A COMPARISON BETWEEN GINGER AND METOCLOPRAMIDE IN THE PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN HOSPITAL UNIVERSITI SAINS MALAYSIA

by

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DEDICATIONS

Annually, anaesthesia is given to more than 75 million patients worldwide. In an average, about one third of these patients suffer from post operative nausea and vomiting. (Apfel CC et al., 2004) The needs for these surgical patients suffering from post operative nausea and vomiting and for quality preventive care have been a great source of inspiration and motivation for me to undertake this preliminary study as my research project.

This dissertation is dedicated to all anaesthetists in Malaysia, as we believe in the richness of learning and acquisition of new knowledge put into good clinical practice.

This is a new scope of study in Malaysia and as such, I would also like to dedicate it for future researchers, who look into creating a better and concern medical services in Malaysia.

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LIST OF ABREVIATIONS

A	Alpha
ASA	American Society of Anaesthesiologists
ASA 1	ASA physical health status grade 1
ASA 2	ASA physical health status grade 2
B	Beta
CCAS	Continuous Chromatic Analogue Scale
CI	Confidence Interval
CTZ	Chemo Triggering Zone
D	Duration
DS	Discrete Scale
D2	Dopamine Type 2 receptor
E	Entity
GIT	Gastro Intestinal Tract
HUSM	Hospital Universiti Sains Malaysia
IV	Intra Venous
MI	Maximal Intensity
N	Population size
n	sample size, number of data points, or number of trials in
OT	Operation Theatre
p	Probability value

PONV	Post Operative Nausea and Vomiting
PONRV	Post Operative Nausea, Retching and Vomiting
SD	Standard deviation
TISS-76	Therapeutic Intervention Scoring System
USM	Universiti Sains Malaysia
VAS	Visual Analogue Scale
5HT3	5-Hydroxytryptamine Type 3 receptor

ABSTRAK

Latarbelakang: Secara kesuluruhannya, telah diakui di peringkat dunia bahawa gejala loya-loya dan muntah selepas pembedahan berlaku dengan insiden sebanyak 30% daripada semua pesakit yang dibius. Ia adalah gejala yang sangat menganggu pesakit selepas pembedahan. Ia boleh ditangani dengan perubatan moden seperti metoclopramide atau perubatan alternatif, seperti halia yang digunakan dalam kajian ini.

Metodologi: Ini adalah suatu kajian secara 'randomized controlled trial' untuk mengkaji halia sebagai agen anti muntah yang dibandingkan dengan ubat metoclopramide yang biasa digunakan dalam bidang anestesia dan perubatan. Pesakit-pesakit akan dimasukkan secara rawak dan 'double blinded' dalam dua kumpulan iaitu kumpulan A yang mengambil ubat metoclopramide dan kumpulan B yang mengambil halia. Analisis statistik dijalankan untuk melihat kaitan gejala loya-loya, 'retching' dan muntah selepas pembedahan dengan kedua-dua kumpulan ini.

Hasilan: Faktor-faktor karektor demografi adalah agak sama apabila dibandingkan kedua-dua kumpulan kajian ini. Suatu hasil yang signifikan dari segi statistik telah diperolehi melalui kajian ini, iaitu perbandingan keberkesanan halia dengan ubat metoclopramide dalam mengelakkan muntah selepas pembedahan pada 0 hingga 6 jam, dengan nilai p =0.025 melalui 'Fisher' exact test'. Keputusan kajian yang lain-lain seperti perbandingan keberkesanan halia berbanding ubat metoclopramide dalam mengelakkan

loya-loya dan ‘retching’ selepas pembedahan pada 0 hingga 6 jam dan selepas 6 hingga 12 jam serta mengelakan muntah selepas 6 hingga 12 jam adalah tidak signifikan secara statistik.

Kesimpulan: Keputusan positif halia yang diperolehi melalui kajian ini adalah sesuatu yang mengujakan dalam bidang anestesia dan perubatan. Yakni, kami berharap ini akan memberikan pemangkin yang diperlukan untuk kajian di masa depan tentang keberkesanan halia di Malaysia. Seterusnya, meningkatkan mutu perubatan secara holistik di Malaysia.

ABSTRACT

Background: In general in today's modern world, post operative nausea and vomiting is as common as 30 % of the total patients going under anaesthesia through multiple studies (Lermen J. et al. 1992, Saeeda I. et al. 2004) done around the globe. Post operative nausea and vomiting is a very disturbing outcome after anaesthesia. It may be managed with modern medicine, such as metoclopramide or with alternative medication, such as ginger as studied in this dissertation.

Methodology: This is a randomized controlled trial study to look at effectiveness of ginger against a commonly used, metoclopramide as an anti emetic agent to prevent post operative nausea and vomiting. Patients were grouped into 2 comparable arms in a double blinded method to look at outcome symptoms of nausea, retching and vomiting. Primary and secondary statistical analysis were used to look at the association of post operative nausea, retching and vomiting against tablet metoclopramide and ginger given prior to anaesthesia.

Results: The demographic characteristics were comparable between both groups. There was a significant finding statistically with p-value of 0.025 through Fisher' exact test for association between post operative vomiting within 6 hours for ginger group against metoclopramide group. Other findings of the outcome symptoms of nausea and retching within 0 to 6 hours and more than 6 hours to 12 hours as well as vomiting more than 6 hours to 12 hours were not statistically significant.

Conclusion: This significant results of effectiveness of ginger as a preventive for post operative vomiting is a very promising finding in anaesthetic medical practices. We believe the positive result of ginger will be a catalyser for future study on the effectiveness of ginger in Malaysia. Ultimately, this will help in development of our holistic medicine in Malaysia.

CHAPTER ONE

INTRODUCTION
LITERATURE REVIEW

1.1 Definition of post operative nausea and vomiting

Nausea is an unpleasant sensation in the mouth and upper gastro intestinal tract (Dorland's et al., 2001) that is associated with salivation and giddiness. It may lead to retching or contraction of upper gastro intestinal tract muscles in a reverse direction (John BW et al., 1990) that commonly ends up in throwing out content of stomach known as vomiting. The symptom of nausea and vomiting that happens during the period after reversal from anaesthesia following a surgery is post operative nausea and vomiting. Through literature reviews, the time period is generally taken up to 24 hours post operatively. Post operative pain is undeniably the most worrying matter in any patient going for an operation. However, many adults find post operative nausea and vomiting more distressing than post operative pain itself. (Koivuranta M et al., 1997) Since nausea is a subjective feeling, there is no objective 'standard' method for its measurement until today.

1.2 Epidemiology of post operative nausea and vomiting

The incidence of postoperative nausea and vomiting (ponv) in an untreated adult surgical population receiving general anaesthesia is around 20–30% as cited by Wengritzky et al. in 2010 but this increases up to 80% as elaborated by Myles et al in

2000 in patients with two or more risk factors for ponv. Overall, as discussed in related studies, the incidence of post operative nausea and vomiting in recovery room is 10% (Lerman J et al., 1992), but ranges from 20% to 30% during first 24 hours after surgery (Cohen MM et al., 1994, Quinn AC et al., 1994)

Until late 1960's, the period before introduction of modern anaesthetic agents, the incidence of ponv was significantly very high. It was the time when ether based anaesthetic agents was still commonly used. The incidence of post operative nausea and vomiting was as high as 80% in this 'era of ether'. (Julien et al., 1992, Watcha MF et al., 1992)

1.3 Risk factors for post operative nausea and vomiting

A variety of risk factors have been observed and implicated in contributing post operative nausea and vomiting. (Ravikiran N et al., 2007) These factors are not necessarily treatable as it depends on the origin of the cause. The factors can be divided into patient-related, anaesthesia-related and surgery-related factors. In most of situation, the patient-related factors are non treatable. These patient-related factors are age, weight, gender, pre existing diseases, history of motion sickness or ponv, smoking habit, high level of anxiety and intercurrent illness. Anaesthesia-related factors are anxiolytics taken during pre medication, use of opioids for analgesia, other analgesics usage, reversal drugs usage, gastric distension, inadequate hydration and residual sympathectomy. The surgery-related factors are types of operative procedures, duration of surgeries, blood in gastro intestinal tract (GIT), forcing oral intake in post operative surgical wards, use of opioids, use of other analgesics, pre

mature ambulation (that cause postural hypotension) and pain. The surgical and anaesthetic origins are the possible avoidable and modifiable factors. (Islam S et al., 2004, Haynes GR et al., 1996, Gan TJ et al., 2002, Korttila K et al., 1992, Apfel C et al., 2004 and Tramer MR et al., 2003)

Types of the surgeries are an important predicament for post operative nausea and vomiting (ponv). Certain surgeries that involve abdominal and gynaecology are particularly emetogenic. The incidence of ponv following laparoscopic approach, such as laparoscopic cholecystectomy procedure is as high as 40%. (Nzoghe NP et al., 2001 and Hedayati B et al., 1999) Location of surgeries also plays an important role, typically surgeries in oral and throat, such as tonsillitis has shown to have higher incidences of ponv. The reason for high incidence of ponv in laparoscopic surgeries is due to significant increases in the intra abdominal pressure and diffusion of extra carbon dioxide gas during operation. Whereas, reason high incidence for surgeries in oral and throat are due to irritation in the upper airway and GIT, which leads to increase secretion and stimulation of gag reflex. Anaesthetic method, especially general anaesthesia causes higher incidence of nausea and vomiting in comparison to regional anaesthesia (Cohen et al., 1994) due to direct manipulation of upper airway and side effects of more than one anaesthetic drug. The inhalational agents are directly associated with nausea and vomiting. Inhalational agents, such as cyclopropane, are associated with high incidence, documented as high as 60% in the ‘era of ether’ (Watcha MF et al., 1992) while isoflurane, enflurane and sevoflurane cause less nausea and vomiting. Intravenous anaesthetics are associated in influencing different degrees of emesis (Rabey PG et al., 1992) though the newer agent like

propofol is less emetogenic than the older anaesthetics. Opiods, such as morphine and pethidine, which are commonly used throughout surgery, are strong emetogens. (Kenny GN et al., 1994) It was noted that nausea and vomiting is three times more prevalent in adult female than in males (White PF et al., 1973 and Julien FB et al., 1992). Previous history of motion sickness is a known risk factor. Smokers have decreased risk; however it would not be advised by any physician. Incidence is highest in paediatric age at pre adolescent of 11-14 years old (Rowley et al., 1982) and shows a trend of decreasing as age rises in adulthood. (Burthes P et al., 1957 and Julien FB et al., 1992) Explanation for aging process is the degenerative process that causes reduced reflexes in the physiological responses to vomiting stimuli. Obesity shows higher occurrence of nausea and vomiting because of inhalational agents are stored in adipose tissue and are slowly released into the bloodstream after operation (Palazzo MGA et al., 1984 and Julien FB et al., 1992).

1.4 Physiology of post operative nausea and vomiting

Vomiting is an important defence mechanism against ingestion of toxins. It also commonly happens as a non specific symptom during febrile illness and taking most of common medicines due to higher centre action (brain). In general, the act of emesis involves a sequence of events that are divided into three phases; pre ejection, ejection and post ejection phases. The pre ejection phase comprises of prodromal symptoms of nausea, along side with autonomic signs, such are salivation, swallowing, pallor and tachycardia. The ejection phase comprises of retching and vomiting. Retching is characterized by rhythmic, synchronous, inspiratory movements of the diaphragm,

involving all of the abdominal wall muscles together with external intercostal muscles of thorax. The mouth and glottis are kept closed with antral portion of the stomach contracts, the proximal portion relaxes and the gastric contents moves up and down between stomach and oesophagus. During retching, hiatal portion of the diaphragm does not relax; the increasing pressure of intra abdominal is associated with decreasing pressure in intra thoracic area. Vomiting, which is the expulsion of gastric contents, is the ultimate results of combination of contraction of the rectus abdominis and external oblique abdominis muscles, relaxation of the oesophageal sphincter, increase in intra thoracic and intra gastric pressure, reverse peristalsis motion of stomach and oesophagus with opened glottis and mouth. The post ejection phase consists of autonomic and visceral responses that return the body muscles to a relaxed phase, with or without residual nausea. The complex act of vomiting involves coordination of the respiratory, gastro intestinal and abdominal musculature. (Julien FB et al., 1992) This is controlled by an area in brain, called emetic centre. The evidence for such a centre is based on electrical stimulation on brain and brainstem lesion study. (Borison HL et al., 1989) Anatomic studies have shown that the parvicellular reticular formation has access to motor pathways that are responsible for the visceral and the somatic output involved in vomiting action. This area is situated in the lateral reticular formation close to tractus solitarius in brain stem and is believed to be the emetic centre. (Borison HL et al., 1989 and Andrews PLR et al., 1990) Electrical stimulation of the emetic centre and tractus solitarius will cause immediate vomiting. Stimuli from several areas within the central nervous system can affect the emetic centre. These include afferents from the pharynx, gastro intestinal

tract and mediastinum, as well as afferents from the higher cortical centres (including visual centre and the vestibular portion of vestibulocochlear cranial nerve) and the chemoreceptor trigger zone (CTZ) in the postrema area. (Borison HL et al., 1989 and Andrews PLR et al., 1990) The postrema area is highly vascularized and the vessels terminate in fenestrated capillaries surrounded by large perivascular spaces. No effective blood brain barrier exists in this area and thus the CTZ can be activated by chemical stimuli received through the blood as well as the cerebrospinal fluid from sources like infection and its intermediates, medicines and injury or pressures in the brain. However, direct electrical stimulation of the CTZ does not result in emesis. (Borison HL et al., 1989) The area postrema of the brain stem is rich in dopamine, opioids and serotonin or 5-hydroxytryptamine type 3 (5HT3) receptors. The nucleus tractus solitarius is rich in histaminic and muscarinic cholinergic receptors. These receptors play an important role in the transmission of impulses to the emetic centre.

1.5 Measurement of nausea and vomiting

Nausea is not an observable phenomenon. Thus, it is impossible for an observer to be aware that the patient is nauseated unless the patient tells the observer or doctor. Therefore, only patients can consent to allow nausea to be measured using a self report scale, or through an interview with the patient by a medical staff.

Measurement of nausea and vomiting is important for the evaluation of efficiency of anti emetic treatment. Frequency, duration and intensity of nausea will be assessed in all patients and clinical trial studies. Three different methods are commonly used which are: (i) Discrete Scale (DS), (ii) Visual Analogue Scale (VAS) and (iii) Continuous Chromatic Analogue Scale (ACCS) of measuring nausea and vomiting.

Four different dimensions are studied: (i) Maximal Intensity (MI), (ii) Entity (E), (iii) Duration (D) and (iv) Quantity (Q). (Faverol D et al., 1992) Many instruments are available and have been used to measure the quantitative and qualitative aspects of nausea but they have not been adequately validated and standardized.

The measurement of frequency can be as simple as 'yes or no' answer to a specific question by the patient on the presence of nausea. It can also be measured based on a four to10 point scale. (Faverol D et al., 1992) The duration of nausea has been reported as low in studies. This is because nausea is an intermittent phenomenon and it is difficult to measure. Thus, it requires frequent assessment. (Faverol D et al., 1992)

1.6 Effectiveness of metoclopramide used in post operative nausea and vomiting

Metoclopramide is an anti emetic and gastro prokinetic agent. It is primarily used to treat nausea and vomiting and to facilitate gastric emptying in patients with gastro paresis. The anti emetic action of metoclopramide is due to its antagonist activity at D2 (dopamine type 2 receptor) in the Chemo Triggering Zone (CTZ) in the central nervous system. This action prevents nausea and vomiting triggered by most stimuli. The prokinetic activity of metoclopramide is mediated by muscarinic activity; D2 receptor antagonist and 5-hydroxytryptamine type 4 (5-HT4) receptor agonist activities. It increases peristalsis of the jejunum and duodenum, increases tone and amplitude of gastric contractions and relaxes the pyloric sphincter as well as duodenal bulb. Apart from preventing nausea and vomiting, metoclopramide is used to treat

heartburn caused by gastro oesophageal reflux in people who have used other medications without relief of symptoms. It is also used to treat slow gastric emptying in people with diabetes (also called diabetic gastro paresis), which can cause nausea, vomiting, heartburn, loss of appetite and a feeling of fullness after meals. However, metoclopramide should not be taken if patient has history of allergy to it, or if patients have bleeding or blockage in stomach or intestines, epilepsy or other seizures disorder of brain and adrenal tumour (phaechromocytoma).

1.7 Effectiveness of ginger used in post operative nausea and vomiting

Ginger is a plant that grows in warm climates countries like India, China and South Asia. The ginger plant belongs to *Zingiberaceae* family and is also known as *Zingiber officinale Roscoe*, and occasionally *Z. capitatum* or *Z. zerumbet Smith*. (DerMarderosian et al., 1990) The roots and rhizomes of ginger have played an important role in Indian, Chinese, Japanese, West Indies, South East Asia and African medicine. (DerMarderosian et al., 1990) Ginger has been promoted by people from these countries for various ailments, such as dyspepsia and loss of appetite, as well as an agent of carminative, antiemetic, gastrointestinal stimulant and antibacterial. (Liu WHD et al., 1990)

Ginger is a small plant, typically growing two to four feet in height. It has preferences in warm and humid climate. (Kathryn L et al., 2000) It has narrow, glossy, bright green leaves, and its summer flowers are yellowish green. The rhizome is the part used for culinary and medicinal purposes. In China and Japan, it is commonly been prescribed for headaches, nausea and other stomach problems and colds.

(Yoshikawan M et al., 1994) Ginger is famously, referred by these people as spicy and hot, that warms body and treat cold extremities, improves fatigability and strengthen body after blood loss. (Chang CP et al., 1995) In India, ginger is used in both fresh and dry powdered forms for cooking and Ayurvedic medical practice. (Sharma H et al., 1998) Ayurvedic practitioners describe ginger as pungent with a sweet aftertaste, ginger's virya, or potency is hot. It is used to balance doshas (three organizing principles providing for homeostasis in Ayurvedic medicine), improves symptoms of colds and viral infections, enhances digestion, stimulate appetite and lessen arthritis. In some African countries like Nigeria, ginger has been used to treat malaria and yellow fever. Nevertheless, it has been used to treat urinary tract infections in West Indies. (Bone K et al., 1997)

The rhizome contains different amounts of fatty oil, protein, carbohydrates, raw fiber and water, 2-4% volatile oil and 1% pungent substances. (DerMarderosian et al., 1999 and Fleming T et al., 1998) The volatile oil contains various chemical components including zingiberene, zingiberol and camphorene, which gives ginger its characteristic aroma. (DerMarderosian et al., 1999, Liu WHD et al 1990 and Fleming T et al., 1998) The pharmacology activity of ginger is attributed to presence of the pungent substances of gingerols, shogaol, gingerdiones and zingerone. (DerMarderosian et al., 1999 and Fleming T et al., 1998)

The mechanism of action of ginger in nausea and vomiting has not been fully explained. Nevertheless, studies suggest that its anti emetic action is likely based in the gastro intestinal tract as opposed to the central nervous system. (Lumb AB et al., 1993 and Yamahara J et al., 1990) Holtmann et al. in 1989, studied response of 38

subjects to vestibular or ocular stimulation after premedication with placebo, ginger root and dimenhydrinate. They concluded that neither the vestibular nor the oculomotor system, both of which play a role in motion sickness, were influence by ginger. These observations and the lack of central nervous system side effects in the ginger group lead investigators to rule out central nervous system as site of mechanism of action for ginger in motion sickness. (Holtmann et al., 1989) In another specific study on mode of action of ginger using animal study, the conclusion has been that, the GIT, along the stomach and intestinal lumen is primary site for the action of ginger. The prokinetic action of ginger extract had shown presence of a unique combination of spasmonergic and spasmolytic activities mediated through cholinergic and calcium antagonist mechanism. (Muhammad NG et al., 1996)

1.8 Justification of the Study

Post operative nausea and vomiting is still one of the most common complaints in recovery rooms and post operative surgical wards. In spite of recent advances in modern medicine and anaesthetic practices, there has been no definitive gold standard anti emetic for prevention of post operative nausea and vomiting. (Tramer MR et al., 2001 and 2003) Patients often rate ponv as worse than post operative pain. (Koivuntara M et al., 1997) It results in pain, haematoma, electrolytes imbalance with its complications and wound dehiscence, which causes delay in discharges and inevitably additional resources. (Nakata DA et al., 1999) Even though, multiple studies have been done in this field, the incidences of about 30% are still reported all over the world. This leaves a huge vacuum space for researches to do studies for

improvement in better management of post operative nausea and vomiting. There has not been a study done that looks specifically on the effectiveness of ginger for prevention of post operative nausea and vomiting in Malaysia.

1.9 Objectives of Study

General objective:

The general objective of this study is to compare the effectiveness of tablet ginger against commonly used and established, tablet metoclopramide as an anti emetic agent to prevent post operative nausea, retching and vomiting in anaesthesia practices.

Specific objective:

1. To determine the association of tablet ginger and tablet metoclopramide in terms of clinical status of participants
2. To compare tablet ginger and tablet metoclopramide in terms of reducing incidence of post operative nausea, retching and vomiting
3. To determine the association of tablet ginger and tablet metoclopramide in terms of socio-demographic data

CHAPTER TWO

MATERIALS AND METHODS

2.1 Introduction

This chapter describes the overall view of the designs used in the study. Details of the methodology are explained below. The study was conducted in Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, in the state of Kelantan in Malaysia.

2.2 Study design

This is a double blinded randomized controlled trial study. The overall design is as depicted in Figure 2.0.

Flow Chart of Study Design and Research Methodology

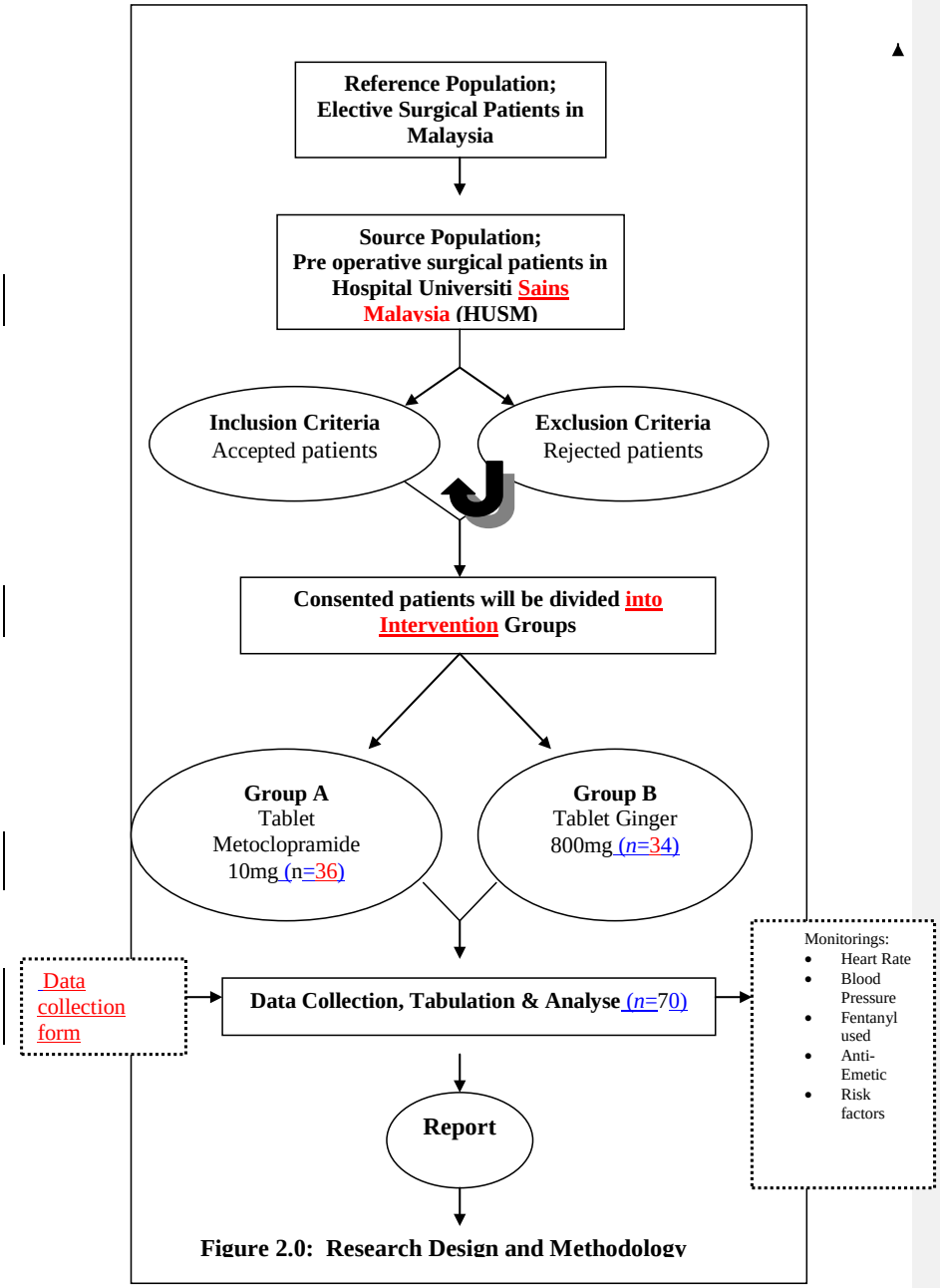

Figure 2.0: Research Design and Methodology

2.3 Study population and sample

The source population are patients who were scheduled for elective surgeries in Hospital Universiti Sains Malaysia (HUSM) with mild to moderate risk to general anaesthesia. The patients were categorised using American Society of Anaesthesiologists (ASA) physical health status grading system with grade 1, which refer to patients who had no underlying medical illness and was in good health for operation. Grade 2 ASA was used to refer to patients who had good control of underlying medical conditions or disease with or without medications. Patients were categorised into four main disciplines of surgeries which were; (i) General Surgery, (ii) Orthopaedic, (iii) Otorhinolarhingology and (iv) Gynaecology. Selection of patients was done by screening patients using inclusion and exclusion criteria. These criteria are as shown in Table 1. The demographic characteristic information recorded from the sample population were (i) Age, (ii) Gender, (iii) Race, (iv) Height and weight with body mass index, (v) Clinical status in ASA grading, (vi) Relevant investigations and (vii) Type of operations. These data is shown in Appendix 2, the Data Collection Observational Indicator form.

2.4 Study Setting and Period of Study

The study was conducted in Hospital Universiti Sains Malaysia (HUSM) within a period of fifteen (15) months from July 2009 till October 2010. Patients were included in the study, 1 day prior to their operation. They were given explanation and recruited after they agreed to give a written consent in ward. They would be followed up from the time of post operative period in recovery, right up to 24 hours after the

time they were reversed from anaesthesia for their operation. Some of these patients were contacted through phone at home, as they were discharged within that 24 hours period in view of their good clinical recovery by their managing doctor in ward.

This inclusion and exclusion criteria are as shown in the table below.

Table 2.1 Inclusion and Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
ASA Physical Health Status Grade 1	Emergency surgery
ASA Physical Health Status Grade 2	Patients who had vomited or had received any antiemetic within 24 hours prior to surgery
Age between 18-70	ASA Physical Health Status Grade 3 to 5
Scheduled for elective surgery	Patients with psychiatric illnesses
	History of drug dependence or alcoholism
	Pregnant Ladies
	Patient who has recent history of taking ginger in any form or taken any anti emetic (within 24 hours)

Key: ASA = American Society of Anaesthesiologists
(Grading system of physical status of patients going for operation)

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Patients were screened and recruited using inclusion and exclusion criteria. The inclusion criteria are: (i) Elective surgical patients, (ii) Aged between 18 till 70 years old and (iii) Pre-operative ASA physical health status grading system category one and two. Patients were excluded from the study if, they had: (i) Emergency surgeries,

(ii) ASA physical health status of grading system category three onwards, (iii) Psychiatric disturbance that precluded complete cooperation, (iv) History of alcohol or drug dependence, (v) Distress or any severe pre-existing medical conditions that limited objective assessment after operation, (vi) Patients, who had taken ginger in form of supplement or in their food or taken any type of anti emetic within 24 hours prior to operation, (vii) Pregnant ladies and (viii) Presence of any life-threatening postoperative complications. This criterion was modified from Wengritzky et al. published in 2009. Based on the inclusion and exclusion criteria, 70 patients were recruited into this study.

2.5 Sampling method and sample size determination

The sample size was calculated using the formula below using 80% power, alpha 0.05 and drop out rate of 20%.

$$n = \frac{P1(1-P1)+P2(1-P2)}{(P1 - P2)^2} \int \alpha\beta$$

Where; n= is sample size; α=alpha; β=beta; P1 is the metoclopramide group (control group); P2 is the ginger group (experimental group)

Based on this formula, the required sample was 330 patients. However, after multiple discussion sessions with supervisors and anaesthetists in Department of Anaesthesiology, HUSM, we have made a decision to include only 70 patients in this

study. The reasons were: (i) Due to short period of time, (ii) Resources factors that were limited and (iii) This will become a 'Pilot Study' in the university (USM). Recalculation for sampling was 35 in each group after considering 20% drop out. The final calculation after drop out was 36 in group A and 34 in group B.

~~2.2.3~~ 2.5.1 Expected limitation (expected drop-out)

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The potential expected limitations of study were (i) patient's refusal in any stage of study period, (ii) cancellation of operation, (iii) incomplete data form (DCOI) entries, (iv) complicated cases that required long duration operation time.

2.6 Description of the data collection instrument

Literature search was done and the data collection observation form was developed based on literature search and review. The demographic data of observation form was taken from Muhammad Jamil's creation in 2005 at Ayub Medical College, Abbottabad. Demographic variables included were age, sex, race, height, weight, body mass index, education level and status of employment.

The section on clinical status included were diagnosis, type of surgery, duration of surgery, underlying illness, vital signs, height, weight, body mass index (BMI), laboratory results and pre operative physical health status.

In addition, the measurement for nausea, retching and vomiting was modified and incorporated from the 'Index of Nausea and Vomiting' that was developed by Rhodes et al. in 1984, who measured 3 dimensions, nausea, retching and vomiting. This 'Data Collection Observation Instrument' (DCOI) also included operative procedures and

pre operative drug treatment for nausea and vomiting, types and dosage of analgesia agents administered (total amount of fentanyl and parecoxib given). The BMI was calculated from weight and height of the patient. The calculation of BMI is weight (in kilograms) divided by height (in metres) multiplied by height (in metres). In view of majority of patients were Malay (94%), the race was recategorized to Malay and non-Malay.

Scoring system was divided into 3 tables, which requires observation of the three symptoms of nausea, retching and vomiting. An important matter to know here is that all these 3 symptoms are related to each other especially when vomiting is produced. This physiological relation was explained in chapter one. The severe the symptom, the higher class it will be scored in this data collection observational instrument (DCOI). Each table, also scores the time, at when this symptom occurs. Time is referred to as the time, a studied symptom occurs from the time of post operative period (reversal from anaesthesia). Patient's response to either study drugs were scored in periodic tables that also look into degree of severity of these symptoms.

2.7 The Procedure

A preliminary survey was done to find out the number of operations performed in operation theatres in HUSM from the medical records and surgical admission books. This survey was done to ensure the possibility of achieving an adequate sample size using inclusion and exclusion criteria. The DCOI was evaluated. The finding of the survey was discussed and adjustments were made until it was feasible to do the study.

Content and face validity was done among the specialists in the Anaesthesiology Department of HUSM.

A written consent was given to patient to be kept for their reference. Patients were informed about the study flows, their rights as a study participant with necessary contact numbers and addresses of the research faculty and researchers. They received explanations about the procedures of the study and possible risks involves by an anaesthetic medical officer on duty. Patients would sign if they agreed. They were given the option to withdraw at any time during the study.

Patients, who fulfilled the criteria at the admission day, which was 1 day prior to operation, will be included in the study. Selected patients were grouped into Group A and Group B in a double blinded method. Group A was given tablet metoclopramide while group B was given tablet ginger at approximately 30 minutes prior to anaesthesia. Study drug A is metoclopramide; it is in tablet form, round shaped, white coloured, with dosage of 10 mg. It is readily available and prescribed in Malaysian Ministry of Health (KKM) hospitals in Malaysia. Its chemical or systemic name is 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2-methoxybenzamide. Whereas, the experimental drug B; tablet ginger was almost identical. The ginger tablet was round shaped, white coloured with dosage of 400 mg of *Zingiber officinale* root powder. Two tablets of ginger drug will be used to get a dose of 800 mg. Its size is slightly bigger than metoclopramide at about 2.5 mm differences in diameter. The ginger tablet was manufactured by Blackmores LTD, Australia with a Malaysian Ministry of Health approval. Number of approval is MAL 06051553TCR. Many efforts were made to make the study tablets double blinded among the medical staffs and patients

involved in the study. These efforts were: (i) both metoclopramide and ginger tablets were sealed in exactly same type of white mini medication pack, measuring about 3 cm by 6 cm and labelled respectively with capital A and B, where A was blinded metoclopramide tablet and B was blinded ginger tablets, (ii) all the sealed tablets were mixed in a random manner and kept together in a wrapped square shaped box, measuring about 35 cm by 13 cm by 10 cm in dimension with a small oval shaped opening on top and (iii) the preparation and allocation of the drugs were done by a person who is not involved in administrating the drug or documenting observation of patient's conditions intra operatively as well as post operatively.

A standard anaesthesia technique was used for all the patients. Induction of anaesthesia was performed with intravenous (IV) fentanyl 1.0 mcg/kg, followed by IV 1 % propofol 1.5 mg/kg. If ventilation was good and adequate through manual bagging, then IV rocuronium 0.6mg/kg used to paralyze and facilitate intubation. Ventilation of paralyzed patient was controlled mechanically to achieve tidal volume of 8-10 ml/kg and respiratory rate maintained based on end tidal carbon dioxide ($ETCO_2$) guidance to achieve value of 35 to 45 mmHg.

Intra operatively, patient's anaesthesia was maintained with IV rocuronium 0.2 mg/kg at interval of 30 to 40 minutes as required and IV fentanyl 0.5 mcg/kg as required, (the total amount of fentanyl required will be evaluated). No morphine was used in the study. Oxygen and air at 50% ratio and sevoflurane were maintained at 2%. Nitrous oxide was also not used in this study. Data collections intra operatively were heart rate, systolic and diastolic blood pressure were obtained via non-invasive monitoring at regular intervals of 10 minutes during

operation. At the completion of the surgical procedures, both study groups of patients were reversed with IV neostigmine 0.05 mg/kg and IV atropine 0.02 mg/kg. Once stable, the patients were monitored closely in the recovery bay. Rescue antiemetic, IV ondansetron 150 mcg/kg was kept in emergency trolley throughout the period of the study.

Post operatively, all patients were observed and recorded for clinical manifestations for 24 hours. The times of onset of the manifestations were grouped into three periods of time which are: (i) zero to six hours (immediate), (ii) more than six hours to twelve hours (intermediate) and (iii) more than twelve hours to 24 hours (delayed). The onset and manifestation of nausea, retching and vomiting were recorded with a standard scaling system for all study subjects as shown below.

The scaling for nausea is as follows:

0 –No discomfort in mouth and throat

1 –Feeling of discomfort in mouth or throat, with or without giddiness (mild)

2 –No 1 associated with giddiness with or without increase salivation (moderate)

3 –No 2 associated with increase salivation and pre vomiting pressure (severe)

The scaling for retching is as follows:

0 –No pressured feeling in mouth or throat

1 –Feeling of increase pressure without vomiting (mild)

2 –No 1 with gag reflex (moderate)

3 –No 2 with vomitus taste without vomiting (severe)

The scaling for vomiting is as follows:

0 –No vomiting

1 –Minimal vomitus and stops immediately (mild)

2 –Large amount of vomitus and stops after one projectile action (moderate)

3 –Large amount of vomitus with more than one episode (severe)

(Please refer to Appendix 2, the DCOI form)

2.8 Ethical Issues

The study was presented to Research Ethics Committee (Human) of Universiti Sains Malaysia (USM) on 28th September 2009. Issues discussed were introduction of a new drug, ginger tablet for patients in the study, patient's flexibility in accepting as a participant and their confidentiality.

Ethical committee were pleased to approve as the ginger tablet is from an approved source (by Malaysian Ministry of Health) and generally ginger is widely taken by local community in their daily food. Date of approval is 8th October 2009 (Ref. No. USMKK/PPP/JEPeM [217.3.(02). (Please refer to Appendix 1)

2.9 Statistical Analysis

Descriptive and inferential statistics were used to analyze the data. Data was checked, explored and cleaned using PASW version 18.0. Descriptive statistics were used for demographic data. Means, standard deviations, medians and inter-quartile ranges were calculated for numerical variables. Frequency and percentages were calculated for categorical variables.

Simple logistic regression was done to test at univariate level the associated study factors with post operative nausea, retching and vomiting (PONRV) as dependent variable. The results of simple logistic regression values, the crude odds ratio (OR), *p* value and 95% confidence interval (CI) were recorded for each variable. In all statistical analyses, $P < 0.05$, was taken as statistical significant. The data was presented with *p* values as well as 95% confidence intervals whenever appropriate.

To compare the socio-demographic characteristics and clinical variables, chi-square (χ^2) test was used for categorical values. Multiple logistic regression was performed to the model for the associated factors of post operative nausea, retching and vomiting. This, multiple logistic regression analysis was used to control the confounders, at the same time, to detect the association of each factor to post operative nausea, retching and vomiting independently. Interaction term between independent variables, multicollinearity problem and model assumptions were checked for each model. Steps in modelling multiple logistic regression were; (i) Univariable analysis, (ii) Variable selection, (iii) Check multicollinearity, (iv) Check 2-way interaction term, (v) Assess the goodness-of-fit of the model and (vi) Establish final model.

Inferential statistics were used to compare differences of effectiveness of Drug A versus Drug B between the two groups. Independent t-test was used to study the effectiveness of the two study drugs against relation with BMI and duration of operation. Chi-square test was used to look for effectiveness of the two study drugs against gender and occupation. Whereas, Fisher' exact test was used to look for effectiveness of the two study drugs against ASA grading and races. The presence of

nausea, retching and vomiting in both study drugs were analysed with Fisher's exact test for duration of 0 to 6 hours and more than 6 hours to 12 hours, except for nausea within 6 hours period, which was analysed with Chi-square test.