A. Palonosetron (Aloxi): a second-generation 5-HT_3 receptor antagonist for chemotherapy-induced nausea and vomiting. Proc (Bayl Univ Med Cent). 2006 Oct;19(4):413–6.

109. Gan TJ. Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy. CNS Drugs. 2007;21(10):813–33.

110. Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006;(3):CD004125.

111. Dershwitz M, Conant JA, Chang Y, Rosow CE, Connors PM. A randomized, double-blind, dose-response study of ondansetron in the prevention of postoperative nausea and vomiting. J Clin Anesth. 1998 Jun;10(4):314–20.

112. Scuderi P, Wetchler B, Sung YF, Mingus M, DuPen S, Claybon L, et al. Treatment of postoperative nausea and vomiting after outpatient surgery with the 5-HT3 antagonist ondansetron. Anesthesiology. 1993 Jan;78(1):15–20.

113. Claybon L. Single dose intravenous ondansetron for the 24-hour treatment of postoperative nausea and vomiting. Anaesthesia. 1994 Jan;49 Suppl:24–9.

114. Tramèr MR, Moore RA, Reynolds DJ, McQuay HJ. A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting. BMJ. 1997 Apr 12;314(7087):1088–92.

115. Tang J, Wang B, White PF, Watcha MF, Qi J, Wender RH. The effect of timing of ondansetron administration on its efficacy, cost-effectiveness, and cost-benefit as a prophylactic antiemetic in the ambulatory setting. Anesth. Analg. 1998 Feb;86(2):274–82.

116. Sun R, Klein KW, White PF. The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. Anesth. Analg. 1997 Feb;84(2):331–6.

117. Korttila KT, Jokinen JD. Timing of administration of dolasetron affects dose necessary to prevent postoperative nausea and vomiting. J Clin Anesth. 2004 Aug;16(5):364–70.

118. Chen X, Tang J, White PF, Wender RH, Quon R, Sloninsky A, et al. The effect of timing of dolasetron administration on its efficacy as a prophylactic antiemetic in the ambulatory setting. Anesth. Analg. 2001 Oct;93(4):906–11.

119. Andrews PL, Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR. Are all 5-HT3 receptor antagonists the same? Eur. J. Cancer. 1992;28A Suppl 1:S2–6.

120. Mikawa K, Takao Y, Nishina K, Shiga M, Maekawa N, Obara H. Optimal dose of granisetron for prophylaxis against postoperative emesis after gynecological surgery. Anesth. Analg. 1997 Sep;85(3):652–6.

121. D'Angelo R, Philip B, Gan TJ, Kovac A, Hantler C, Doblar D, et al. A randomized, double-blind, close-ranging, pilot study of intravenous granisetron in the prevention of postoperative nausea and vomiting in patients abdominal hysterectomy. Eur J Anaesthesiol. 2005 Oct;22(10):774–9.

122. Hafermann MJ, Namdar R, Seibold GE, Page RL 2nd. Effect of intravenous ondansetron on QT interval prolongation in patients with cardiovascular disease and additional risk factors for torsades: a prospective, observational study. Drug Healthc Patient Saf. 2011;3:53–8.

123. Keller GA, Ponte ML, Di Girolamo G. Other drugs acting on nervous system associated with QT-interval prolongation. Curr Drug Saf. 2010 Jan;5(1):105–11.

124. Charbit B, Alvarez JC, Dasque E, Abe E, Démolis JL, Funck-Brentano C. Droperidol and ondansetron-induced QT interval prolongation: a clinical drug interaction study. Anesthesiology. 2008 Aug;109(2):206–12.

125. Kovac AL, Eberhart L, Kotarski J, Clerici G, Apfel C. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period. Anesth. Analg. 2008 Aug;107(2):439–44.

126. Rojas C, Stathis M, Thomas AG, Massuda EB, Massuda EB, Alt J, et al. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. Anesth. Analg. 2008 Aug;107(2):469–78.

127. Rojas C, Thomas AG, Alt J, Stathis M, Zhang J, Rubenstein EB, et al. Palonosetron triggers 5-HT(3) receptor internalization and causes prolonged inhibition of receptor function. Eur. J. Pharmacol. 2010 Jan 25;626(2-3):193–9.

128. Rojas C, Li Y, Zhang J, Stathis M, Alt J, Thomas AG, et al. The antiemetic 5-HT3 receptor antagonist Palonosetron inhibits substance P-mediated responses in vitro and in vivo. J. Pharmacol. Exp. Ther. 2010 Nov;335(2):362–8.

129. Grover VK, Mathew PJ, Hegde H. Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomised, double-blind placebo controlled study. Anaesthesia. 2009 Jun;64(6):595–600.

130. Rueffert H, Thieme V, Wallenborn J, Lemnitz N, Bergmann A, Rudlof K, et al. Do variations in the 5-HT3A and 5-HT3B serotonin receptor genes (HTR3A and HTR3B) influence the occurrence of postoperative vomiting? Anesth. Analg. 2009 Nov;109(5):1442–7.

131. Morimoto M, Morita N, Ozawa H, Yokoyama K, Kawata M. Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. Neurosci. Res. 1996 Nov;26(3):235–69.

132. Funder JW. Mineralocorticoid receptors and glucocorticoid receptors. Clin. Endocrinol. (Oxf). 1996 Dec;45(6):651–6.

133. Henzi I, Walder B, Tramèr MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth. Analg. 2000 Jan;90(1):186–94.

134. Wang JJ, Ho ST, Lee SC, Liu YC, Ho CM. The use of dexamethasone for preventing postoperative nausea and vomiting in females undergoing thyroidectomy: a dose-ranging study. Anesth. Analg. 2000 Dec;91(6):1404–7.

135. Wang JJ, Ho ST, Tzeng JI, Tang CS. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesth. Analg. 2000 Jul;91(1):136–9.

136. Karanicolas PJ, Smith SE, Kanbur B, Davies E, Guyatt GH. The impact of prophylactic dexamethasone on nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. Ann. Surg. 2008 Nov;248(5):751–62.

137. Elhakim M, Nafie M, Mahmoud K, Atef A. Dexamethasone 8 mg in combination with ondansetron 4 mg appears to be the optimal dose for the prevention of nausea and vomiting after laparoscopic cholecystectomy. Can J Anaesth. 2002 Nov;49(9):922–6.

138. Tattersall FD, Rycroft W, Francis B, Pearce D, Merchant K, MacLeod AM, et al. Tachykinin NK1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. Neuropharmacology. 1996;35(8):1121–9.

139. Saito R, Takano Y, Kamiya H-O. Roles of substance P and NK(1) receptor in the brainstem in the development of emesis. J. Pharmacol. Sci. 2003 Feb;91(2):87–94.

140. Minami M, Endo T, Kikuchi K, Ihira E, Hirafuji M, Hamaue N, et al. Antiemetic effects of sendide, a peptide tachykinin NK1 receptor antagonist, in the ferret. Eur. J. Pharmacol. 1998 Dec 11;363(1):49–55.

141. Apfel CC, Malhotra A, Leslie JB. The role of neurokinin-1 receptor antagonists for the management of postoperative nausea and vomiting. Curr Opin Anaesthesiol. 2008 Aug;21(4):427–32.

142. Gan TJ, Apfel CC, Kovac A, Philip BK, Singla N, Minkowitz H, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. Anesth. Analg. 2007 May;104(5):1082–1089, tables of contents.

143. Tattersall FD, Rycroft W, Hill RG, Hargreaves RJ. Enantioselective inhibition of apomorphine-induced emesis in the ferret by the neurokinin1 receptor antagonist CP-99,994. Neuropharmacology. 1994 Feb;33(2):259–60.

144. Diemunsch P, Gan TJ, Philip BK, Girao MJ, Eberhart L, Irwin MG, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth. 2007 Aug;99(2):202–11.

145. emend_pi.pdf [Internet]. [cited 2012 Dec 9]. Available from: http://www.merck.com/product/usa/pi_circulars/e/emend/emend_pi.pdf

146. Diemunsch P, Grélot L. Potential of substance P antagonists as antiemetics. Drugs. 2000 Sep;60(3):533–46.

147. DiIorio TM, Sharkey PF, Hewitt AM, Parvizi J. Antiemesis after total joint arthroplasty: does a single preoperative dose of aprepitant reduce nausea and vomiting? Clin. Orthop. Relat. Res. 2010 Sep;468(9):2405–9.

148. Diemunsch P, Joshi GP, Brichant J-F. Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting. Br J Anaesth. 2009 Jul;103(1):7–13.

149. Lim R, Morrill JM, Prushik SG, Reed KL, Gower AC, Leeman SE, et al. An FDA approved neurokinin-1 receptor antagonist is effective in reducing intraabdominal adhesions when administered intraperitoneally, but not orally. J. Gastrointest. Surg. 2008 Oct;12(10):1754–61.

150. Reid K, Palmer JL, Wright RJ, Clemes SA, Troakes C, Somal HS, et al. Comparison of the neurokinin-1 antagonist GR205171, alone and in combination with the 5-HT3 antagonist ondansetron, hyoscine and placebo in the prevention of motion-induced nausea in man. Br J Clin Pharmacol. 2000 Jul;50(1):61–4.

151. Singla NK, Singla SK, Chung F, Kutsogiannis DJ, Blackburn L, Lane SR, et al. Phase II study to evaluate the safety and efficacy of the oral neurokinin-1 receptor antagonist casopitant (GW679769) administered with ondansetron for the prevention of postoperative and postdischarge nausea and vomiting in high-risk patients. Anesthesiology. 2010 Jul;113(1):74–82.

152. Altorjay A, Melson T, Chinachoit T, Kett A, Aqua K, Levin J, et al. Casopitant and ondansetron for postoperative nausea and vomiting prevention in women at high risk for emesis: a phase 3 study. Arch Surg. 2011 Feb;146(2):201–6.

153. Rothenberg DM, Parnass SM, Litwack K, McCarthy RJ, Newman LM. Efficacy of ephedrine in the prevention of postoperative nausea and vomiting. Anesth. Analg. 1991 Jan;72(1):58–61.

154. DeBalli P. The use of propofol as an antiemetic. Int Anesthesiol Clin. 2003;41(4):67–77.

155. Cechetto DF, Diab T, Gibson CJ, Gelb AW. The effects of propofol in the area postrema of rats. Anesth. Analg. 2001 Apr;92(4):934–42.

156. Gan TJ, Glass PS, Howell ST, Canada AT, Grant AP, Ginsberg B. Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. Anesthesiology. 1997 Oct;87(4):779–84.

157. Gupta A, Stierer T, Zuckerman R, Sakima N, Parker SD, Fleisher LA. Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review. Anesth. Analg. 2004 Mar;98(3):632–641, table of contents.

158. Visser K, Hassink EA, Bonsel GJ, Moen J, Kalkman CJ. Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-

nitrous oxide: postoperative nausea with vomiting and economic analysis. Anesthesiology. 2001 Sep;95(3):616–26.

159. White H, Black RJ, Jones M, Mar Fan GC. Randomized comparison of two anti-emetic strategies in high-risk patients undergoing day-case gynaecological surgery. Br J Anaesth. 2007 Apr;98(4):470–6.

160. Visser K, Hassink EA, Bonsel GJ, Moen J, Kalkman CJ. Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide: postoperative nausea with vomiting and economic analysis. Anesthesiology. 2001 Sep;95(3):616–26.

161. Smith I, Thwaites AJ. Target-controlled propofol vs. sevoflurane: a double-blind, randomised comparison in day-case anaesthesia. Anaesthesia. 1999 Aug;54(8):745–52.

162. Ozkose Z, Ercan B, Unal Y, Yardim S, Kaymaz M, Dogulu F, et al. Inhalation versus total intravenous anesthesia for lumbar disc herniation: comparison of hemodynamic effects, recovery characteristics, and cost. J Neurosurg Anesthesiol. 2001 Oct;13(4):296–302.

163. Oddby-Muhrbeck E, Eksborg S, Bergendahl HTG, Muhrbeck O, Lönnqvist PA. Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. Anesthesiology. 2002 May;96(5):1109–14.

164. Taheri A, Javadimanesh MA, Ashraf H. The effect of oral clonidine premedication on nausea and vomiting after ear surgery. Middle East J Anesthesiol. 2010 Jun;20(5):691–4.

165. Handa F, Fujii Y. The efficacy of oral clonidine premedication in the prevention of postoperative vomiting in children following strabismus surgery. Paediatr Anaesth. 2001 Jan;11(1):71–4.

166. Splinter WM, MacNeill HB, Menard EA, Rhine EJ, Roberts DJ, Gould MH. Midazolam reduces vomiting after tonsillectomy in children. Can J Anaesth. 1995 Mar;42(3):201–3.

167. Heffernan AM, Rowbotham DJ. Postoperative nausea and vomiting--time for balanced antiemesis? Br J Anaesth. 2000 Nov;85(5):675–7.

168. McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. Anesth. Analg. 1994 Nov;79(5):961–4.

169. Splinter WM, Rhine EJ. Low-dose ondansetron with dexamethasone more effectively decreases vomiting after strabismus surgery in children than does high-dose ondansetron. Anesthesiology. 1998 Jan;88(1):72–5.

170. McKenzie R, Uy NT, Riley TJ, Hamilton DL. Droperidol/ondansetron combination controls nausea and vomiting after tubal banding. Anesth. Analg. 1996 Dec;83(6):1218–22.

171. López-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Sáez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth. 1996 Jun;76(6):835–40.

172. Ahmed AB, Hobbs GJ, Curran JP. Randomized, placebo-controlled trial of combination antiemetic prophylaxis for day-case gynaecological laparoscopic surgery. Br J Anaesth. 2000 Nov;85(5):678–82.

173. Scuderi PE, James RL, Harris L, Mims GR 3rd. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. Anesth. Analg. 2000 Dec;91(6):1408–14.

174. Fujii Y, Itakura M. A prospective, randomized, double-blind, placebo-controlled study to assess the antiemetic effects of midazolam on postoperative nausea and vomiting in women undergoing laparoscopic gynecologic surgery. Clin Ther. 2010 Aug;32(9):1633–7.

175. Jung JS, Park JS, Kim SO, Lim DG, Park SS, Kwak KH, et al. Prophylactic antiemetic effect of midazolam after middle ear surgery. Otolaryngol Head Neck Surg. 2007 Nov;137(5):753–6.

176. Gómez-Hernández J, Orozco-Alatorre AL, Domínguez-Contreras M, Oceguera-Villanueva A, Gómez-Romo S, Alvarez Villaseñor AS, et al. Preoperative dexamethasone reduces postoperative pain, nausea and vomiting following mastectomy for breast cancer. BMC Cancer. 2010;10:692.

177. Chandrakantan A, Glass PSA. Multimodal therapies for postoperative nausea and vomiting, and pain. Br J Anaesth. 2011 Dec;107 Suppl 1:i27–40.

178. Jensen K, Kehlet H, Lund CM. Post-operative recovery profile after laparoscopic cholecystectomy: a prospective, observational study of a multimodal anaesthetic regime. Acta Anaesthesiol Scand. 2007 Apr;51(4):464–71.

179. Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anesthesia: a review. Anesthesiology. 2003 Feb;98(2):530–47.

180. Chaudhary S, Sethi AK, Motiani P, Adatia C. Pre-operative intravenous fluid therapy with crystalloids or colloids on post-operative nausea & vomiting. Indian J. Med. Res. 2008 Jun;127(6):577–81.

181. Haentjens LL, Ghoundiwal D, Touhiri K, Renard M, Engelman E, Anaf V, et al. Does infusion of colloid influence the occurrence of postoperative nausea and vomiting after elective surgery in women? Anesth. Analg. 2009 Jun;108(6):1788–93.

182. Dershwitz M, Michałowski P, Chang Y, Rosow CE, Conlay LA. Postoperative nausea and vomiting after total intravenous anesthesia with propofol and remifentanil or alfentanil: how important is the opioid? J Clin Anesth. 2002 Jun;14(4):275–8.

183. Camu F, Beecher T, Recker DP, Verburg KM. Valdecoxib, a COX-2-specific inhibitor, is an efficacious, opioid-sparing analgesic in patients undergoing hip arthroplasty. Am J Ther. 2002 Feb;9(1):43–51.

184. Salman MA, Yücebaş ME, Coşkun F, Aypar U. Day-case laparoscopy: a comparison of prophylactic opioid, NSAID or local anesthesia for postoperative analgesia. Acta Anaesthesiol Scand. 2000 May;44(5):536–42.

185. Shende D, Das K. Comparative effects of intravenous ketorolac and pethidine on perioperative analgesia and postoperative nausea and vomiting (PONV) for paediatric strabismus surgery. Acta Anaesthesiol Scand. 1999 Mar;43(3):265–9.

186. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology. 2005 Jun;102(6):1249–60.

187. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth. Analg. 2004 Aug;99(2):482–495, table of contents.

188. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.

189. Lee A, Fan LT. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2009;(2):CD003281.

190. Lee A, Done ML. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. Anesth. Analg. 1999 Jun;88(6):1362–9.

191. Hines S, Steels E, Chang A, Gibbons K. Aromatherapy for treatment of postoperative nausea and vomiting. Cochrane Database Syst Rev. 2012;4:CD007598.

192. Sahai H, Khurshid A. Formulae and tables for the determination of sample sizes and power in clinical trials for testing differences in proportions for the two-sample design: a review. Stat Med. 1996 Jan 15;15(1):1–21.

193. Jung WS, Kim YB, Park HY, Choi WJ, Yang HS. Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy. J Anesth. 2012 Dec 6;

194. Kovac AL, O'Connor TA, Pearman MH, Kekoler LJ, Edmondson D, Baughman VL, et al. Efficacy of repeat intravenous dosing of ondansetron in controlling postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled multicenter trial. J Clin Anesth. 1999 Sep;11(6):453–9.

APPENDIX

PATIENT INFORMATION SHEET

Department of Anaesthesia CMC hospital Vellore, Tamilnadu	Informed consent form no .....

The title of my research is *"comparing the efficacy of Ondansetron vs Aprepitant to prevent Nausea and Vomiting after surgery"*.

Person carrying out research: Dr.....

I'm Dr....., a senior registrar working in the department of Anaesthesia, CMC Vellore. I'm doing a research study comparing two medications used in preventing vomiting after surgery.

I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask me or the anaesthetist on the day of surgery.

Purpose of the research:

The chance of having nausea or vomiting after surgery is around 30 % despite treatment. I intend to study an oral medication called 'Aprepitant' to prevent vomiting after surgery. We generally give injection ondansetron to prevent vomiting after surgery.

You are being requested to participate in a study comparing the antiemetic efficacy of either Aprepitant 40 mg given in a capsule form within 3 hours before surgery or Ondansetron 8 mg given as an intravenous injection at the end of the surgery and at regular intervals in the first 24 hours after the operation.

One of the above mentioned medications will be given to you based on random allocation in either group. You will receive either of the drugs not both. If further nausea and vomiting occurs in the post operative period, you will receive prompt treatment for the same.

After the operation I will be reviewing you in the ward for complaints of nausea and vomiting.

The benefits of both these medications include relief of post operative nausea and vomiting after anaesthesia. The side effects of these medications include occasional headache, constipation and itching. However, theses side effects are rare and the benefits outweigh the side effects significantly.

I plan to include patients who undergo surgery on the thyroid and breast in this hospital. Your participation in this study is purely voluntary and you can withdraw from the study at any time, even immediately before the surgery. Your refusal to participate will not involve any penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate in this research project, you will receive the routine treatment for vomiting offered in this hospital.

Confidentiality: your name will not be mentioned anywhere neither the data sheet nor the final published study. Your data will bear a study number and the number will be used till analysis. The master sheet will have your study number.

Reimbursements: You will not be charged the cost of Ondansetron or Aprepitant. There are no other incentives.

Sharing of the result: the results of research are property of Christian medical college and I'm entitled to publish it in a journal or present in a conference.

This proposal has been reviewed and approved by [IRB, Christian Medical College], which is a committee whose task it is to make sure that research participants are protected from harm.

If you wish to find about more about the IRB,

contact

Research Office,

second floor,

Carman block,

Christian Medical College,

Bagayam, Vellore 632002.

Email: research@cmcvellore.ac.in, telephone: 04162284294.

It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study.

In case of doubts or questions, please contact Dr....., Department of Anaesthesia, Christian Medical College and Hospital, Vellore. Ph.No. .....

CERTIFICATE OF CONSENT

I have read the foregoing information/ it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate Thumb impression (R / L)

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ ***AND*** ***Thumb print of participant***

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Capsule Aprepitant or placebo will be given prior to the surgery.

2. Injection Ondansetron or placebo will be given at the end of surgery.

3. Participation is voluntary and cost of ondansetron or aprepitant will be borne by the research fund.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

PROFORMA FOR POST OPERATIVE NAUSEA AND VOMITING STUDY

COMPARING ONDANSETRON AND APREPITANT

NAME: AGE/SEX: H.NO:
SL. NO:

ASA : 1 / 2 HT: WT: BMI:
DATE:

RISK FACTORS FOR PONV: FEMALE GENDER

NON SMOKING STATUS

H/O PONV / MOTION SICKNESS

POST OP OPIOID USE

DIAGNOSIS:

OPERATION DONE:

PREMEDICATION- DRUG/TIME:

TIME OF COMMENCEMENT OF OPERATION: DURATION OF ANAESTHESIA:

PONV

FIRST 2 HOURS 2-12 HOURS 12-24 HOURS

NO OF EMETIC EPISODES

NAUSEA -MILD

-MODERATE

-SEVERE

PEAK NAUSEA SCORE AND TIMING:

TIME TO FIRST VOMITING:

TIME TO FIRST USE OF RESCUE ANTIEMETIC:

NO. OF TIMES RESCUE ANTIEMETIC GIVEN IN 24 HOURS:

SATISFACTION WITH CONTROL OF PONV:

VERY SATISFIED (5)

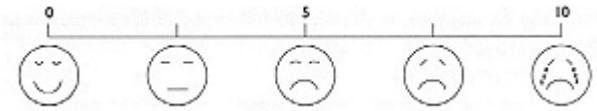
SOMEWHAT SATISFIED (4)

NEITHER SATISFIED OR DISSATISFIED (3)

SOMEWHAT DISSATISFIED (2)

VERY DISSATISFIED (1)

VERBAL RATING SCORE FOR POST OP NAUSEA - SCALE OF 0-10



0 - NO NAUSEA

10 –NAUSEA AS BAD AS IT COULD BE

MILD – 0 TO 3

MODERATE – 4 TO 7

SEVERE – 8 TO 10

STUDY PROTOCOL

This is a double blinded, randomized clinical control trial, approved by the ethics and research committee of our institution. All ASA 1 and 2 female patients, aged 18 to 65 years scheduled for thyroidectomy and mastectomy are eligible for the study. Patients who are receiving antiemetics or steroid medication or drugs known to cause emesis currently or in the immediate past, patients with known hypersensitivity to ondansetron or aprepitant, pregnant and nursing mothers, patients on medications known to induce CYP3A4 such as phenytoin, carbamazepine, barbiturates, rifampicin, rifabutin, or CYP3A4 inhibitors (clarithromycin, ketoconazole, itraconazole),and those known to be CYP3A4 substrates (terfenadine, pimozide, cisapride or astemizole) are excluded from the study. On the day before the surgery, an informed consent is obtained from those who are willing to participate in the study.

Patients will be randomized into 2 groups - 60 patients in each group. The randomization schedule is a computer generated random sequence, done by the biostatistician who is otherwise not involved with the study.

STUDY GROUP

C.Aprepitant within 1 hour preoperatively (along with the pre medication)

Inj.placebo 4 ml in the post operative period every 8 hours - 3 doses

(1 st dose will be given in theatre at the end of surgery & the next 2 doses will be given in the ward).

CONTROL GROUP

C.placebo within 1 hour preoperatively

Inj. Ondansetron 4 ml(8 mg) in the post operative period every 8 hours - 3 doses.

(1 st dose will be given in theatre at the end of surgery & the next 2 doses will be given in the ward).

Prevention of Postoperative Nausea and Vomiting (PONV)

The recommended oral dosage of Aprepitant is 40 mg within 1 to 3 hours prior to induction of anesthesia.

DCGI approval

Aprepitant 40mg capsules (additional strength)	Prevention of post-operative nausea & vomiting (additional indication)	24.04.07

ADVERSE REACTIONS

Clinical adverse experiences for the Aprepitant PONV regimen are: constipation, nausea, pruritus, pyrexia, headache, fatigue, dizziness. There were no serious adverse drug-related experiences reported in the postoperative nausea and vomiting clinical studies in patients taking 40 mg aprepitant.

DRUG INTERACTIONS

Aprepitant is a substrate for CYP3A4; therefore, coadministration with drugs that inhibit or induce CYP3A4 activity may result in increased or reduced plasma concentrations of aprepitant respectively.

Aprepitant is an inducer of CYP2C9; therefore, coadministration with drugs that are metabolized by CYP2C9 (e.g. warfarin,tolbutamide), may result in lower plasma concentrations of these drugs .

DATA SHEET

serial no.	group	age	sex	hospi. no	ASA	height	weight	BMI
1	1	28	1	125528f	1	145	50	22.8
2	2	49	1	087559f	2	148	53	24.2
3	2	53	1	186521f	1	153	60	25.6
4	1	35	1	030494f	1	158	49	19.6
5	1	26	1	831144b	1	155	61	25.4
6	2	45	1	091301c	2	155	61	25.4
7	2	38	1	952148d	1	156	60	24.7
8	1	33	1	715380d	2	151	53	23.2
9	2	57	1	171441f	2	144	59	28.5
10	1	65	1	193313f	1	157	56	22.7
11	1	44	1	093006f	2	158	79	31.6
12	2	55	1	114040f	2	150	70	31.1
13	1	60	1	181941f	2	151	59	25.9
14	2	47	1	129537f	1	140	55	28.1
15	1	49	1	115841f	1	152	65	28.1
16	2	45	1	188268f	1	154	54	22.8
17	2	56	1	195844f	1	141	56	28.2
18	1	62	1	188570f	2	152	65	27.7
19	1	55	1	192579f	2	144	60	28.9
20	2	58	1	167700f	2	152	60	26
21	1	54	1	132035f	1	143	55	26.9
22	2	34	1	250129d	2	156	75	30.8
23	2	58	1	351427d	2	155	65	27.1
24	1	39	1	143998f	1	150	60	26.7
25	2	60	1	393046c	1	158	77	30.8
26	1	46	1	186137f	2	152	78	33.8
27	2	28	1	196276f				
28	1	46	1	145517f	1	155	56	23.3
29	1	46	1	129795f	1	152	70	30.3

30	2	40	1	130104f	2	152	61	26.4
31	1	44	1	138732f	1	154	60	25.3
32	2	36	1	138679f	1	162	87	33.2
33	2	37	1	141490f	2	145	67	31.9
34	1	36	1	150188f	2	154	64	27
35	1	35	1	103148f	2	152	70	34.2
36	2	65	1	900843d	2	140	51	26
37	1	41	1	149857f	1	154	68	28.7
38	2	48	1	176457f	1	147	81	37.5
39	1	64	1	125212f	2	145	54	25.7
40	2	25	1	146674f	1	152	56	24.2
41	1	37	1	087319f				
42	1	25	1	127537f	2	143	55	26.9
43	2	36	1	840891d	1	150	73	32.4
44	2	51	1	109116f	1	143	50	24.5
45	2	45	1	155524f	2	155	65	27.1
46	1	18	1	185130f	1	156	45	16.8
47	2	28	1	217131f	1	155	65	27.1
48	1	55	1	150744f	1	152	48	20.8
49	2	51	1	952117d	1	154	40	16.9
50	2	55	1	171358f	2	150	55	24.4
51	1	42	1	746733c	2	150	47	20.9
52	1	31	1	203021f	2	155	51	21.2
53	2	38	1	167105f	2	159	48	19
54	2	47	1	181018f	1	147	40	18.5
55	1	39	1	179873f	1	156	45	18.5
56	1	58	1	225023f	2	156	64	26.3
57	2	26	1	224280f	2	152	42	18.2
58	1	51	1	192113f	2	151	65	28.5
59	2	49	1	047680f	2	145	59	28.1

sl no.	Risk 1	risk 2	risk 3	risk 4	diagnosis	operation	pre med	p m time
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3	1	1	2	2	1	1	1	10:40:00
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59	1	1	2	2	1	1	5	06:30:00

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32	11:15:00	01:40:00	0		0	0	0
33	09:25:00	01:45:00	2		0	0	5
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sno	vrsn12_24	pns	n12_24	vt_1	pns_t	vt_1	res1	res_24	res24	satis
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61	0	2			05:30:00				1	4
62	0	0							0	5
63	0	0							0	5
64	0	0							0	5
65	0	0							0	5
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82	0	0							0	5
83	0	0							0	5
84	0	3		00:30:00	00:15:00		00:30:00		0	4
85	0	2		00:40:00	00:40:00		00:40:00		0	4
86	0	0							0	5
87	0	4		00:15:00	00:15:00		00:05:00		1	3
88	0	2			09:00:00				0	4
89	0	4		00:25:00	00:25:00				1	2
90	0	0							0	5
91	0	4		02:15:00	02:15:00				0	3
92	0	3		00:50:00	00:50:00				0	4
93	0	0							0	5

94	0	0							0	5
95	0	0							0	5
96	0	0							0	5
97	0	4		01:00:00	01:00:00		01:00:00		1	3
98	0	0							0	5
99	3	3		12:05:00	12:05:00		12:05:00		1	4
100	0	0							0	5
101	0	0							0	5
102	0	0							0	5
103	0	4		06:00:00	06:00:00		06:00:00		2	4
104	0	0							0	5
105	0	3		00:55:00	00:55:00		00:55:00		1	4
106	0	0							0	5
107	0	3		03:00:00	03:00:00		03:00:00		0	4
108	0	0							0	5
109	0	2			03:30:00				2	4
110	0	0							0	5
111	0	0							0	5
112	0	4		00:15:00	00:15:00		00:15:00		1	3
113	0	3			10:10:00				0	4
114	0	4		00:10:00	00:10:00		00:10:00		1	4
115	0	0							0	5
116	0	3		05:25:00	05:25:00		05:25:00		0	4
117										
118	0	0							0	5
119	0	5		00:15:00	00:10:00		00:15:00		1	4
120	0	0							0	5
121										
122	0	0							0	5
123	0	0							0	5
124										
125	0	0							0	5