EVALUATION OF EFFICIENCY OF COMBINING PROPOFOL AS INDUCTION AGENT AND SINGLE SUBHYPNOTIC DOSE 'SANDWICH TECHNIQUE' FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING

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CERTIFICATE

This is to certify that the dissertation entitled **"EVALUATION OF EFFICIENCY OF COMBINING PROPOFOL AS INDUCTION AGENT AND SINGLE SUBHYPNOTIC DOSE 'SANDWICH TECHNIQUE' FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING ",** is a bonafide record work done by **DR.S.SIVAPRASATH**, in the Department of Anaesthesiology, Government Rajaji Hospital, Madurai Medical College, Madurai.

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DECLARATION

I, **Dr. S.SIVA PRASATH**, solemnly declare that the dissertation titled ***"*EVALUATION OF EFFICIENCY OF COMBINING PROPOFOL AS INDUCTION AGENT AND SINGLE SUBHYPNOTIC DOSE 'SANDWICH TECHNIQUE' FOR PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING *",*** has been prepared by me.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment of the regulations for the award of MD degree Branch [Anaesthesiology].

Madurai. **Dr. S. SIVA PRASATH**
Date:

CONTENTS

INTRODUCTION

Nausea and Vomiting is one of the most distressing post operative complications, for the patients and health care providers. It is rated equal to pain and drains hospital resources in terms of delayed discharges, increased medication, complications like wound dehiscence and aspiration pneumonitis.

There are certain risk factors that predispose the patient to an post operative nausea and vomiting. They include patient factors, anaethetic drugs, the surgery perse etc.

ENT surgery is one of the surgical factors leading to higher risk of post operative vomiting, especially in adenotonsillectomics and mastoidectomy surgery.

Propofol is a versatile intravenous anaesthetic agent which has clear advantages over other agents in terms of early recovery and its antiemetic effect. Whenever it is included in an anaesthetic regime, it does offer protection to against post operative nausea and vomiting through varying degrees.

In our hospital, Mastoidectomy for the age upto 20 years is done under general anesthesia.

The usual General anaesthetic technique is of intravenous induction, opioid, Oxygen, nitrous oxide technique. But this technique which contains two major predisposing factors, i.e. opioids and nitrous oxide, along with other factors, and the surgical factors incapacitate the patient with nausea and vomiting in the post operative period.

Middle ear surgeries are a special risk factor for post operative nausea and vomiting. During middle ear procedures, the stimulation of vestibular afferents, middle ear cavities, leads to post operative nausea and vomiting. during tympanoplasty procedures nitrous oxide fills the

middle ear cavities. Administration of Nitrous oxide should be stopped atleast 15 mins prior to application of graft. Residual nitrous oxide not only disrupts the graft but also stimulation the vestibular nerves causing nausea and vomiting.

Many regimes and doses of propofol are studied which provide the best protection form post operative nausea and vomiting. Apart from propofol offering protection during maintenance doses, it has been found that low dose subhypnotic infusions, and small subhypnotic bolus offer protection from nausea and vomiting .This is cost effective.

The advantages of using propofol in ENT surgeries are low incidence of post operative nausea and vomiting , reduction in blood pressure with out increase in heart rate, preservation of middle ear blood flow and excellent recovery profile

AIM OF THE STUDY

To evaluate the efficiency of combing propofol as induction agent and single subhypnotic dose of propofol at the end of surgery for prevention of post operative nausea and vomiting in modified radical mastoidectomy surgeries.

PHARMACOLOGY OF PROPOFOL

History:

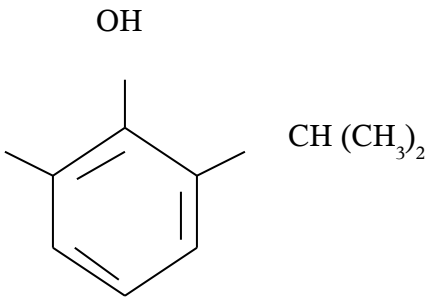
Work in the early 1970's on substituted derivatives of phenol with hypnotic properties resulted in development of 2, 6, di isopropofol. The first clinical trial reported by Kay and Rolly in 1977, confirmed the potential of Propofol as an induction agent. With recognition of rapid clearance of Propofol, its use as an maintenance agent, sedation in Intensive care units and during regional anaesthesia came into use.

Propofol is insoluble in water and was therefore initially prepared with Cremaphor EL. Because of the anaphylactoid reactions with cremaphor EL, this preparation was withdrawn from the market and propofol was reformulated as an emulsion. Propofol become commercially available in 1986. It is more expensive than thiopentone or methohexitol but it has become popular due to its favourable recovery characteristics and antiemetic effect.

Propofol in extremely useful where volatile anaesthetic cannot used and an intravenous technique must be employed as in rigid bronchoscopy, tracheobronchial surgery and in patients susceptible to malignant hyperthermia

Chemical Structure:

$(CH_3)_2$ CH



Chemical Name: 2,6,-di isopropyl phenol

Physio Chemical Properties.

Propofol is one of a group of Alkyl phenols.

Alkyl phenols are oils at room temperature, insoluble in water, and highly lipid soluble

Formulation:

a) Propofol 1%

Soya bean oil 10%

Glycerol 2.25%

Purified egg phosphatide 1.2%

Preservatives: Disodium Edetate (0.005%) or Metabisulphite

b) Formulation with medium chain triglycerides and long chain triglycerides is available

c) Clear propofol is available , but has not gained popularity.

<u>Availability</u>

10ml ampoules vials of 1% propofol

20ml vials of 1% propofol

20ml vials of 2% propofol

50ml vials of 1% propofol

50ml 1,2% Prefilled syringes for target controlled infusion techniques.

All formulations are stable at room temperature and are not sensitive to light.

Change in diluent may result in slight changes in pharmacokinetics, cracking of emulsion and spontaneous degradation of propofol.

Propofol is compatible with 5% dextrose and can be used as dilutant .

Mechanism of Action

Propofol is presumed to exert its sedative-hypnotic effects through an interaction with Gamma-AminoButyric acid (GABA), the principal inhibitory neurotransmitter in the CNS, When the GABA receptor is activated, transmembrane chloride conductance increases, resulting in hyperpolarization of the postsynaptic cell membrane and functional inhibition of the postsynaptic neuron. The interaction of Propofol (also barbiturates) with specific components of the GABA receptor complex appears to decrease the rate of dissociation of GABA from its receptor, thereby increasing the duration of the GABA-activated opening of the chloride channel with resulting hyperpolarization of cell membranes.

Pharmacokinetics

Clearance of Propofol from the plasma exceeds hepatic blood flow, emphasizing that tissue uptake , possibly into the lungs, as well as metabolism, is important in removal of this drug from the plasma. Hepatic metabolism is rapid and extensive, resulting in inactive, water-soluble Sulfate and Glucouronic acid metabolites that are excreted by the kidneys. Less than 0.3% of a dose is excreted unchanged in urine. The elimination half-time is 0.5 to 1.5 hours, but more important, the context-sensitive half-time for propofol infusion lasting up to 8 hours is <40 minutes (Hughes et al.1992). The context-sensitive half-time of propofol is minimally influenced by the duration of the infusion because of rapid metabolic clearance. When the infusion is discontinued such that the drug that returns from tissue storage sites to the

circulation is not available to retard the decrease in plasma concentrations of the drug. Propofol, like thiopental and alfentanil, has a short effect-site equilibration time such that effects on the brain occur promptly after IV administration.

Despite the rapid clearance of Propofol by metabolism, there is no evidence of impaired elimination in patients with cirrhosis of the liver. Renal dysfunction does not influence the clearance of Propofol despite the observation that nearly three-fourths of propofol metabolites are eliminated in urine in the first 24 hours. Patients older than 60 years of age exhibit a decreased rate of plasma clearance of propofol compared with younger adults. The rapid clearance of propofol confirms this drug can be administered as a continuous infusion without an excessive cumulative effect. Propofol readily crosses the placenta but is rapidly cleared from the neonatal circulation (Dailland et al., 1989). The effect of instituting cardiopulmonary bypass on the plasma propofol concentration is unpredictable, with some studies reporting a decrease whereas other observations fail to document any change .

Clinical Uses

1. Propofol has become the induction drug of choice for many forms of anesthesia, especially when rapid and complete awakening is considered essential.
2. Continuous intravenous infusion of Propofol, with or without other anesthetic drugs, has become a commonly used method for producing IV “conscious” sedation or as part of a balanced or total IV anesthetic.
3. Administration of propofol as a continuous infusion can be used for sedation of patients in Intensive care units, a 2% solution may be useful to decrease the volume of lipid emulsion administered with long-term sedation.

Induction of Anesthesia

The induction dose of Propofol in healthy adults is 1.5 to 2.5 mg/kg IV, with blood levels of 2 to 6 μg/ml producing unconsciousness depending on associated medications and the patient's age. As with barbiturates, children require higher induction doses of Propofol on a milligram per kilogram basis, presumably reflecting a larger central distribution volume and higher clearance rate. Elderly patients require a lower induction dose (25% to 50% decrease) as a result of a smaller central distribution volume and decreased clearance rate (smith et al., 1994). Awakening typically occurs at plasma Propofol concentrations of 1.0 to 1.5 μg/ml. The complete awakening without residual CNS effects that is characteristic of Propofol is the principal reason this drug has replaced thiopental for induction of anesthesia in many clinical situations. Although Propofol is more expensive than thiopental, the additional expense may be offset by decreased costs made possible by prompt awakening.

Intravenous Sedation

The short context-sensitive half-time of Propofol, even with prolonged periods of infusion, combined with the short effect-site equilibration time, make this an easily titratable drug for production of IV sedation. The prompt recovery without residual sedation and low incidence of nausea and vomiting make Propofol particularly well suited to ambulatory conscious sedation techniques. The typical conscious sedation dose of 25 to 100 μg/kg/minute IV produces minimal amnestic effects (Smith et l., 1994). In selected patients, midazolam or an opioid may be added to Propofol for continuous IV sedation. A sense of well-being may

accompany recovery from conscious sedation with propofol, although this may be related more to the patient's relief that the procedure is over than to a specific pharmacologic effect of propofol. A conventional patient-controlled analgesia delivery system set to deliver 0.7-mg/kg doses of propofol with a 3-minute lockout period is an alternative to continuous infusion

Sedation techniques

Propofol has been administered as a sedative during mechanical ventilation in the ICU in a variety of patient population including postoperative patients (cardiac surgery, neurosurgery) and in patients with head injury . Propofol also provides control of stress responses and has anticonvulsant and amnestic properties. After cardiac surgery, Propofol sedation appears to modulate postoperative hemodynamic responses by decreasing the incidence and severity of tachycardia and hypertension. Increasing metabolic acidosis, lipemic plasma, bradycardia, and progressive myocardial failure has been described in a few children who were sedated with Propofol during management of acute respiratory failure in the ICU (Parke et al., 1992).

Maintenance of Anesthesia

The typical dose of Propofol for maintenance of anesthesia is 100 to 300 μg/kg/minute IV often in combination with a short-acting opioid (Smith et al., 1994). Although Propofol has proved to be a valuable adjuvant during short ambulatory procedures, its use for more prolonged operations (>2 hours) is questionable based on the cost of the drug and only modest differences in recovery times compared with Propofol is generally associated with minimal postoperative nausea and vomiting, and awakening prompt, with minimal residual sedative effects.

Nonhypnotic Therapeutic Applications

In addition to its clinical application as an IV induction drug, Propofol has been shown

to have beneficial effects that were not anticipated when the drug was initially introduced.

Antiemetic Effects

The incidence of postoperative nausea and vomiting is decreased when Propofol is administered, regardless of the anesthetic technique or anesthetic drug used. Subhypnotic doses of Propofol (10 to 20mg IV) may be used in the postanesthesia care unit to treat nausea and vomiting, particularly if it is not of vagal origin. In the postoperative period, the advantage of Propofol is it' s rapid onset of action and the absence of serious side effects. Propofol is efficacious in treating postoperative nausea and vomiting at plasma concentration that do not produce increased sedation. Studies indicate that antiemetic plasma concentrations of propofol are achieved by a single IV dose of 10 mg followed by 10 μg/kg/minute (Ganet al., 1997). Propofol in subhypnotic doses is effective against chemotherapy-induce nausea and vomiting. When administered to induce and maintain anesthesia, it is more effective than ondansetron in preventing postoperative nausea and vomiting (Gan et al., 1996).

Propofol has a profile of CNS depression that differs from other anesthetic drugs. In contrast to thiopental, for example, Propofol uniformly depresses CNS structures, including subcortical centers. Most drugs of known antiemetic efficacy exert this effect via subcortical structures, and it is possible that Propofol modulates subcortical pathways to inhibit nausea and vomiting center. Nevertheless, the mechanisms mediating the antiemetic effects of Propofol remain unknown. An antiemetic system is unlikely in view of the observation that subhypnotic doses of Propofol fail to increase plasma prolactin concentration is characteristic of drugs that block the dopaminergic system. The antiemetic effect of Propofol is not due to the intralipid emulsion in the formulation (Gan et al., 1997).

Antipruritic Effects

Propofol,10 mg IV, is effective in the treatment of pruritus associated with neuraxial opioids or cholestasis. The quality of analgesia is not affected by Propofol. The mechanism of the antipruritic effect may be related to the drug's ability to depress spinal cord activity. In this regard, there is evidence that intrathecal opioids produce pruritus by segmental excitation within the spinal cord.

Anticonvulsant Activity

Propofol possesses antiepileptic properties, presumably reflecting GABA-mediated presynaptic and postsynaptic inhibition. In this regard, propofol in doses of>1 mg/kg IV decreases seizure duration 35% to 45% in patients undergoing electroconvulsive therapy (avramov et al., 1995). The incidentce of excitatory movements and associated electroencephalogram (EEG) changes are low after the administration of Propofol. Propofol does not produce seizure activity on the EEG when administered to patients with epilepsy, including those undergoing cortical resection

EFFECTS ON ORGAN SYSTEM

Central Nervous System

Propofol decreases cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow, and intracranial pressure (ICP). Large doses of propofol, however, may decrease systemic blood pressure sufficiently to also decrease cerebral perfusion pressure. Cerebrovascular autoregulation in response to change in systemic blood pressure and reactivity of the cerebral blood flow to changes in carbon dioxide partial pressure are not affected by Propofol. Indeed, cerebral blood flow velocity changes in parallel with changes in $PaCo_2$ in the presence of propofol and midazolam. Propofol produces cortical EEG changes that are similar to those of

thiopental, including the ability of high doses to produce burst suppression. Propofol produces a decrease in the changes in the end-tidal Pco_2 ($PETCO_2$) produce corresponding changes in the cerebral blood flow velocity (CBFV) during infusion of propofol or midazolam. Cerebral vasomotor responsiveness to carbon dioxide is preserved during propofol and midazolam anesthesia in humans. Propofol does not interfere with the adequacy of electrocorticographic recording during awake craniotomy performed for the management of refractory epilepsy, provided administration is discoutinued at least 15 minutes before recording (Herrick et al ., 1997). At equal sedation, propofol produces the same degree of memory impairment as midazolam, whereas thiopental has mild memory effect and fentanyl has none .

Cardiovascular System

Propofol produces decreases in systemic blood pressure that are greater than those evoked by comparable doses of thiopental (Rouby et al ., 1991). These decreases in blood pressure are often accompanied by corresponding changes in cardiac output and systemic vascular resistance. The relaxation of vascular smooth muscle produced by Propofol is primarily due to inhibition of sympathetic vasoconstrictor nerve activity . A negative inotropic effect of Propofol may result from a decreases in intracellular calcium availability secondary to inhibition of trans-sarcolemmal calcium influx. Stimulation produced by direct laryngoscopy and intubation of the trachea reverses the blood pressure effects of Propofol, although this drug is more effective than thiopental in blunting the magnitude of this pressor response. Propofol also effectively blunts the hypertensive responses to placement of a laryngeal mask airway. Although able to blunt the increase in epinephrine concentration that accompanies a sudden increase in the delivered desflurane concentration, propofol, 2mg/kg IV, does not attenuate the transient cardiovascular response to a rapid increase in the concentration of this volatile

anesthetic to>1 MAC. The blood pressure effects of propofol may be exaggerated in hypovolemic patients, elderly patients, and patients with compromised left ventricular function due to coronary artery disease. Adequate hydration before rapid IV administration of Propofol is recommended to minimize the blood pressure effects of this drug. Addition of nitrous oxide does not alter the cardiovascular effects of Propofol.

Despite decreases in systemic blood pressure, heart rate often remains unchanged in contrast to the modest increases that typically accompany the rapid IV injection of thiopental. Bradycardia and asystole have been observed after induction of anesthesia with Propofol, resulting in the occasional recommendation that anticholinergic drugs be administered when vagal stimulation is likely to occur in association with administration of Propofol. Propofol may decrease sympathetic nervous system activity to a greater extent than parasympathetic nervous system activity, resulting in a predominance of parasympathetic activity (Bryson et al., 1995). There is also evidence that Propofol does not alter sinoatrial or atriventricular node function in normal patients or in patients with Wolff-Parkinson-White syndrome. Baroreceptor reflex control of heart rate may be depressed by propofol (Deutschman et al., 1994).

Bradycardia – Related Death

Profound bradycardia and asystole after administration of propofol have been described in healthy adult patients, despite prophylactic anticholinergics (Egan and Brock, 1991; Freysz et al., 1991; James et al., 1989; Tramer et al., 1997c). The risk of bradycardia-related death during propofol anesthesia has been estimated to be 1.4 in 100,000. Severe, refractory, and fatal bradycardia in children in the ICU has been observed with long-term propofol sedation (Bray, 1995; Dearlove and Dobson, 1995). Propofol anesthesia, compared with other anesthetics, increase the incidence of the oculocardiac reflex in pediatric strabismus surgery,

despite prior administration of anticholinergics (tramer et al., 1995c).

Lungs

Propofol produces dose-dependent depression of ventilation, with apnea occurring in 25% to 35% of patients after induction of anesthesia with Propofol. Opioids administered with the preoperative medication may enhance this ventilatory effect. Painful surgical stimulation is likely to counteract the ventilatory depressant effects of propofol. A maintenance infusion of propofol decreases tidal volume and frequency of breathing. The ventilatory response to carbon dioxide and arterial hypoxemia are decreased by propofol (Blouin et al., 1993). Propofol can produce bronchodilation and decrease the incidence of intraoperative wheezing in patients with asthma. Propofol infusion to produce conscious sedation significantly decreases the slope and causes a downward shift of the ventilatory response to hypoxia (Blouin et al., 1993). Hypoxic pulmonary vasoconstriction seems to remain intact in patients receiving Propofol.

Hepatic and Renal Function

Propofol does not adversely affect hepatic or renal function as reflected by measurements of liver transaminase enzymes or creatinine concentrations. Prolonged infusions of Propofol may result in excretion of green urine, reflecting the presence of phenols in the urine. This discoloration does not alter renal function. Urinary uric acid excretion is increased after administration of Propofol and may manifest as cloudy urine when the uric acid crystallizes in the urine under conditions of low pH and temperature (Masuda et al., 1997). This cloudy urine is not considered to be detrimental or indication of adverse renal effects of Propofol.

Intraocular Pressure

Propofol is associated with significant decreases in intraocular pressure that occur immediately after induction of anesthesia and are sustained during tracheal intubation .

SIDE EFFECTS

Allergic Reactions

Allergenic components of Propofol include the phenyl nucleus and diisopropyl side chain. Patients who develop evidence of anaphylaxis on first exposure to Propofol may have been previously sensitized to the diisopropyl radical, which is present in many dermatologic preparations. Likewise, the phenol nucleus is common to many drugs. Indeed, anaphylaxis to Propofol during the first exposure to this drug has been observed, especially in patients with a history of other drug allergies, often to neuromuscular-blocking drugs.

Proconvulsant Activity

The majority of reported Propofol-induced seizures during induction of anesthesia or emergence from anesthesia reflect spontaneous excitatory movements of sub-cortical origin. These responses are not thought to be due to cortical epileptic activity, although some recommend caution in administering Propofol to patients with poorly controlled epilepsy. Prolonged myoclonus associated with meningismus has been associated with Propofol administration (Hughes and Lyons, 1995).

Abuse Potential

Intense dreaming activity, amorous behaviour, and hallucinations have been reported during recovery from the effects of Propofol. Addiction to virtually all opioids and hypnotics, including propofol, has been described (Follette and Farley, 1992).

Bacterial growth

Propofol strongly supports the growth of Escherichia coli and Pseudomonas aeruginosa, whereas the solvent appears to be bactericidal for these same organisms and bacteriostatic for Candida albicans. Clusters of postoperative surgical infections manifesting as temperature elevations have been attributed to extrinsic contamination of Propofol (Nichols and Smith, 1995). For this reason, it is recommended that (a) an aseptic technique be used in handling Propofol as reflected by disinfecting the ampoule's neck surface or vial rubber stopper with 70% isopropyl alcohol; (b) the contents of the ampoule containing Propofol should be withdrawn into a sterile syringe immediately after opening and administered promptly; and (c) and contents of an opened ampoules must be discarded if they are not used within 6 hours. In the ICU, the tubing and any unused portion of propofol must be discarded after 12 hours. Despite these concern, there is evidence that when Propofol is aseptically drawn into an uncapped syringe, it will remain sterile at room temperature for several days

Antioxidant Properties

Propofol has potent antioxidant properties that resemble those of the endogenous antioxidant vitamin E . A neuroprotective effect of propofol may be at least partially related to the antioxidant potential of propofol's phenol ring structure. For example, propofol reacts with lipid peroxyl radicals and thus inhibits lipid peroxidation by forming relatively stable propofol phenoyl radicals. In addition, propofol also scavenges peroxynitrite, which is one of the most potent reactive metabolites for the initiation of lipid peroxidation. Because peroxynitrite-scavenging activity to suppress phagocytosis , propofol might be beneficial in disease states, such as acute lung injury, in which peroxynitrite formation is thought to play an important role

(Kooy et al., 1995).

Pain on Injection

Pain on injection is the most commonly reported adverse event associated with propofol administration to awake patients. This unpleasant side effect of propofol occurs in <10% of patients when the drug is injected into a large vein rather than a dorsum vein on the hand. By prior administration of a potent short-acting opioid or 1% lidocaine decreases the incidence of discomfort experienced by the patient. The incidence of thrombosis or phlebitis is usually <1%. Changing the composition of the carrier fat emulsion for propofol to long- and medium chain trigelycerides decreases the incidence of pain on injection (Doenicke et al., 1997).

Accidental intra-arterial injection of propofol has been described as producing severe pain but no vascular compromise (Holley and Cuthrell, 1990). In an animal model, propofol-exposed arteries showed no changes in the vascular smooth muscle, and the endothelium was not damaged (MacPherson et al., 1992).

Miscellaneous Effects

Propofol does not trigger malignant hyperthermia and has been administered to patients with hereditary coproporphyrias without ontoward incidents. Secretion of cortisol is not influenced by propofol, even when administered for prolonged periods in the ICU. Temporary abolition of tremors in patients with Parkinson's disease may occur after the administration of propofol. For this reason, propofol may not be ideally suited for patients undergoing sertrotactic neurosurgery such as pallidotomy.

HISTORICAL ASPECTS :

POSTOPERATIVE NAUSEA AND VOMITING

During ether era, reported incidence of post operative nausea and vomiting was as high as 75-80%. Various techniques including olive oil and glucose insulin injection were reported to be effective as reported by Robert Ferguson in 1912. The effect of atropine was appreciated by Brown Sequard as early as 1883.

In second half of the century the incidence of post operative nausea and vomiting decreased to about 50% due to the use of non opoid, non-ether regional anaesthetics techniques, refinement of surgical techniques and identification of patient's predictive emetogenic factors. There are 3 kinds of vomiting, the first of which is attributed to anaesthetics such as ether, second due to the reflex responses, third due to the medication used intra operatively. Subsequent investigation unfolded a spectrum of non-anesthetic factors in the pathogenesis of post operative nausea and vomiting.

Over years numerous of drugs have been used in the management of post operative nausea and vomiting. Phenothiazines were synthesized in late 19^{th} century by chemists in dyeing industry. Promethazines were found in 1930 to have good anti emetic property. However sedative action of it, limited its use. Phenothiazine derivatives have been exclusively used in the treatment of post operative nausea and vomiting.

Antiemetics may be antagonists at the dopamine (D_2-e.g. metoclopramide, droperidol, prochlorperazine), 5-HT_3 (e.g.ondansetron, dolasteron) and cholinergic (e.g. cyclizine)

receptors.

There are new antiemetics like neurokinin -1, (substance – P antagonists) in development.

1. **Complexity of the problem:** The variables are many that it becomes difficult to assess the effects of an intervention as it requires considerable number of patients of well controlled trails.
2. **Inadequate quantification of phenomena:** The phenomena has been poorly defined i.e. nausea, vomiting, retching etc.
3. **Inadequate antiemetic regimen:** Unable to identify a good drug which can prevent nausea and vomiting.
4. **Animal Model:** A lack of model to study the physiology and pharmacology of mechanism of post operative nausea and vomiting, though monkey and dogs are available they don't suffer from pregnancy and motion sickness and post operative and post anesthetic emesis.

POST OPERATIVE NAUSEA AND VOMITING

Morbidity and mortality resulting directly from anaesthesia is now extremely rare. However, postoperative nausea and vomiting (post operative nausea and vomiting) is still very common. Surveys have confirmed that post operative nausea and vomiting is feared considerably by patients undergoing surgery. Indeed, it often comes before postoperative pain when patients are asked to rank their concerns. Therefore, every anaesthetist must be aware of the physiology of post operative nausea and vomiting and its consequences, causes, associated

factors and management.

VOMITING REFLEX

All reflexes, including the vomiting reflex, consist or afferent inputs, a degree of central processing and motor efferents.

VOMITING CENTRE

The vomiting centre is not an anatomical entity but represents several nuclei in the brain stem (e.g. nucleus tractus solitarius, respiratory neural networks) which are responsible for the coordination of the afferent limb of the vomiting reflex. It receives input from the afferent limbs of the reflex and the chemoreceptor trigger zone (CTZ).

CHEMORECEPTOR TRIGGER ZONE

The CTZ is situated in the area postrema in the floor of the fourth ventricle. Evidence from ablation studies by Borison and Wang in the 1950s and the fact that the blood – brain barrier is defective in this area suggest that the CTZ is responsible for detecting toxins circulating in the blood and cerebrospinal fluid. However, it may be that a more precise area for this function is the nearby nucleus tractus solitarius where dopamine and opioid receptors are abundant.

AFFERENT LIMBS OF VOMITING REFLEX

Gastrointestinal tract

Information from mechano-and chemoreceptors in the gastrointestinal tract is relayed via the vagus nerve to the nucleus tractus solitarius in the brain stem. Abnormal gastric or

interstinal distension, increased smooth muscle contraction and abnormal or toxic gastrointestinal contents can trigger the vomiting reflex. Peripheral 5-HT3 receptors are intimately involved in this system. Radiation, chemotherapy and other toxin release 5-HT from chromaffin cells in the gut, which stimulates vagal afferents – a process inhibited by the 5-HT3 antagonist antimetics. Dopamine receptors are also abundant in the upper gastrointestinal tract.

Vestibular system

Input from the vestibular system is responsible for motion sickness, particularly when vestibular and visual signals conflict. Patients with a history of motion sickness and those who are moved excessively in the early postoperative period are more likely to suffer from post operative nausea and vomiting.

Cardiovascular system

Stimulation of afferents from both cardiac ventricles and blood vessels may lead to vomiting. For example, hypotension, and myocardial infarction are often associated with nausea and vomiting.

Higher centers

Input from higher centers often plays a vital role in the genesis of post operative nausea and vomiting. A calm, well informed patient who is denied unpleasant sights, sounds and smells is less likely to experience nausea or vomiting.

Miscellaneous inputs

Nausea and vomiting are frequently induced by stimulation of pharyngeal afferents, e.g. nasopharyngeal tube, endoscopy. Stimulation of the auricular branch of the vagus nerve on

examination of the ear with an auroscope may induce sudden vomiting, especially in children.

The role of sympathetic innervation of the gastrointestinal tract in post operative nausea and vomiting is not clear. However, pain pathways from the viscera reside in the splanchnic nerves and visceral pain is a frequent cause of nausea and vomiting.

EFFERENT LIMB OF THE VOMITING REFLEX

Nausea

Nausea is not an inevitable consequence of vomiting but it is often the most troublesome symptom after surgery and anaesthesia. It is thought to be caused by the same stimuli that are responsible for vomiting, but the nature of the higher centers involved in this sensation are unknown. As a symptom, it is difficult to investigate because it is entirely objective and cannot be measured in animals. However, a consistent finding is that antiemetic therapy is often very effective in reducing the incidence of vomiting or retching, but less so for nausea.

Vomiting

In the prodromal or pre-ejection phase, there is a relaxation of the gastric muscles followed by small intestinal retrograde peristalsis. The latter forces intestinal contents into the relaxed stomach. At the beginning of the ejection phase, the anterior abdominal muscles and the diaphragm contract together, accompanied by retrograde contraction of the striated musculature of the oesophagus. At the same time, the upper oesphageal sphincter becomes widely dilated. During vomiting, the oesophagus is not obstructed by diaphragmatic contraction, as the crural (peri-oesophageal) muscles of the diaphragm are relaxed. This autonomic and somatic activity is coordinated in the brain stem.

Retching

Retching (i.e., unproductive vomiting) often occurs before vomiting and when the retrograde intestinal peristasis reaches the stomach. During retching, the abdominal muscles and diaphragm contract less intensely and there is no retrograde oesophageal contraction or crural relaxation. Clinically, retching is a frequent and distressing symptom, often associated with intense nausea.

ADVERSE EFFECTS OF POST OPERATIVE NAUSEA AND VOMITING

The most important and frequent adverse effect is the profound distress of most patients when they experience nausea and vomiting.

Aspiration of stomach contents is an important cause of anaesthetic mortality and morbidity and can occur in the postoperative period, particularly if the patient is drowsy. Nausea and vomiting make this more likely. Post Operative Nausea and Vomiting may limit significantly the dose of opioid that may be given for pain relief, and prevention with antiemetics enables effective doses to be administered. Oral administration of drugs (e.g. analgesics, antihypertensives), fluids and nutrients are delayed by post operative nausea and vomiting and, if prolonged, may cause significant problems. Post operative nausea and vomiting is often more severe on movement and may delay postoperative mobilization. It is also an important cause of delayed discharge from day-care surgery units, including unscheduled overnight stay.

FACTORS ASSOCIATED WITH POST OPERATIVE NAUSEA AND VOMITING

Many studies have investigated the relative importance of patient, surgical and anaesthetic factors in the incidence of post operative nausea and vomiting. Some factors have

been associated with an increased risk, but presently the likelihood of post operative nausea and vomiting in individual patients cannot be predicted with any certainty.

Patient factors

Studies have revealed several patient factors which are associated with a relatively high risk of post operative nausea and vomiting. A previous history of post operative nausea and vomiting is a strong association. Children and females are at greater risk but there is no difference between the sexes in childhood or old age. The influence of the menstrual cycle and obesity has been investigated but there is no consistent evidence that they are an important factors. However, it is likely that a predisposition to travel sickness is important.

Surgical factors

Major and minor gynaecological procedures are associated consistently with post operative nausea and vomiting. Indeed, gynaecological surgery is often used in studies investigating the efficacy of new antiemetics. Post operative nausea and vomiting after ENT surgery may be more frequent because of stimulation of pharyngeal afferents, blood in the gastrointestinal tract and the fact that it is a common procedure in children. In abdominal surgery, almost all the efferent limbs of the vomiting reflex are stimulated. Duration of surgery and anaesthesia may also be important.

Anaesthetic factors

Choice of induction agent may influence the incidence of post operative nausea and vomiting. Etomidate and methohexital are comparatively more emetogenic. The incidence of post operative nausea and vomiting associated with induction and, maintenance, anaesthesia with propofol is lower than that with other intravenous and volatile agents. Indeed, it has been suggested that propofol has antiemetic properties, but the evidence for this is not yet

convincing.

Nitrous oxide when used alone, e.g., Entonox, may cause nausea and vomiting, but its effect is uncertain when used as part of a balanced anaesthetic technique. Modern volatile agents are less emetogenic compared with older agents, e.g. ether, trichloroethylene, methoxyflurane, but still contribute to the overall likelihood of post operative nausea and vomiting.

It is clear that the perioperative use of opioids (oral, i.m., i.v. epidural, spinal) is associated with an increased incidence of post operative nausea and vomiting and many anaesthetic techniques aim to avoid opioids for the reason. Paradoxically, postoperative pain may cause post operative nausea and vomiting, which may be alleviated by judicious use of opioids.

Antagonism of neuromuscular blockade with neostigmine has been blamed for post operative nausea and vomiting but recent data have not confirmed this. Episodes of hypotension during spinal or epidural anaesthesia are a common cause of nausea and vomiting. Indeed, nausea is often the first sign of this problem. In addition, there is a lower incidence of post operative nausea and vomiting in patients anaesthetized by experienced anaesthetics compared with those managed by novices. The inexperienced tend to maintain anaesthesia at a deeper plane and are more likely to inflate the stomach with air during manual ventilation.

Several post operative nausea and vomiting risk scores are available. One score by Sinclair, Chung and Mezei considers 12 predictors (Sinclair-score) while another, by Apfel and

colleagues, considers just four risk factors (Apfel-score).

Apfel predictors significantly indicate the probability of post operative nausea and vomiting

Multivariable analysis revealed that age, gender, previous history of post operative nausea and vomiting or motion sickness and postoperative use of opioids had an impact on post operative nausea and vomiting. Logistic regression analysis was restricted to these four, strongest factors.

1. **Age** inversely correlated with post operative nausea and vomiting which corresponded to a 17% decrease of the probability of post operative nausea and vomiting for a ten-year increase in age.
2. **Male sex** was also associated with a lower incidence of post operative nausea and vomiting
3. **A previous history** of post operative nausea and vomiting or motion sickness and the
4. Postoperative use of **opioids** increased the risk of post operative nausea and vomiting more than fourfold.

MANAGEMENT OF POST OPERATIVE NAUSEA AND VOMITING

Prevention of post operative nausea and vomiting

Prevention rather than treatment of post operative nausea and vomiting should be the anaesthetist's aim. However, there is no agreed protocol as to which patients should receive preventive antiemetic therapy, but the relative indication for prophylaxis increases as the number of risk factors increase.

There is an important organization factor in the incidence of post operative nausea and vomiting. Antiemetics are often prescribed but not given. The overall incidence of post operative nausea and vomiting in a hospital is reduced if all professionals involved in the care

of the patient understand the importance and nature of antiemetic therapy and an agreed management protocol is in place.

TREATMENT OF POST OPERATIVE NAUSEA AND VOMITING

Treat the cause

An important principle in the management of any symptom is to seek and treat the cause before treating the symptom itself. This is relevant when dealing with a patient with post operative nausea and vomiting.

Post operative nausea and vomiting may indicate postoperative hypotension; simply administering an antiemetic does not help and may mask an important sign. Hypoxaemia should be treated with oxygen and investigated further if necessary. Early fluid intake or mobilization, particularly after day-case surgery is a common cause. psychological factors, e.g. anxiety, loss of control and illness beliefs, play an important role and may respond to appropriate non-pharmacological management. Occasionally, post operative nausea and vomiting may herald significant intra-abdominal or other pathology resulting from a surgical complication. This should be borne in mind constantly, particularly before discharge from the day-care unit.

Opioids are a common cause of post operative nausea and vomiting, particularly if they are administered injudiciously. Changing to a local anaesthetic technique or adopting a more balanced approach to analgesia may solve the problem. It should be remembered that many other drugs are emetogenic. Antibiotics are a common culprit and their use should be reassessed if post operative nausea and vomiting is a severe problem.

Antiemetic therapy

In practice, many patients with post operative nausea and vomiting require parenteral antiemetic therapy. If an antiemetic has been given previously, there are several factors to consider when choosing the appropriate drug. If the previous drug was effective for some time and it is likely that is plasma concentrations are now low, it is probably appropriate to administer the same drug. However, if the drug was administered relatively recently, a different antiemetic is required. It makes pharmacological sense to choose a drug which acts at a different receptor.

Types of antiemetic

Dexamethasone and cannabinoids (e.g., nabilone, dronabinol) are effective against chemotherapy-induced emesis. The efficacy of cannabinoids for post operative nausea and vomiting is uncertain but there is increasing evidence that dexamethasone is effective. Antagonists at the NK-1 receptor are antiemetic also and their site of action is probably in the brain stem where there is an abundance of these receptors. They are presently undergoing clinical trials.

Non pharmacological methods : Acupuncture , Acupressure

The effect of P6 acupressure point ahs been described but its effect on preventing post operative nausea vomiting is doubtful.

ANTIEMETIC EFFECT OF PROPOFOL

Propofol possesses some interesting properties which is not shown by other anaesthetic agents. They are its antiemetic effect, its antipruritic effect, its antioxidant effect and a sense of well being after a Propofol anaesthetic. Of these characteristics, its antiemetic effect is the one much investigated and used property. Its antiemetic effects shows up in the post anaesthetic period as a large reduction in the incidence of post operative nausea and vomiting. Studies and researches done on antiemetic effect of propofol varies from dosage, routes of administration, effective plasma concentration required to prevent nausea and vomiting to receptor - cellular level where propofol exerts its antiemetic effect.

Mechanism of action

A biological basis for propofol being an antiemetic is lacking.

1. Propofol does not interact with D2 Dopamine receptors, and propofol did not prevent vomiting induced by dopamine agonist apomorphine.
2. Other vague mechanism includes direct depressant effects on chemoreceptor trigger zone, vagal nuclei and other centres implicated in nausea and vomiting.
3. Propofols' antiemetic action may be explained by the decrease in serotonin levels that it produces in area Postrema through its action on GABA receptors.
4. In vitro model suggests that propofol has no direct effect on 5-HT_3 receptors

From these studies, though the exact location and mechanism of its antiemetic effect remains obscure, the probable site would be decrease in serotonin levels in area postrema.

Dosage and blood levels

Inclusion of Propofol as an anaesthetic agent itself offers protection against post operative nausea and vomiting, since most anaesthetic agents are emetogenic unlike propofol.

The blood levels needed to achieve loss of consciousness are 2.5 to 4.5 μg/ml and that required for surgery are 2.5 to 8 μg/ml. The median concentration of propofol that gives antiemetic effect is 343ng/ml with a range of 200ng/ml to 600ng/ml. (Gan et al)

a. As an induction agent

The use of propofol at 2mg/kg for induction produces adequate blood levels to prevent vomiting, which are sustained for about 30 minutes. After 30 minutes, blood levels start falling and the beneficial antiemetic effect also wanes off. So, an induction dose can protect the patients from vomiting, in a short duration surgery lasting for less than 30 minutes, for upto a period of 45-60 minutes. However, it propofol is used as an induction agent in longer and major procedures, the incidence of nausea and vomiting are similar to other techniques.

b. Maintenance agent

Propofol, when used as an maintenance agents, achieves more than necessary blood levels for its antiemetic effect and offers excellent protection from post operative nausea and vomiting for several hours.

Since the blood levels necessary to maintain anaesthesia was far higher than for producing antiemetic effect, the concept of administering subhypnotic dose was introduced.

c. Infusion of subhypnotic dose

After standard induction dose of 2mg/kg (or) even with a loading, small dose of propofol, 10mg to 20 mg, and then starting an infusion of propofol at 10μg/kg/minutes

produces good antiemetic effect. The major advantage of such infusion is that this infusion can be continued in the post operative period for prolonged protection from post operative nausea and vomiting, without any major side effects and the patient will be more comfortable. This technique can be used even when the patient is undergoing surgery in regional anaesthesia.

d. Single subhypnotic dose at end of surgery

Studies have shown that a single subhypnotic dose of 0.5mg/kg or 10mg-20mg is adequate to provide good antiemetic effect upto 4 hrs to 6 hrs post operatively. Even the emetic events were far less in the first 24 hours period. This technique has been tried in mastoidectomy, thyroidectomy, and specific gynaecological procedures done under spinal anaesthesia. A single subhypnotic dose of 20mg intravenously at the end of surgery has been shown to be as good as 4mg of ondansetron or 10mg metoclopromide.

e. "Sandwich technique"

The use of propofol as an induction agent during general anaesthesia and a subsequent single dose of 20mg (or) 0.5 mg/kg, at the end of surgery is called the "sandwich technique". It has been shown to be very effective in procedures lasting for 1-2 hours, with effective post operative relief of nausea and vomiting from 16-24 hours. The main advantage of this sandwich technique is its cost effectiveness in affording antiemesis upto a period of 24 hours. Studies have shown that this technique reduces the need for a rescue anti emetic in the post operative period.

REVIEW OF LITERATURE

1. Yoshitaka fuji et al., in archives of otolaryngology and head and neck surgery 2001, have compared propofol as an antiemetic agent with droperidol and metoclopromide for middle ear surgeries and found Propofol to be a superior agent in preventing post operative nausea and vomiting. In their prospective randomized double blind study on ninety patients undergoing middle ear surgeries, they have administered Propofol 0.5 mg/kg or Droperidol 20µg/kg or Metoclopromide 0.2mg/kg intravenously at the end of surgery. They have observed the patients from 0 hour to 3 hours for early events and from 3 rd hour to 24 hours post operatively for late events. The incidence of patients who were emesis free during the 0- to 3-hour period after receiving anesthesia was 93% for those who received Propofol, 73% for those who received Droperidol, and 70% for those who received Metoclopramide, respectively; the respective corresponding incidence during the 3- to 24-hour period after receiving anesthesia was 90%, 67%, and 60%.

They have concluded that a small dose of propofol is a better antiemetic than droperidol or metoclopramide for the prevention of postoperative nausea and vomiting after middle ear surgery.

2. A Borgeal et al have published a paper on subhypnotic doses of propofol and its direct antiemetic events. They have used a single small subhypnotic dose (10mg=1ml) of propofol and have described large reduction of post operative nausea and vomiting from 81% in control group to 33% in propofol group.

3.Mitsuko Numazaki MD et al – Canadian journal of anaesthesia 2005 Vol 52. In their study on 80 thyroidectomy patients with a single small dose of propofol, (0.5mg/kg) it was proved that propofol has direct antiemetc effects. Further, 3 small single bolus doses were evaluated – 0.25mg/kg, 0.5mg/kg, 0.75mg/kg on thyroidectomy patients. In this study they have used a standard intravenous induction with Thiopentone, maintainance with sevoflurane. At the end of surgery they have randomly administered a small sub hypnotic dose of Popofol intravenously. The subjects were divided into 3 groups and each group received Popofol in doses of – 0.25 mg/kg , 0.5 mg/kg, 0.75 mg/kg. The patients were observed for 24 hours in the post operative period for incidence of nausea and vomiting. The rate of emetic symptoms from 0 to 24 hr after anesthesia was less in patients who had received propofol 0.5 $mg \cdot kg^{-1}$ (15%) or 0.75 $mg \cdot kg^{-1}$ (15%) than in those who had received placebo (60%); ($P < 0.05$). However, there was no difference between propofol 0.25 $mg \cdot kg^{-1}$ (55%) and placebo. This study proves the efficiency of subhypnotic doses of propofol in preventing post operative nausea and vomiting.

4. Ramanathan et al In Internet journal of anaesthesia ,2003 . have used a small single bolus dose of propofol 20mg IV and have compared with a control group of 2ml normal saline IV, and have shown that there was reduction in incidence of post operative nausea and vomiting when 20mg propofol was administered at the end of surgery. Their study group consisted of 40 female patients undergoing vaginal hysterectomy under subarachanoid block. The antiemetic effect in their study lasted from 4 hours to 24 hours. The incidence of post operative nausea and vomiting in the study group was 25% only while the incidence was 65 % in the control group.

This study proves the efficiency of a small dose of propofol – 20 mg intravenous for

regional anaesthesia procedures in preventing nausea and vomiting in the post operative period.

5. Bouley and Craig R, - in their article in current opinion in Anaesthesiology, December 2001, have described high incidence of post operative nausea and vomiting in otolarygological procedures and that inclusions injection propofol in the anaesthetic technique reduced the incidence as much as 40%.

6. Soppitt AJ, Glass PS, Howell S, Gan TJ have surveyed the use of propofol for its antiemetic effects in United States.

In their survey they found that in a group of 150 anaesthesiologist, 84% used propofol as an anaesthetic agent because it had antiemetic properties. 63% reported that a single induction dose of propofol for surgeries less than 1 hour prevented post operative nausea and vomiting.

7. Tong J. Gan et al – Deparment of Anaesthesia , duke medical center U.S.A, have given elaborate guidelines regarding investigation and evaluation of agents that prevent post operative nausea and vomiting. In their study they have enumerated the risk factors for post operative nausea and vomiting and have outlined the measures to prevent it. They have reported propofol as an antiemetic under guideline IA.

8. Apfel et al – in their classic study with 2722 patients developed a simplified risk score consisting of four predictors. 1) female gender, 2) previous history of motion sickness (or) post operative nausea and vomiting, 3) non smoking status, 4) use of opiods. The risk indices were 10%, 21%, 39%, 61%, 79% respectively.

9. Cliff A. Megerian et al – Archieve of otolaryngology , Head and Neck surgery 2000, have studied the effects of post operative nausea and vomiting in outpatient tympanomastoid procedures. They have reported that it is the major reason for readmission after 23 hrs and the cause for prolonged stay in hospital.

10. P. Ewalenko, S Janny, G. Andry – In British journal of Anaesthesia, 1996 , Vol. 77 . They have studied the effect of a 20 hour post operative infusion of propofol 0.1mg/kg/hr and compared with control during their 20 hour study period. There was no incidence of post operative nausea and vomiting in the study group.

MATERIALS AND METHODS

This is a prospective double blind study conducted at Government Rajaji Hospital attached to Madurai Medical College.

After approval by ethical committee, 90 patients of ASA grade I of age group 10-20 years, coming for Modified radical Mastoidectomy were enrolled in the study.

Patients with history of allergy to egg proteins, inadequate starvation, history of smoking, history of motion sickness were excluded from the study.

Patients were randomly allocated into one of the three study groups, each group consisting of thirty patients (n = 30).

Patients were premedicated with injection Pentazocine 0.6mg/kg and Atropine 0.02mg/ kg intramuscularly 45 minutes prior to induction of anaesthesia.

On arrival to the operation theatre, intravenous access was established. Injection ranitidine 50mg was given intravenously. Ringers lactate infusion started.

Pulse oximeter and non invasive blood pressure monitor was attached and pre induction values were recorded.

Fluid infusion rates were calculated from 4:2:1 rule and adequate fluid balance was taken care.

According to the randomly allocated group patients received:

Group A (n=30)

Injection Thiopentone 5mg/kg intravenously for induction.

Normal saline 2 ml at the end of surgery

Group B (n=30)

Injection propofol 2mg/kg intravenously.

Normal saline 2 ml at the end of surgery

Group C (n=30)

Injection Propofol 2 mg/kg intravenously

Injection Propofol 0.5 mg/kg made upto 2ml at the end of surgery

All the 90 patients were maintained with 66% Nitrous oxide and 33% oxygen, injection Atracurium in titrated doses for immobility and facilitating controlled ventilation.

Injection pentazocine was used as analgesic.

After positioning, surgery proceeded. Pulse, blood pressure, oxygen saturation were monitored continuously.

Duration of the surgery was recorded. At the end of surgery, patient ventilated with 100% oxygen for 10 minutes and residual neuromuscular blockade was antagonised with Neostigmine 0.04mg/kg and Atropine 0.02mg/kg intravenously.

If the patient belonged to study Group C, patient received 0.5mg/kg of propofol at the end of surgery, when the last sutures were being applied.

when propofol was administered as induction agent it was mixed with 1ml of 2% preservative free Lignocaine.

All the patients were extubated inside the operation theatre and observed for 10 minutes before shifting to recovery room.

Patients were observed for 4 hours in recovery room and for 24 hours in post operative

ward.

The nausea and vomiting were graded as follows:

Emesis score

0 - no nausea

1 - mild nausea

2 - severe nausea

3 - retching

4 - one episode of vomiting

5 - vomiting greater than one episode

Parameters observed during intraoperative period were- pulse rate, blood pressure and oxygen saturation.

The post operative analgesia was injection diclofenac – 25 to 50mg intra muscular.

All the emetic events were recorded on hourly basis.

0-1 hours	**1-2 hours**	**2-3 hours**	**3-4 hours**	**4-24 hours**	**Rescue anti emetic**

The patient was assessed at the end of the each hour and data was collected about the emetic events that occurred during that hour.

If vomiting occurred more than twice in that hour, the score was recorded as 5, and rescue anti emetic, injection .Metoclopromide 10 mg was given intravenously. The time for first antiemetic administration was noted.

All the events were recorded in the data entry charts and noseworthy anaesthesia record charts.

The study ends at 24 hours from the time of extubation.

The results were analysed with epiinfo software for statistics for epidemiology develop by World health organization

RESULTS AND ANALYSIS

The data that were collected and analysed in this study were emetic events graded on a 5 point scale system

0 – no nausea

1- mild nausea

2- severe nausea

3- retching

4- vomiting 1 episode

5- vomiting > 1 episode

Periods of observation were from 0 to 1 hour, 1 to 2 hours, 2to 3 hours, 3 to 4 hours and from 4 to 24 hours.

During statistical analysis Scores 0 and 1 (no nausea or mild nausea) were considered FAVOURABLE EVENTS, and scores 3, 4, 5 – (severe nausea, retching, vomiting 1 time or vomiting > 1 time) were considered UNFAVOURABLE EVENTS.

Statistical analysis was done for each time period in each of the study group to ascertain the incidence of emetic events in that group and compared it with other groups.

The statistical significance was determined with KrausKall Wallis CHI SQUARE TEST. A P value < 0.05 was considered significant

The age and sex comparison were as follows

Table 1. age distribution

Age group	Group A		Group B		Group C	
	Number	Percent	Number	Percent	Number	Percent
10 – 15	6	20 %	11	36.7 %	10	33.3 %
15- 20	24	80 %	19	63.3 %	20	66.7%
Total	30	100%	30	100%	30	100%
Mean	17.2		16.2		16.2	
S.D.	2.7		3.2		3.5	

From the table it is evident that age distribution is comparable in the three groups and distribution of patients in the age group 15 to 20 years is more.

Table 2: sex distribution

Sex	Group A		Group B		Group C	
Male	24	80 %	15	50 %	11	36.7 %
Female	6	20 %	15	50 %	19	63.3 %

Group A consists of more male patients

Group B consists of equal gender distribution

Group C Consists of more female patients

Analysis of the immediate recovery period: 0 hour to 1 hour:

Event	Group A		Group B		Group C	
points↓	**Score**	**Percent**	**Score**	**Percent**	**Score**	**Percent**
0	9	30 %	6	20 %	11	36.7 %
1	1	3.3 %	13	43 %	9	30 %
2	0	0 %	6	20 %	4	13.3 %
3	7	23.3 %	4	13.3 %	3	10 %
4	10	33.3 %	1	3.3 %	3	10 %
5	3	10 %	0	0 %	0	0 %

Analysis:

Group A – Favourable event points – 10

Unfavourable events points – 20

Group B – Favourable event points- 19

Unfavourable event points – 11

Group C – Favourable event points – 20

Unfavourable event points – 10

Statistical significance:

P value between Group A and Group B - 0.0388 (significant)

P value between Group A and Group C - 0.0201 (significant)

P value between Group B and Group C - 0.9999 (not significant)

Thus in the analysis we can see that in both group B and Group C the incidence of emetic events are very low and similar , where as the incidence is high in group A.

Analysis of early events : 1 hour to 2 hours

event	Group A		Group B		Group C	
Points↓	Score	Percent	Score	Percent	Score	Percent
0	1	3.3 %	9	30 %	14	40.7 %
1	5	16.7 %	13	43 %	7	23.3 %
2	6	20 %	6	20 %	5	16.7 %
3	7	23.3 %	2	6.1 %	2	6.7 %
4	3	10 %	0	0 %	2	6.7 %
5	8	26.7 %	0	0 %	0	0 %

Analysis:

Group A – Favourable event points – 6

Unfavourable event points – 24

Group B – Favourable event points- 22

Unfavourable event points – 8

Group C – Favourable event points – 21

Unfavourable event points – 9

Statistical significance:

P value between Group A and Group B - 0.0001 (significant)

P value between Group A and Group C - 0.0002 (significant)

P value between Group B and Group C - 0.9999 (not significant)

In the second hour analysis we can see that the emetic events are high in group A and comparably lower in the groups B and C

Analysis of 2nd to 3rd post operative hours

Event	Group A		Group B		Group C	
Points↓	Score	Percent	Score	Percent	Score	Percent
0	5	16.7%	7	23.3 %	13	43.3 %
1	6	20 %	4	13.3 %	7	23.3 %

2	5	16.7 %	7	23.3 %	3	10 %
3	2	6.7 %	5	16.7 %	3	10 %
4	5	16.7 %	2	6.7 %	3	10 %
5	7	23.3 %	5	16.7 %	1	3.3 %

Analysis:

Group A – Favourable event points – 11

Unfavourable events points – 19

Group B – Favourable event points- 11

Unfavourable event points – 19

Group C – Favourable event points – 20

Unfavourable event points – 10

Statistical significance:

P value between Group A and Group B - 0.7888 (not significant)

P value between Group A and Group C - 0.0388 (significant)

P value between Group B and Group C - 0.0388 (significant)

The emetic events are almost similar in Group A and Group B at the 2nd to 3rd hour. The incidence of nausea and vomiting is still lower in Group C when compared to Group A and B

Analysis of 3rd to 4th hour

event	Group A	Group B	Group C

Points↓	Score	Percent	Score	Percent	Score	Percent
0	6	20 %	5	16.7 %	15	50 %
1	5	16.7 %	5	16.7 %	5	16.7 %
2	4	13.3 %	8	26.7 %	2	6.7 %
3	6	20 %	4	13.3 %	6	20.0 %
4	2	6.7 %	2	6.6 %	2	6.7 %
5	7	23.3 %	6	20.0 %	0	0 %

Analysis:

Group A – Favourable event points – 11

Unfavourable events points – 19

Group B – Favourable event points- 10

Unfavourable event points – 20

Group C – Favourable event points – 20

Unfavourable event points – 10

Statistical significance:

P value between Group A and Group B - 0.7884 (not significant)

P value between Group A and Group C - 0.0387 (significant)

P value between Group B and Group C - 0.0201 (significant)

The patients in group C still have a distinct advantage of low incidence of emetic events than that of Group A and B. The emetic events in group B is similar to that of Group A.

Analysis of 4th hour to 24th hour – late events

Event	Group A		Group B		Group C	
Points↓	**Score**	**Percent**	**Score**	**Percent**	**Score**	**Percent**
0	7	23.3 %	7	23.3 %	12	40 %
1	6	20 %	5	16.7 %	5	16.7 %
2	4	13.3 %	7	23.3 %	3	10 %
3	5	16.7 %	2	6.7 %	3	10 %
4	4	13.3 %	2	6.7 %	0	0 %
5	4	13.3 %	7	23.3 %	7	23.3 %

Analysis:

Group A – Favourable event points – 13

Unfavourable events points – 17

Group B – Favourable event points- 12

Unfavourable event points – 18

Group c – Favourable event points – 17

Unfavourable event points – 13

Statistical significance:

P value between Group A and Group B - 0.9999 (not significant)

P value between Group A and Group C - 0.4386 (not significant)

P value between Group B and Group C - 0.3014 (not significant)

The analysis of late postoperative emetic events implicate that group c patients have low incidence of nausea and vomiting while the difference is not seen in group A and B

SEVERITY OF POST OPERATIVE NAUSEA AND VOMITING: QUANTIFICATION OF EMETIC EVENTS

	GROUP A	GROUP B	GROUP C
RANGE	0-22	0 – 15	0 – 20
MEAN	12.77	8.94	6.83
S.D.	4.95	4.38	5.45

The above table quantifies the range of event point that were scored by the patients in the study.

RANGE: The lowest score that was obtained by a patient in any of the group was 0 – no

nausea and vomiting throughout the 24 hour period. The highest score was recorded in the group A is 22, 15 in group B and 20 in Group C.

MEAN: The average emetic event score obtained by patient belonging to Group A is 12.77 which is higher than Group B- 8.94 and Group C - 5.45. The value of mean is lowest in group C suggesting that the average scores obtained by patients if group C is lower than group A and B .

RESCUE ANTI EMETIC REQUIREMENT

	GROUP A		GROUP B		GROUP C	
	Number	**Percent**	**Number**	**Percent**	**Number**	**Percent**
GIVEN	22	73.3	17	56.7	10	33.3
NOT GIVEN	8	26.7	13	43.3	20	66.7

Statistical significance:

P value between Group A and Group B - 0.2789 (not significant)

P value between Group A and Group C - 0.0044 (significant)

P value between Group B and Group C - 0.1194 (not significant)

On analyzing the statistical significance in rescue anti emetic administration, we can see that group A had highest requirement of rescue antiemetics which is not very higher than that from Group B. but requirement in Group C is very low and comparable with that in Group A

	GROUP A	GROUP B	GROUP C
RANGE	45 – 260	150 - 290	150 - 460
MEAN	133.9	220.6	335.0
S.D.	68.7	42.3	125.9

From this we can see that group A patients required rescue antiemetic earlier (133 minutes) than group B and C. group C patients required rescue antiemetic only after an average of 335 minutes

Mean arterial pressure

	GROUP A	GROUP B	GROUP C
RANGE	88-110	82 -108	80-106
MEAN	95.6	90.3	91.3
S.D.	4.6	18	5.8

Mean arterial pressure is comparable in all the 3 groups

DISCUSSION

Post operative nausea and vomiting is a major post operative problem in mastoidectomy surgeries. It is due to various factors like middle ear handling, use of nitrous oxide and opioids. In centres where Tympanomastoid surgeries are done as out patient procedures, post operative nausea and vomiting is the major cause for readmission. There are many prophylactic and treatment modalities to prevent and treat post operative nausea and vomiting. Of special interest is use of Propofol. Propofol is an intravenous induction agent that has two distinct and clear cut advantages - one is its quick recovery and other is its antiemetic effect when used in day care surgeries

Use of propofol as maintenance agent has clear advantages in preventing post operative nausea and vomiting. But this regime is costly. Use of subhypnotic dose in addition to using propofol for induction dose has been described as sandwich technique and has been shown to prevent post operative nausea and vomiting for upto 24 hours post operatively.

In our study, the control group, Group A consisted of mastoidectomy under general anaesthesia with thiopentone induction, nitrous oxide, oxygen, opioid, (Pentazocine) maintenance. In this group, Nausea and vomiting in the first 4 hours and subsequent 20 hours was distressing to the patients. Nearly 65% (20 out or 30) had severe vomiting that required an rescue antiemetic therapy, early in the post operative period. This group also had persistent vomiting that required a second dose of antiemetic agent.

In their study, Cliff A. Megerian has described the same fact that in out -patient tympanomastoid surgeries, only one third patients could be safely discharged on the same day.

75% patients had pain or post operative nausea and vomiting as the factor that prevented their discharge, out of which post operative nausea and vomiting contributed to the 65%. The main reason being pain could be tackled early and effectively NSAID therapy, but nausea and vomiting could not be treated with the same precision using a single drug regime.

Bailey Craig R, in the journal current opinion in anaesthesiology have described propofol as intravenous induction agent that could provide clear headed recovery, less incidence of nausea and vomiting, and earlier hour discharge in outpatients procedures with lesser use of antiemetic agents. When studying mastoidectomy surgeries, even though propofol protected the patient during early recovery period upto 3 hours, and patients were discharged early, readmission to hospital before 23 hours was still high due to post operative nausea and vomiting. The main reason was induction dose did protect the patient from post operative nausea and vomiting to be discharged early, but vomiting occured in the late post operative period necessitating a readmission.

This is true in the study group B. The patients were induced with propofol and normal saline 2ml was given at end of surgery. Though the incidence of nausea and vomiting in the first 2 hour post operative period was significantly low (36.7%,26.7%), the incidence was still higher in the remaining 22 hours. The only difference was, the rescue antiemetic requirement was (56% in group B and 75% in group A) less and the need for a second dose of rescue antiemetic was low.

In our study group C, propofol in a does of 2mg / kg was used to induce general anaesthesia. Anaesthesia was maintained with opioid , nitrous oxide and oxygen. At end of

surgery, propofol 0.5mg /kg was administered. After adequate recovery from neuromuscular blockers, patient was extubated. The incidence of Nausea and vomiting was very low (43%) in the immediate recovery for the first 4 hours. During the 4-24 hour period, though the incidence of nausea was the same, events of retching and vomiting were very low. The duration of administration of the first antiemetic in also significantly longer (335 Minutes in group C compared with 130 minutes in group A and 220 minutes in group B) . Moreover, second dose of antic emetic was rarely needed in this group.

Yoshitaka et al have done a comparative study with 0.5 mg/kg of propofol administered at the end of surgery the incidence of emesis free period in the first 3 hours postoperatively was 93% and in the 3-24 hour period was as low as 90%. There were no clinically adverse events in any of the study groups.

Propofol at such small doses lack sedative, dysphoric and extrapyramidal effects

SUMMARY AND CONCLUSION

Mastoidectomy done under general anaesthesia predisposes the patient to nausea and vomiting in the postoperative period

Use of propofol as an induction agent in mastoidectomy surgery protects the patient from nausea and vomiting in the early post operative period (0-4 hours). The antiemetic effect in more pronounced in the first and second post operative hour. But after 4 hours, the incidence of nausea and vomiting reaches the same value of any technique which does not use propofol.

Use of propofol for induction and then administering a subhypnotic dose (sandwich technique) at end of surgery afford protection from nausea and vomiting for upto 24 hours. The incidence of nausea and vomiting in the early post operative period is lower than using propofol for induction alone, and significantly lower in the remaining 4-24 hours as reflected by lower incidence of rescue antiemetic requirement and longer time intervals for administration of first antiemetic dose.

Combination of induction dose of propofol and subhypnotic dose of propofol at the end of surgery prevents nausea and vomiting in both early and late post operative period.

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PROFORMA AND OBSEVATON SHEET

STUDY GROUP: DATE:

A	THIOPENTONE(I)	
B	PROPOFOL(I)	
C	PRO(I)+ PRO(SH)	

NAME: AGE: SEX: IP.NO.

SYSTEMIC DISEASES:

PREVIOUS SURGERIES/ANAESTHESIA:

ALLERGY/DRUG INTAKE:

VITALS: WEIGHT: PULSE: BLOOD PRESSURE: R.R.

GENERAL: ANEMIA: CYANOSIS: EDEMA:

SYSTEMIC:
CVS: RS: P/A: CNS:

STARVATION: HYDRATION:

ASA RISK:

AIRWAY ASSESSMENT:
PREMEDICATION:
INDUCTION:
INTUBATION:
MAINTAINANCE:
FLUIDS:
MONITOIRING:
DURATION OF SURGERY:
REVERSAL:
INTRAOP EVENTS IF ANY:
RECOVERY TIME:

TIME											
PULSE											
BP											
SPO2											

MODIFIED ALDERETE RECOVERY SCORE: AFTER EXTUBATION

ACTIVITY	
RESPIRATION	
CIRCULATION	
CONCIOUSNESS	
OXYGEN SATURATION	

ACTIVITY: 2- MOVES ALL 4 LIMBS, 1- MOVES 2 LIMBS, 0- UNABLE TO MOVE

RESPIRATION: 2- BREATHES DEEP& COUGHES, 1-DYSPNEIC & SHALLOW, 0-APNEIC

CIRCULATION: 2- BP=BASELINE BP+20, 1- BP= BL BP+ 20-50, 0- BP=>BL BP+50

CONCIOUSNESS: 2- FULLY AWAKE, 1- AROUSABLE, 0- NO RESPONSE

O2 SATURATION: 2- SPO2> 92%, 1- SPO2 >92% WITH O2 , 0- SPO2<90% WITH O2

PONV score:
0 = No nausea/vomiting

1 = Mild Nausea

2 = Severe Nausea

3= Retching

4=One episode of vomiting

5= Vomiting greater than 1 episode

0-1 HOURS	1-2hrs	2-3 hrs	3-4 hrs	4-24 hrs

EARLY EVENTS: **LATE EVENTS:**

-

Minimum score: 0
Maximum score: 25
Observed score: ____

TIME INTERVAL BETWEEN EXTUBATION AND FIRST DOSE ANTI

EMETIC:_____

RESCUE ANTIEMETIC-

INJ METOCLOPROMIDE 10 MG IV IF PONV SCORE EXCEEDS 5- (YES/NO)

PHARMACOLOGIST VIEW OF EMETIC STIMULI