THE EFFECT OF RACE ON THE INCIDENCE OF POST OPERATIVE NAUSEA AND VOMITING IN MODERATE TO HIGH RISK PATIENTS IN SOUTH AFRICA: A PROSPECTIVE STUDY

AHMAD ALLI

A RESEARCH REPORT SUBMITTED TO THE FACULTY OF HEALTH SCIENCES, UNIVERSITY OF THE WITWATERSRAND, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF MEDICINE

JOHANNESBURG

11 SEPTEMBER 2013

DECLARATION

I, **Ahmad Alli**, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

_____

Signed

_____

Signed at

_____

On this date

ABSTRACT

Author: Alli, Ahmad (halothane@gmail.com, Cell: 0827184989)

Co-Authors: French, Shirley (Shirley.French@wits.ac.za, Cell: 0832667556)

Omar, Shahed (Shahed@analyzit.co.za, Cell: 0835695363)

Naik, Bhiken (naikbi@yahoo.com)

Institution: Department of Anaesthesia, University of the Witwatersrand, Johannesburg, South Africa

The effect of race on the incidence of postoperative nausea and vomiting in moderate to high risk patients in South Africa: A prospective study

Background:

Postoperative nausea and vomiting (PONV) is a multifactorial, complex phenomenon that has been widely studied. Little work has been done in assessing the risk of PONV in South African population groups. The aim of the study was to compare the effect of racial background on the incidence of PONV in moderate to high-risk black versus non-black South African patients undergoing general anaesthesia.

Methods

A prospective, controlled observational study was carried out. After an initial power calculation, 82 patients in each group (164 in total) were required for the study. However, due to researcher availability, time constraints and a readjustment of the power calculation, 95 patients at moderate to high risk for PONV were enrolled onto the study over an extended study period of 20 months (initially the study period was planned to be 6 months). 89 patients fulfilling the inclusion criteria were divided according to race into two cohorts. Ondansetron and dexamethasone were used as PONV prophylaxis after induction of general anaesthesia. Propofol was used as the induction hypnotic with isoflurane to maintain anaesthesia. Nitrous oxide, ketamine and droperidol were avoided. Use of analgesics was unrestricted, but neuraxial and nerve plexus regional anaesthesia were avoided. If a

non-depolarising neuromuscular blocking agent was used, a maximum of 2.5mg of neostigmine was given to reverse neuromuscular blockade. Nausea and vomiting were assessed by means of a visual analogue scale in the recovery room and ward. Time intervals to assess degree of PONV were 0 hours (defined by first assessment of a modified Aldrete recovery score of at least 9 out of 10 and Glasgow Coma Scale of at least 14/15), 15 minutes, 90 minutes, 180 minutes, and 24 hours. Reports of incidents of vomiting and complaints of nausea between interviews were obtained from patients through questioning.

Results

There were 59 black participants and 30 non-black participants. There were 17 males and 72 females. There were no differences in the black and non-black groups with regard to gender, past history of motion sickness, past history of post operative nausea and vomiting, ASA status, smoking and anaesthetic time ($p>0.05$). There was a significant difference in the distribution of surgical procedures in the black and non-black participants (Mann Whitney U test, $p= 0.02$), although this did not affect the final result.
On univariate analysis there were significant correlations between black South African ethnicity and nausea at all time intervals and also vomiting. Using multivariate regression analysis, non-black South African ethnicity was identified as a risk factor for PONV. It was found that black South African patients were protected against postoperative nausea, with a RR of 0.41 (95% CI, 0.28-0.60).

Conclusion

In this study we found that black South African ethnicity reduced the risk of PONV as compared with non-black South African ethnicity. We found that non-black South Africans had a similar risk of PONV to that published in international literature and predicted by the Apfel score, whereas the risk of PONV in similar Apfel scored black South African patients was much lower.

PRESENTATIONS ARISING FROM THIS PROJECT

ORAL PRESENTATIONS:

- **South African Society of Anaesthesiologists (SASA) annual congress, 28 February 2011.**

ACKNOWLEDGEMENTS

I am indebted to the following people. Dr Shirley French, my anaesthetic consultant supervisor from the Chris Hani Baragwanath Hospital Department of Anaesthesia, for overall assistance and guidance throughout. Consultant colleagues and head of department (Prof E Oosthuizen) from the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Department of Anaesthesia, for allowing me time on the work schedule to collect data and write up the report. Ward and theatre nurses, at CMJAH, for their patience and assistance with the collection of data. The anaesthetic registrars who agreed to participate in the controlled aspects of the study during the performance of anaesthesia on study participants. Dr Shahed Omar, my critical care consultant colleague, for his advice and assistance in performing the statistical analysis. Juan Scribante and Helen Perrie, from the research office at the CMJAH Department of Anaesthesia, for their invaluable guidance during all aspects of the project. Dr Bhiken Naik, my critical care consultant colleague, whose help was vital during the inception of the project. The South African Society of Anaesthesiologists for the Jan Pretorius grant of funding.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1 - PROTOCOL

Title: The effect of ethnicity on the incidence of post operative nausea and vomiting in moderate to high risk patients in South Africa: A prospective observational study

Dr A Alli, MBBCh (Wits), FCA(SA), Cert Crit Care (SA)
Dr S French, MBBCh (Wits), FCA (SA)
Dr S Omar, MBChB(Medunsa), FC Path(SA), DA(SA), Cert Crit Care(SA)
Dr B Naik, MBBCh (Wits), DA (SA), Diplomate of the American Board of Anesthesiology, Board Certified – Critical Care Medicine

1.1 INTRODUCTION

Postoperative nausea and vomiting (PONV) is common after administration of general anaesthesia. The incidence is up to 70% in high-risk patient groups despite newer antiemetic drugs and various treatment modalities (1). The overall incidence in patients receiving general anaesthesia is approximately 30% (2). Although not associated with increased mortality, PONV is uncomfortable for patients, and can prolong hospital stay, causing reduced patient satisfaction, and increased cost of stay (3,4).

There are specific risk factors that have been associated with increased risk of PONV, and patients with these risk factors receive antiemetic prophylaxis preoperatively (See Table 1.1). Recognised risk factors for postoperative nausea and vomiting have been divided into patient risk factors, anaesthetic risk factors and surgical risk factors.
Patient risk factors are age less than 50 years, female sex, non-smoking status, and history of previous PONV or motion sickness (2,5,6). Anaesthetic risk factors are the use of opioids (7), neostigmine (doses larger than 2.5mg) (8), and the use of volatile agents and nitrous oxide (9,10). The major surgical risk factor is the length of surgery (each thirty minutes of surgery, increases risk by 60%) (5).

Table 1.1: Risk factors for PONV (2-10)

Patient risk factors	• Age – <50 yrs • Sex - female • Non-smokers • History of previous PONV or motion sickness
Anaesthetic risk factors	• Use of opioids • Use of nitrous oxide/ volatiles • High doses of neostigmine (>2.5 mg)
Surgical risk factors	• Long surgical procedures (>30mins duration)

Based on the afore-mentioned factors patients are stratified into high, moderate, and low risk groups. Various scoring systems have been delineated. Logistic regression models have been developed (6,12), but are not used widely. A more recent scoring system uses 4 risk factors (1). These risk factors are female gender, history of motion sickness or PONV, non-smoking status and the use of postoperative opioids for pain relief. In this study, if one, two, three or four of these risk factors were present, the incidences of PONV were 10, 21, 39, 79% respectively.

A composite of the above scoring systems results in a simplified scoring system (13) (See Table 1.2). Patients who have a history of PONV on one occasion, or two of the following other risk factors – female gender, postoperative opioid use, history of motion sickness or non-smoking status, fall into a low to moderate risk group. Patients falling into a moderate to high-risk group are those who have a history of PONV on one occasion and one other risk factor, or three separate risk factors. Patients that fall into a high-risk group are those who have a history of PONV on more than one occasion and one other risk factor.

Table 1.2: A suggested scheme for risk stratification (13)

	Low to Moderate Risk	**Moderate to High Risk**	**High Risk**
Criteria	**A** on one occasion or 2 factors from **B**	**A** on one occasion PLUS > 1 factor from **B** OR >3 factors from **B**	**A** on more than one occasion PLUS > 1 factor from **B**
Prophylaxis	One Agent	Dual Agent	Multimodal (anti emetic drugs and changing modifiable risk factors)

A: History of PONV

B: Female gender, Postoperative opioid use, history of motion sickness, non-smoker, expected surgery greater than 30 mins duration

Ethnic origin may have an effect on the incidence of PONV. There has been a recent retrospective study by Rodseth et al examining the effect of ethnicity on the incidence of PONV in the South African population. The incidence of PONV in non-African patients was 45% and that in African patients was 27%. The authors performed stepwise logistic regression analysis which identified ethnicity as a risk factor for PONV. (14)

It has been reported that Chinese or Asian-American patients are more susceptible to PONV (15). Studies in a laboratory induced motion sickness setting suggest that ethnicity could be a risk factor for PONV (16). It has also been reported that Chinese patients have a higher susceptibility to laboratory- induced motion sickness than Caucasian patients (17). An investigation of patients receiving opioid drugs revealed a difference in the incidence of nausea and vomiting between different race groups (18).

From the available literature there appears to be a correlation between ethnic origin and risk of nausea and vomiting in both a surgical and non-surgical context. This has not as yet been investigated prospectively.

1.2 PROBLEM STATEMENT

PONV is a multifactorial, complex phenomenon that has been widely studied. Although rarely life threatening, it is an extremely unpleasant and costly sequelae to anaesthesia. As ambulatory surgery is becoming increasingly common, methods and drugs to prevent PONV have been investigated. However, these measures are only cost-effective, and efficacious in higher risk patient groups.

There has been little prospective study to assess the risk of PONV in the population groups that we serve in South Africa.

1.3 AIM

To compare the effect of ethnicity on the incidence of PONV in moderate to high risk black versus non-black South African patients undergoing general anaesthesia.

1.4 OBJECTIVES

- To document the incidence of nausea in moderate to high risk non-black patients at predetermined time intervals
- To document the incidence of vomiting in moderate to high risk non-black patients at predetermined time intervals
- To document the incidence of nausea in moderate to high risk black patients at predetermined time intervals
- To document the incidence of vomiting in moderate to high risk black patients at predetermined time intervals
- To document the use of rescue antiemetics in the treatment of PONV in moderate to high risk non-black patients in the postoperative period
- To document the use of rescue antiemetics in the treatment of PONV in moderate to high risk black patients in the postoperative period
- To compare the incidence of nausea in moderate to high risk non-black patients

versus the incidence of nausea in moderate to high risk black patients at predetermined time intervals

- To compare the incidence of vomiting in moderate to high risk non-black patients versus the incidence of nausea in moderate to high risk black patients at predetermined time intervals
- To compare the amount and frequency of rescue antiemetic administration in the treatment of PONV in moderate to high risk non-black patients versus that in moderate to high risk black patients in the postoperative period

1.5 DEFINITIONS

Nausea – This is a patient-defined, subjective feeling. It is best described as the desire to vomit without physical expulsive muscular activity (diaphragmatic flattening, spasmodic anterior abdominal wall and chest contractions, pharyngeal relaxation, soft palate elevation) (19).

Retching – There is no material brought up to the mouth from the stomach despite expulsive muscular activity. This usually indicates vomiting on an empty stomach (19).

Vomiting – Any amount of material being brought up to the mouth from the stomach resulting from expulsive muscular activity is known as vomiting(19).

Postoperative nausea and vomiting (PONV) – This is defined as nausea (PON) and/or vomiting (POV) occurring after the awakening/recovery from the administration of general anaesthesia (19).

American Society of Anesthesiologists(ASA) – This is an educational, research and scientific association of physicians organised to raise and maintain the standards of anesthesiology worldwide (20).

Non-black South Africans – South African patients who are considered to be by social

consensus white, indian or chinese, and who are not considered to be ethnically of Southern African origin.

Black South Africans – South African patients who are considered by social consensus to be ethnically of Southern African origin.

Early Postoperative Period - This is considered to be from zero to two hours post extubation (21).

Late Postoperative Period – This is considered to be from two to 24 hours post extubation (21).

1.6 NULL HYPOTHESIS

The ethnicity of patients undergoing general anaesthesia affects the incidence of PONV.

1.7 METHODOLOGY

Study period

This will include recruitment of patients and data collection, planned over a six month period (extended, however, to 20 months due to patient and researcher availability).

Recruitment of patients

Our patient population will be drawn from one site in Johannesburg– the Charlotte Maxeke Johannesburg Academic Hospital. Both black and non-black South African groups will be drawn from the same hospital.

To show statistical significance 82 patients were planned to be recruited into each group. After a revised power calculation however, in consultation with a statistician, it is decided that a smaller number can be recruited. In total 89 patients will be recruited (59 in the black cohort, and 30 in the non-black cohort); these changes being made due to researcher availability and time constraints. Patients of mixed ethnicity will be included in the

non-black group. Institutional approval for the study will be obtained.

Inclusion criteria:

- 18-70 years old
- Undergoing elective surgery
- Patients receiving general anaesthesia of at least 30 minutes duration (no maximum duration will be specified)
- Moderate to high risk for PONV (See Table 1.1). Patients at moderate or high risk will be selected.
- American Society of Anesthesiologists (ASA) grades 1-3
- Informed consent obtainable

Exclusion criteria:

- Patients expected to undergo total intravenous anaesthesia or regional anaesthesia
- Emergency surgery
- Patients unable to give informed consent
- Patients unable to understand the visual analogue scale (VAS)

Patients will be assessed on the day before surgery, to assess their eligibility, and to obtain informed consent. Anaesthetists responsible for anaesthesia of patients enrolled in the study will be informed that their patients are involved in the study. They will also be informed about the method of standardisation of anaesthesia.

<u>Standardisation of anaesthesia</u>

- Standardised prophylaxis will be given for all patients recruited into the trial. This will be a combination of ondansetron and dexamethasone, at their recommended dose for this indication, as per the South African Medicines Formulary.
- No nitrous oxide will be used.
- Propofol will be the induction agent of choice. This is the induction agent most in use for elective surgery in the study hospital.
- If neuromuscular blockade is to be used, a maximum of 2.5mg neostigmine is to be

given for neuromuscular blockade reversal.

- The remainder of the anaesthetic will be up to the individual anaesthetist involved.

Determination of degree of PONV

The investigator will determine the presence of PONV in the recovery room after confirming that the patient is alert and orientated. This will be defined by the modified Aldrete recovery score and Glasgow coma scale, with minimum values of 9/10 and 14/15 respectively being prerequisites (see Appendix C, p 107).

Assessment of the degree of nausea will be done using a visual analog scale (see Appendix B, p 106), as well as with a questionnaire (see Appendix A, p 104). All data collection will be performed by the lead study investigator (Dr Ahmad Alli).

The visual analog scale (VAS) will be a 10 cm line from zero to 10 with gradations at every centimeter. The patient will have already been introduced to this scale during the taking of informed consent. The patient will be reminded that zero on the scale means "no symptoms" and 10 on the scale means "maximum symptoms". The patient will then be asked to make a mark on the scale. All patients will be required to complete the VAS. There are several drawbacks in using a VAS for assessment of subjective feeling. Patients have differing awareness towards perception of sensations such as nausea. Another disadvantage is that there is a possibility of misunderstanding the method of using the VAS. Despite these disadvantages, the VAS method of nausea assessment for PONV has been previously validated (22). Should patients not be able to communicate adequately in English, standard questions regarding nausea and vomiting will be in the home language of the patient. The 11 official languages in South Africa are English, Afrikaans, isiNdebele, isiXhosa, isiZulu, Sepedi, Sesotho, Setswana, SiSwati, Tshivenda and Xitsonga.

Time intervals to assess degree of PONV will be 0 hours (defined by first assessment of the patient as being alert and oriented), 15 mins, 90 mins, 180 mins, and 24 hours. These assessment time intervals have been validated in previous studies for PONV (21).

Incidents of vomiting and complaints of nausea may occur in between questionnaires. These

reports will be specifically sought out by the investigator at the next planned questionnaire time point and the investigator will add additional notes as necessary to each questionnaire. Administration of rescue anti-emetic, as recorded on the patient medication chart, will also be noted.

After data collection and analysis, results from the two groups will be compared against each other.

Ethical considerations

The patients in the study sample will be extensively advised about their rights if they decided to participate in the study and will be given a patient information leaflet (see Appendix D, p 108). Full informed consent will be taken (see Appendix E, p 110). The Human Research Ethics Committee and the Post Graduate Committee from the University of the Witwatersrand will extensively review the study prior to commencement (see Appendix F, p 111). The study will not be approved for performance if there are any ethical contraventions. The hospital superintendent will also approve the study before it can be conducted (see Appendix G, p112).

The above measures are aimed at protecting the rights and health of the potential study participants.

Costing and acquisition of study materials

The antiemetic prophylactic drugs used will ondansetron and dexamethasone. Funding has been obtained from the South African Society of Anaesthesiologists (Jan Pretorius Fund) to purchase ondansetron for purposes of the study. Dexamethasone is widely available in the hospital and is used for PONV prophylaxis routinely in high risk patient groups.

Questions targeted to patients (see Appendix A, p 104) will be translated into the 11 official South African languages by the Wits Language School at no cost.

1.8 LIMITATIONS OF THE STUDY

Study design

Due to their observational nature, traditional cohort studies do not provide as strong evidence as randomised control trials, and often provide empiric initial evidence in order to motivate for larger, randomised trials. We shall try to minimise bias by controlling some factors that we have identified as potential confounders that could skew the results obtained. Double blinded randomized placebo controlled trials provide the best evidence from a prospective study. The investigator and patients will not be blinded about the group allocation in this study. Withholding treatment or prophylaxis from the patients in this study, or administration of placebo to patients in this study, will not be considered to be justifiable, and thus no placebo or non-treatment group will be included.

Assessment of post operative nausea and vomiting

Although assessment of nausea is difficult as it is a subjective sensation, the degree of nausea can be measured by using a visual analogue scale. This is a validated method of assessing the degree of nausea (21).

Assessment of retching and vomiting is simpler, and the occurrence of these signs can be observed and noted by research or hospital staff.

Social and language issues

Our study samples will be drawn from a patient population with a heterogeneous degree of understanding of English.

We shall address this issue by using, as far as is possible, the patient's home language to conduct the informed consent, and the data collection.

If the patient has an understanding of English sufficient for the purposes of the study (as judged by the investigator), we shall use English to communicate with that patient.

There seems to be a perception that black patients from lower socioeconomic groupings

complain less of symptoms than their counterparts from other races or wealthier groups. There is no direct evidence of this in the literature. Since this could be an issue that may alter the nature of data collected, we shall attempt to minimize the potential of this by ensuring full patient cooperation and understanding during the informed consent procedure.

CHAPTER 2 - LITERATURE REVIEW

This chapter consists of a discussion of the available literature on PONV. It begins by discussing the initial development of the PONV concept, and early ideas about its pathogenesis and treatment. It then discusses the neurophysiology, prophylaxis, treatment and risk factors for PONV. The chapter is concluded by an examination of ethnicity as a risk factor and limitations of risk factor research.

2.1 DEVELOPMENT OF THE PONV CONCEPT

2.1.1 EVOLUTIONARY IDEAS ABOUT NAUSEA AND VOMITING

The human species has evolved various protective mechanisms in order to survive in the habitats that we live in, pain being the most obvious example. On experiencing pain, an individual will reflexively withdraw from the painful stimulus, and a subsequent learned response for the future will be created (130). Another example is diarrhoea; on ingestion of noxious substances gastrointestinal motility and secretion will increase in order to expel the substance from the body with reduced systemic absorption – it is thought that nausea and vomiting fits into a similar context (130). On ingestion of a noxious substance, vomiting will be initiated in order to expel that substance before it passes to the absorptive sites of the gastrointestinal tract. This is the postulated reason for the existence of emetogenic receptors within the intraluminal surface of the stomach (e.g. 5HT3 receptors) (130). Receptors also exist systemically so that if a substance is absorbed into the bloodstream, there is a second emetogenic barrier (e.g. the chemoreceptor trigger zone) that will initiate emesis so that further absorption is limited. Vomiting is involuntary and does not require a cerebral decision making process. The sensation of nausea may act as a stimulus for learned behaviour, and will deter an individual from ingesting the same substance again. Apart from an organism protective phenomenon, nausea and vomiting can also be seen to be a species protective phenomenon (130). For example, nausea and vomiting are more common in children and younger individuals and in pregnant women. Children have less world experience, and are more likely to ingest poisonous substances. In the context of pregnancy,

the first trimester is critical for early foetal development, and spontaneous miscarriages could occur if any ingested toxin reaches the foetus (130).

2.1.2 HISTORY OF NAUSEA AND VOMITING RELATED TO ANAESTHESIA

Nausea and vomiting has been a problem since the inception of general anaesthesia in the 19th century. Even as early as Morton's first few cases of ether based anaesthesia in the 1840's, vomiting was a problem. Vomiting and subsequent aspiration of stomach contents lead to serious morbidity and mortality during general anaesthesia. However, anaesthesia was still in the early stages, and not much attention was paid to this problem. Techniques of airway management, pain relief, and new anaesthetic drug development were at the forefront of anaesthetic research. Nausea and vomiting was not a priority until these "basics" of anaesthetic practice were well established.

Due to instances of high morbidity and mortality due to aspiration, in 1934 it was published in a report that vomiting was the worrisome complication of general anaesthesia (23). This observation was repeated by in 1951 (24). Subsequently, it was discovered that the incidence of anaesthetic death secondary to vomiting and aspiration was more than 10 percent (25). Due to the safety issues regarding vomiting during and after general anaesthesia, the subjective and qualitative sensation of nausea was not considered to be as important.

After World War II, general anaesthesia became much safer, and even more so, after the accelerated drug and technique developments made in the 1980's and 1990's. The cost of anaesthesia also decreased. As a result of this, concerns of safety gave way to concerns of quality of anaesthesia. The subjective sensation of nausea began to play a more important role. Patients were less concerned about the safety of anaesthesia, and more concerned about the quality of care they received.

2.1.3 ANTIEMETIC DRUG DEVELOPMENT

Atropine was the cornerstone of the treatment of nausea and vomiting since the mid-1800s. Anticholinergics were subsequently the most used drugs for the treatment and prevention

of postoperative nausea and vomiting for a long time. As anaesthetic technique grew safer, however, interest in other drugs and techniques for the prevention of postoperative nausea and vomiting became evident (26).

Although having methodological flaws, in one study it was found that there was a significant reduction in the incidence of PONV in patients who received cyclizine for prophylaxis (27). Techniques, such as omission of volatile agents, and use of sole intravenous agents for general anaesthesia were also investigated. Investigators found that less PONV occurred when barbiturates alone were used for general anaesthesia (20). In this study though, the benefits (i.e. less PONV), were outweighed by the disadvantages of barbiturates (i.e. sedation, hypotension). In 1957, it was discovered that less PONV occurred in patients who were given neuroleptics or antihistamines (28). It was studies such as these that fuelled accelerated research into the development of drugs for PONV from classes such as neuroleptics, antihistamines and anticholinergics in 1950's and 1960's (29). A double blind study published in 1970, resulted in metoclopramide becoming the first line treatment for PONV (30). Although many anaesthetic drugs had been known to be risk factors for PONV (31), propofol was much later discovered to have antiemetic properties (32).

The advent of 5HT3 antagonists was a significant leap in the treatment and prophylaxis of PONV (33). Interest in these compounds grew quickly, as they were as effective as existing prophylaxis (i.e. neuroleptic agents), but without the accompanying side effect profile (34). This became the first class of antiemetic agents that was specifically manufactured to prevent and treat emesis secondary to chemotherapy, and postoperative nausea.

The introduction of ondansentron allowed the performance of a large number of relatively well designed and controlled clinical trials examining prophylaxis in PONV. There was concern regarding the performance of these trials, summarised eloquently in a review by Tramer et al (35), due to the fact that the trials all examined a single drug made by a single drug company. The trials performed were often against placebo, and not against an alternative drug. Negative trials were not published, and the quality of anaesthesia during the trials was questioned. These concerns added further fuel to the theories that these trials were biased due to a conflict of interest. However, more 5HT3 antagonists, such as dolasetron and granisetron, were developed by other manufacturers, and this resulted in more widely accepted research being published.

2.1.4 NON-PHARMACOLOGICAL MEASURES AND OTHER DRUGS

Many observations about non-pharmacological measures to prevent and treat PONV have been made. In the 1860s, John Snow used morphine to premedicate patients, and found that this reduced the risk of PONV. This may seem counterintuitive, as opioids are considered to be emetogenic, but it has been found subsequently that adequate analgesia, using opioid or other agents, actually reduces the incidence of PONV (36).

As first noted in patients with brain metastases who were being treated with corticosteroids to reduce brain oedema, these agents were also found to reduce emesis. The mechanism of corticosteroid action in the prevention of PONV has been extensively studied, but still remains unclear (37,38). Wang et al have done extensive work investigating dexamethasone (38,39). Recent work investigating the Chinese acupuncture point P6 has revealed promising results regarding the use of this technique for prophylaxis of PONV (40).

The P6 acupuncture point is situated between the tendons of flexor carpi radialis and palmaris longus on the anterior aspect of the forearm approximately 4cm from the proximal wrist crease. The mechanism by which this is effective is as of yet uncertain (40).

2.1.5 PONV IN THE LITERATURE

Many reviews with differing viewpoints regarding the pathogenesis, prophylaxis and treatment of PONV have been published since the 1930's. The earliest notable publication, which only dealt with postoperative vomiting was in by Smith 1934 (23). Subsequently, other articles reviewing postoperative vomiting were published in the years spanning 1955-1972 (27,41-44). Although the whole concept of PONV was first examined by Palazzo et al in 1984 (45), the actual term "postoperative nausea and vomiting", was first used in the literature in a paper about serotonin receptor mechanisms published in 1992. This term was easily remembered as the acronym "PONV", and has become synonymous with the concept of postoperative emesis. An important systematic review on the pathogenesis, treatment and prevention of PONV by Watcha et al in 1992 remains one of the most widely cited article about the subject (46).

During the late 1980’s and early 1990's, the meta-analysis was developed as a tool for

analysing large pools of data. This, together with the information technology revolution, made it much easier to review the existing evidence regarding all aspects of PONV. Furthermore risk factor research, including the formation of complex risk prediction scores, was made possible by advances in multiple logical regression analysis.
These statistical tools have greater power if the studies examining risk factors or new anti-emetic agents are consistent in design. To this end, one the most cited authors in PONV research, C Apfel, published a paper on how to design PONV trials (21).

2.2 THE NEUROPHYSIOLOGY OF VOMITING

The process of vomiting can be conceptualised as having two parts: the sensation of nausea, and the act of emesis (retching or vomiting).

Nausea is an uncomfortable sensation that is difficult to define, often preceding an episode of emesis. It is a symptom that may be mediated through the limbic system and the frontal lobe.

Emesis is initiated through a series of neuronal interactions primarily arising from the hindbrain. The area responsible for this is located between the obex (opening of the central canal into the fourth ventricle) and the rostral portion of the nucleus ambiguous (retrofacial nucleus) (47). Within this area the nucleus tractus solitarius(NTS) receives afferent fibres relaying sensory data from various sources, mainly abdominal viscera, heart, vestibular system, brainstem area postrema (chemoreceptor trigger zone [CTZ]) and other higher brain centres (48). The NTS contains the subnucleus gelatinosus (associated with gastric sensation), subnucleus centralis (associated with swallowing), the medial NTS (associated with baroreceptor function), and the ventrolateral NTS (related to respiration) (47).

Efferent fibres from the NTS provide input to several locations. The areas receiving input from the NTS, which may be involved in vomiting, include the ventral medulla, the hypothalamus, and areas of the hindbrain medulla. These areas in the hindbrain medulla include the rostral nucleus, ambiguous/retrofacial nucleus (which controls laryngeal and

pharyngeal muscles), the Botzinger/ventral respiratory group (which controls respiratory behaviour) and the dorsal motor nucleus of the vagus (which controls motor function of the lower oesophageal sphincter and stomach) (47).
Sites receiving efferent fibres from the NTS, are activated sequentially, resulting in the act of emesis. Due to the nature of the distribution of these sites throughout the medulla, a "vomiting centre" is not easily anatomically described. These sites are more appropriately recognised as forming a "central pattern generator" responsible for the sequence of events that occur during emesis (47).
Efferent fibres from the NTS have also been described to innervate magnocellular hypothalamic neurons leading to increased plasma vasopressin levels and arterial pressure (47).

The sequence of motor events during emesis consists of both respiratory and gastrointestinal muscle contraction. Gastrointestinal changes include changes in gastric myoelectric activity, reduction in gastric tone, and a large retrograde contraction (48). This retrograde contraction causes the contents of the small bowel to enter the stomach prior to expulsion (49). The oesophagus contracts longitudinally which pulls open the cardiac sphincter of the stomach. The diaphragm and abdominal wall muscles contract, forcing the stomach contents through the upper gastrointestinal tract while the glottis remains closed (48).

These signals are mediated primarily through neurotransmitter pathways, including dopaminergic, histaminergic, cholinergic and neurokininergic (49-51). Toxins and drugs (e.g. opioids, ipecac) can also stimulate the nausea and vomiting centres independently of neurotransmitters (52,53).

2.2.1 AFFERENT INPUTS TO THE NTS

2.2.1.1 ABDOMINAL VISCERA

Enterochromaffin cells in the gastrointestinal tract release serotonin which binds to visceral 5HT3 receptors. This stimulates vagal afferents, conducting impulses to the CTZ (47).

2.2.1.2 HEART

Changes in the contractility of the heart feedback impulses to the CTZ and NTS. The physiology underlying this mechanism is poorly understood.

2.2.1.3 VESTIBULAR SYSTEM

Changes in inner ear labyrinthine stimulation provide afferent stimulation to the NTS (47). The vestibular apparatus is responsible for the sensation of motion sickness. Changes in spatial positioning or pathological inner ear conditions can result in stimulation of the NTS.

2.2.1.4 CHEMORECEPTOR TRIGGER ZONE

The CTZ is the area postrema located on the underside of the medulla oblongata. It is an area of the brain that lacks a blood brain barrier, and this allows systemic blood to flow past it (47). This allows the detection of emetic agents in systemic blood (47). Due to its location, it is also exposed to CSF and thus can detect agents therein as well. The CTZ is more sensitive to toxic stimuli than motion sickness (47). The CTZ also receives vagal afferents from the GIT.

2.2.1.5 HIGHER BRAIN CENTRES

Higher brain centres associated with psychogenic and conditioned vomiting include the

cerebral cortex, amygdala, olfactory tubercle, septum fornix, ventral anterior thalamic nucleus and supraoptic area of the hypothalamus (47).

2.2.2 PONV

The neuronal stimuli causing PONV are complex and multiple, and as of yet not completely well elucidated. Due to the sensitivity of the CTZ to emetogenic agents such as anaesthetic drugs and opioids in the blood and CSF, the CTZ appears to be the area most responsible for PONV. However, perioperatively, GIT vagal afferents and limbic afferents feeding both directly into the CTZ and NTS may also contribute to PONV.

2.3 RECEPTORS AND NEUROTRANSMITTERS INVOLVED IN PONV

The neurotransmitters (and respective receptors) involved in the neuronal pathways for PONV are dopaminergic (DA 2), histaminic (H1), muscarinic cholinergic(Ach), neurokininergic(NK1) and serotoninergic (5HT3).

Opioids are not neurotransmitters, but can have a significant effect on PONV, as these are common drugs used perioperatively. The mechanism is discussed below.
The CTZ contains dopaminergic, histaminic, muscarinic cholinergic, neurokininergic, serotoninergic and opioid receptors. The NTS contains dopaminergic, histaminic, muscarinic cholinergic and neurokininergic receptors.

2.3.1 5HT3 RECEPTORS

5HT3 receptors are a subtype of serotonin (5HT) receptors found in the CTZ and in the GIT (54). Serotonin is released from enterochromaffin cells in the GIT due to noxious or mechanical stimulation. This stimulates vagal afferents which stimulate the NTS. The serotonin released also stimulates the CTZ directly (54).

2.3.2 CHOLINERGIC RECEPTORS

The muscarinic cholinergic (Ach) subtype of these receptors is found in high concentrations in both the NTS and CTZ (50).

2.3.3 DOPAMINERGIC RECEPTORS

The DA2 subtype of dopaminergic receptors is found in both the CTZ and NTS.

2.3.4 HISTAMINIC RECEPTORS

The H1 subtype of histaminic receptors is found in both the CTZ and NTS (54).

2.3.5 NEUROKININERGIC RECEPTORS

Substance P is a member of the tachykinin family. It is released from sensory nerve endings in response to noxious stimuli (e.g. surgical, chemotherapy, external beam radiation) (51). It acts as an agonist to neurokinin receptors in the GIT and in the brain. The receptor subtype NK1 is found in the area between the NTS and the central pattern generator (51). Antagonism of this receptor may have beneficial effects in preventing both early, and delayed PONV (51).

2.3.6 MECHANISM FOR OPIOID INDUCED EMESIS

Opioids can have both excitatory and inhibitory effects on the GIT. When administered exogenously, opioids decrease GIT motility and slow gastric emptying by agonism of central mu receptors (53). Agonism of kappa opioid receptors modulates cholinergic transmission (52). Centrally acting opioid antagonists can reduce the effects of central mu receptor agonism.

2.4 GENETICS OF PONV

There is a paucity of literature investigating the risk of PONV and genetic susceptibility. However, pharmacogenetics play a role in the efficacy of anti-emetic treatments and prophylaxis given to patients at risk for PONV. Differential expression of cytochrome P 450 (CYP450) enzymes such as 2D6 (CYP2D6) can create ultrametabolisers or slow metabolisers (55). Patients who have 3 or more copies of the CYP2D6 gene are more likely to be ultrametabolisers, and may develop PONV despite prophylaxis (56).

2.5 PHARMACOLOGY OF ANTIEMETICS

2.5.1 NEUROTRANSMITTER BLOCKERS

2.5.1.1 5HT3 RECEPTOR ANTAGONISTS (5HT RA'S)

Mode of action

5HT3 RA's are compounds that block the 5HT3 receptors in the CTZ and NTS. This prevents serotonin from acting as an agonist at these receptor sites and as a result cause blockade of the serotonin mediated cascade of nausea and vomiting.

Uses

5HT3 RA's have been found to be useful for both prevention and treatment of PONV (54). They are also used successfully for chemotherapy-induced nausea and vomiting. However, they have been found to be less useful in late PONV (54).

Examples

Ondansetron, granisetron, dolasetron, ramosetron and tropisetron are examples of 5HT3 RA's.

Other effects

5HT3 RA's are relatively safe agents having little cross receptor effects. They have no action on dopaminergic, cholinergic or histaminic receptors. Granisetron is the most receptor specific of the agents in this class.

Common adverse events include asymptomatic prolongation of the QT interval, and headache (54).

Less common adverse events include constipation, somnolence, diarrhoea, ataxia, light-headedness, and muscle pain (54).

Metabolism and pharmacogenetics

All 5HT3 RA's are metabolised in the liver by CYP450. Ondansetron and dolasetron are metabolised by the CYP2D6 isoform. This may be associated with adverse drug interactions, poor metabolism in patients with CYP2D6 deficiency (leading to accumulation of free drug) and ultra metabolism in patients with increased CYP2D6 isoform levels (leading to faster metabolism and shorter durations of action) (55).

2.5.1.2 DOPAMINERGIC RECEPTOR ANTAGONISTS(DA2 RA'S)

Mode of action

DA2 RA's act on DA2 receptors in the CTZ and NTS to prevent and treat PONV (54).

Uses

DA2 RA's have been used historically for the treatment of nausea and vomiting. They were also one of the earliest drug classes used for the prevention and treatment of PONV. They are also used as sedative agents and as anti-psychotic agents.

Examples

There are three classes of DA2 RA's. These are the phenothiazines, benzamides and the butyrophenones.

The phenothiazines (e.g. chlorpromazine, fluphenazine, prochlorperazine) have been used historically to treat PONV, but the adverse effects associated with their use (e.g. sedation, lethargy) have limited their usefulness.

The benzamides (e.g. metoclopramide, domperidone) are used for the treatment of PONV and, more frequently, used to treat nausea and vomiting in other contexts (e.g. chemotherapy induced).

The butyrophenones include droperidol and haloperidol.

Other effects

DA2 RA's have different degrees of selectivity for DA2 receptors, and can also act on

cholinergic and serotonergic receptors (54).

Anticholinergic side effects include confusion, dry mouth, constipation, blurred vision and urinary retention (54).

Other DA receptors in extrapyramidal pathways can also be antagonised leading to extrapyramidal side effects such as tardive dyskinesia, myoclonus, akithesia and neuroleptic malignant syndrome (54).

Phenothiazine agents have less extrapyramidal side effects, but have fallen out of favour due to their sedative properties. Benzamide agents are less sedating, but have the potential to cause extrapyramidal side effects. The efficacy of benzamide agents for prevention of PONV is at doses that are more likely to cause adverse effects. Butyrophenones are most selective for the DA2 receptor subtype, and therefore have fewer side effects, but still are sedating, and can have extrapyramidal effects.

Less common side effects include hypotension and supraventricular arrythmias (54).

Droperidol and the FDA "Black box" warning

Droperidol is an effective antiemetic agent that was removed from practice in December 2001, particularly in North America and Europe due to a US Federal Drug Administration "black box" warning. This warning was issued due to an association of droperidol with potentially fatal cardiac dysrythmias of the torsades de pontes variety (57). The FDA based its decision on a review of cases where droperidol was used. In only ten of those cases, was the dose of droperidol less than 1.25 mg (57). There are many confounding factors in the aforementioned cases, and hence it is difficult to draw a conclusive cause and effect relationship. Based on the analyses used, the incidence of fatal cardiac dysrhythmias secondary to droperidol use is estimated to be 74 in 11 million (3). Recent literature has found no difference between QTc prolongation in droperidol versus placebo (58) or droperidol versus ondansetron (59), at antiemetic prophylactic doses of droperidol (i.e. less than 1.25mg). This adds to the controversy of the FDA ruling (60).

2.5.1.3 CHOLINERGIC (MUSCARINIC) RECEPTOR ANTAGONISTS (ACH RA'S)

Mode of Action

Ach RA's block emetic acetylcholine receptors in the pons and cerebral cortex (54).

Uses

Ach RA's are amongst the oldest antiemetics. The relatively high incidence of adverse effects have limited their use in prophylaxis and treatment of PONV. Scopolamine is highly effective in motion sickness induced emesis (109).

Examples

Scopolamine is the agent in this class that remains in relatively common use. It is thought to block the cholinergic transmission between vestibular nuclei and higher centres in the brain, and between the reticular formation and the central pattern generator (54).

Other Effects

Anticholinergic agents cause confusion, dry mouth, sedation, urinary retention, miosis and constipation. These effects are relatively common and limit the use of these agents (54).

2.5.1.4 HISTAMINE (H1) RECEPTOR ANTAGONISTS (H1 RA'S)

Mode of action

H1 receptor agonism causes peripheral effects such as dilation and increased capillary permeability and induction of emesis via the NTS.

H1 RAs block the H1 receptor subtype in the NTS (54). They also block cholinergic receptors in the vestibular apparatus. They are thought to act on the central pattern generator and vestibular system (54).

Uses

H1 RA's are highly effective in treatment of motion sickness, and prevention and treatment of emesis after middle ear surgery (108).

Examples

H1 RA's used to treat and prevent emesis include cyclizine, dimenhydrinate, diphenhydramine, hydroxyzine, promethazine and meclozine.

Other effects

Common adverse effects of H1 RA's include sedation, dry mouth and constipation (54). Less common effects include confusion, blurred vision and urinary retention (54). The combination of promethazine and intravenous opioid can cause significant respiratory depression and sedation.

2.5.1.5 NEUROKININ RECEPTOR ANTAGONISTS (NK1 RA'S)

Mode of Action

NK1 receptors are found in high concentrations in the area postrema (51). These receptors are thought to play an important role in emesis. Substance P acts as an agonist to these receptors. NK1 RA's block the action of substance P. NK1 RA's are thought act on neurons in the area postrema as well as the afferent relay station (51). The afferent relay station is an area that carries neurons from the medial NTS to the central pattern generator (i.e. vomiting centre). This area has not been definitively isolated in humans.

Uses

This is a new class of drugs which is currently being researched with increasing interest. The NK1 RA's are thought to be effective for both delayed and early PONV (51). The first member of this class (aprepitant) has been investigated for use in chemotherapy induced nausea and vomiting.

Examples

Aprepitant is a new agent with NK1 RA activity that has undergone studies in human subjects.

Other effects

Asthenia, hiccups, diarrhoea, elevation in liver function tests, dizziness and gastritis are among the most common side effects observed in patients treated with aprepitant (51).

2.5.2 NON-NEUROTRANSMITTER BLOCKING AGENTS USED FOR PONV

2.5.2.1 CORTICOSTEROIDS (DEXAMETHASONE)

Mode of Action

The mechanism of action of dexamethasone in preventing emesis is not well understood. Dexamethasone has been studied extensively with regard to its use in preventing chemotherapy induced nausea and vomiting (61). Several theories exist about its mechanism of action in this context. A common theory is that corticosteroids exert their anti-emetic action via prostaglandin antagonism (62). A second theory suggests that

dexamethasone causes a release of endorphins leading to an antiemetic state (63). Other theories include reducing the amount of serotonin production by depleting its precursor tryptophan (64), the anti-inflammatory actions of corticosteroids inhibit the release of serotonin from the gut (65), and that dexamethasone may sensitise other receptors to antagonism by other antiemetic agents (66).

In the context of PONV, the mechanism of action is less well understood.

Uses

Dexamethasone in combination with a 5HT3 antagonist has been extensively studied for chemotherapy induced nausea and vomiting, and this appears to be a highly effective regime. This combination has also been studied in the context of PONV, and has also proven to be highly efficacious (66).

Examples

Dexamethasone is the most widely used corticosteroid for purposes of prophylaxis for nausea and vomiting. Betamethasone use has also been described (65).

Other effects

Common adverse effects include insomnia, anxiety and gastrointestinal distress (66). Less common effects include hyperglycaemia, immunosuppression, avascular necrosis of the femoral head, euphoria and facial flushing (66).

2.5.2.2 OPIOID RECEPTOR ANTAGONISTS

This is a rarely used class of drugs for PONV prophylaxis and treatment. They act by causing blockade of peripheral and central opioid receptors, thus reducing the emetic effects of opioids (67-69). However, use of these agents also reduces the beneficial effects of opioid use (i.e. analgesia). Examples of drugs in this class include naloxone, naltrexone, nalmefene and alvimopan. Almivopan does not cross the blood brain barrier, and has been proven to be effective in preventing nausea and vomiting after abdominal surgery (70).

2.5.2.3 PROPOFOL

Propofol, used widely as an intravenous induction agent, is an alkyl phenol that was first

described as having antiemetic properties in 1985 (71,72). The mechanism by which propofol has antiemetic properties is unclear. Antiemetic properties after administration by single dose and continuous infusion have been investigated. Single dose studies focusing predominantly on 5-10mg boluses in the recovery room, have failed to show efficacy in preventing PONV, while infusions given at 1mg/kg/hour either intraoperatively or postoperatively have been shown to be effective albeit with more sedation (73). Patients at high risk for nausea and vomiting are seen to have more pronounced reduction of PONV (73). There has been discussion in the literature as to whether the reduced PONV scores seen with propofol are due to a relatively lower baseline incidence of PONV when propofol is used as an anaesthetic agent or a direct antiemetic effect of propofol itself (73). It is clear that propofol does indeed have an intrinsic antiemetic effect which is dose dependent (73). Adverse effects include hypotension and anaphylaxis.

2.5.2.4 CANNABIS DERIVATIVES

The seeds, flowers and leaves of the Cannabis sativa plant, have been used for years as a recreational drug. Derivatives of this plant are being increasingly used as treatments for specific conditions. Examples of derivatives licensed for medical use are dronabinol, nabilone and delta-9-tetrahydrocannibinol-cannibidiol. In certain countries, special application for the use of herbal marijuana can allow use of this drug for analgesia in terminal illnesses. Dronabinol and nabilone are indicated for chemotherapy induced nausea and vomiting. Dronabinol is also licensed for use for HIV associated anorexia. Delta-9-tetrahydrocannibinol-cannibidiol is used for neuropathic pain associated with multiple sclerosis and cancer. Dronabinol and nabilone have been proven to be efficacious in the treatment of emesis secondary to chemotherapy. There is potential for use of these drugs in the prophylaxis and treatment of PONV. However, there is limited data available regarding use in this context. (74)

2.5.3 ACUPUNCTURE

It has been demonstrated that stimulation of the P6 acupuncture site on the wrist, reduces

the incidence of PONV (75). This is achieved using various techniques such as acupuncture, transcutaneous electrical stimulation, laser acupuncture, capsicum plasters and acupressure. The P6 acupuncture point is situated between the tendons of flexor carpi radialis and palmaris longus on the anterior aspect of the forearm approximately 4cm from the proximal wrist crease. The mechanism of action of acupuncture related reduction in PONV is not well understood. A recent Cochrane review concluded that P6 acupoint stimulation was comparable to anti-emetic agents in the prevention of PONV (76).

2.5.4 OTHER AGENTS/INTERVENTIONS USED

Ephedrine (46), analgesia (78), high fraction inspired oxygen (79), benzodiazepines (80), and adequately maintained fluid status(81) have all been suggested as preventative therapies for PONV, although the evidence regarding these measures is largely conflicting and no consensus regarding the use of such therapy for the prevention of PONV has been reached.

2.6 EVIDENCE FOR PROPHYLAXIS AND TREATMENT REGIMES

Efficacy of prophylactic and treatment agents for PONV has been described using the number needed to treat (NNT). This describes the number of patients that would need to be given antiemetic prophylaxis in order to prevent one event of PONV (nausea or vomiting). Early PONV is an event that occurs between 0 to 2 hours postoperatively. Late PONV is an event that occurs between 2 to 24 hours postoperatively. The number needed to harm (NNH), refers to the amount of people that would need to be treated with an intervention in order for one adverse event (incurred by the intervention) to occur.(21)

2.6.1 PROPHYLAXIS OF PONV

Prior to surgery, the patient has to be assessed and assigned a risk category (mild, moderate or high). This process is detailed below (2.8). Once the category of risk has been determined,

the appropriate regime of prophylaxis will be applied. In addition to administering prophylactic agents though, the baseline risk of the patient will need to be reduced. There is currently not enough evidence to support the use of universal prophylactic antiemetic agents, therefore risk stratification and appropriate prophylactic regimes remain important (77).

2.6.1.1 REDUCTION OF BASELINE RISK FOR PONV

This is achieved by ensuring adequate hydration, using propofol for the induction and maintenance of anaesthesia (or avoiding inhalational agents), avoiding nitrous oxide, minimizing the dose of neostigmine, and minimizing the amount of perioperative opioids given to the patient (77).

Reduction of baseline risk can be greatly aided by avoiding general anaesthesia altogether, and using a regional technique instead. Sinclair et al. found that the risk for PONV is nine times less in patients undergoing regional anaesthesia than those undergoing general anaesthesia (5). The use of propofol decreases the incidence of early PONV (0-6 hours, [NNT=5]) (82).

The IMPACT study evaluated the use of volatile agents or nitrous oxide, and found that the incidence of PONV was 59% in patients who received volatile agents or nitrous oxide (83). Use of propofol in this study reduced the risk by 19% and avoidance of nitrous oxide reduced the risk by 12% (83). A combination regime of TIVA using propofol with an air/oxygen mixture had additive effects, reducing the risk by 25% (83). A randomised placebo controlled trial showed that volatile anaesthetic use is the primary cause of early PONV (0-2 hours). However, they do not have an impact on late PONV risk (2-24hours) (84). In addition, nitrous oxide does not significantly increase risk of PONV in patients who fall into the low risk category (10).

The use of morphine sparing agents such as cyclooxygenase-2 inhibitors (85-87) and ketamine (88) have been shown to reduce the amount of perioperative opioids used. Reduced use of morphine can theoretically reduce the incidence of opioid related PONV. However, there are no randomised controlled trials to demonstrate this.

Reducing the dose or avoidance of neostigmine altogether has also been studied as a means

to reduce baseline risk for PONV. Reducing the dose of neostigmine to below 2.5 mg, can decrease PONV risk (8,89), although the clinical importance of this has been questioned (90).

It was thought previously that high inspired oxygen could decrease the risk of PONV, but systematic reviews of randomised controlled trials have shown that supplemental oxygen has no effect on nausea or vomiting (79,91,92).

2.6.1.2 PATIENTS AT MODERATE TO SEVERE RISK OF PONV

These patients should receive PONV prophylaxis using one to two agents. The IMPACT trial showed that ondansetron 4mg, dexamethasone 4 mg and droperidol 1.25 mg were independently, equally effective in reducing PONV risk by 25% (83).

2.6.1.2.1 5HT3 RECEPTOR ANTAGONISTS (5HT3 RA'S)

The 5HT3 RA's are effective in the prophylaxis of PONV when given at the end of anaesthesia in the case of ondansetron due to its short half life (93), or at any time during anaesthesia when using granisetron or dolasetron (94-97). Ondansetron remains the most widely studied agent in this group, and is known to have more antivomiting than antinausea effects (98). The recommended dose of ondansetron is 4 mg. Ondansetron has a NNT for the prevention of nausea of 7 and a NNT for the prevention of vomiting of 4 (98). The recommended dose of dolasetron is 12.5mg (99). Granisetron at 5-20micrograms/kg body weight has been shown to be effective in PONV prophylaxis(96). As alluded to in a letter by Kranke et al, the data on granisetron may not be as reliable as previously thought (100). Recently, a rigorous review was performed of Y Fujii's published work (101). Y Fujii is the predominant author of work published on granisetron. It was found that the author may be guilty of submitting false data, and therefore a large section of published data on granisetron has been subsequently retracted. All the 5HT3 antagonist agents have similar efficacy for reduction of PONV risk (102).

2.6.1.2.2 DEXAMETHASONE

Dexamethasone should be given at the time of induction of anaesthesia (103). The recommended dose is 4mg. It has been shown to be equally effective to ondansetron (69). No adverse effects have been reported with a single bolus dose (69).

2.6.1.2.3 BUTYROPHENONES

Droperidol is effective when administered at the end of surgery due to its short half life (106). It has been shown to be equally as effective as ondansetron with a NNT of 5 for the prevention of PONV (104). It has also been shown to be highly effective for the prevention of opioid induced nausea and vomiting with a NNT of 3 (104). The recommended dose for PONV prophylaxis is 0.625 to 1.2 mg (106). Droperidol has fallen out of favour due to the controversial FDA "black box" warning (57). Other side effects of droperidol that have limited its use include sedation, drowsiness, extrapyramidal symptoms, restlessness, anxiety and depersonalisation (the so called “locked in syndrome”) (106).
Haloperidol has recently been investigated for prophylaxis of PONV due to decline of droperidol use (107). A meta-analysis of studies investigating haloperidol found that at doses of 0.5-2mg IV or IM, the NNT for PONV prevention was between 4 and 6 (107). The timing of the dose has not been investigated. Haloperidol carries a risk of QTc prolongation and extrapyramidal side effects and is not recommended as first line therapy.

2.6.1.2.4 DIMENHYDRINATE

Dimenhydrinate has shown to be as effective as ondansetron, dexamethasone and droperidol (108). The recommended dose is 1mg/kg IV (108). There is a lack of literature investigating the optimal timing of the dose, and also the dose related side effect profile.

2.6.1.2.5 TRANSDERMAL SCOPOLAMINE

A review of scopolamine use found it to be effective as an adjunct to other therapies for the prevention of PONV (109). The NNT for the transdermal patch is 6. The application of the patch needs to be performed 4 hours prior to the end of anaesthesia (110). For this reason it is often applied the night before surgery. This is due its 2-4 hour onset of effect. It has also been shown to be effective in the setting of opioid induced nausea using a patient controlled analgesia pump (111,112).

2.6.1.2.6 COMBINATION THERAPY

Using two drugs from different classes improves PONV risk reduction (113). Investigated combinations include 5HT3 antagonists and dexamethasone (113), 5HT3 antagonists and droperidol (114), and 5HT3 antagonists and promethazine.
Two agents can be chosen to counterbalance the adverse effects of each other, and enhance the effectiveness. For example, ondansetron causes headache and is primarily antivomiting, and droperidol has a protective effect against headache, and is mostly antinausea.

2.6.1.3 PATIENTS AT HIGH RISK FOR PONV

Patients who fall into the high risk category for PONV should receive multimodal therapy. This includes reducing baseline PONV risk (115), administration of a combination of prophylactic antiemetics and non-pharmacological measures. Scuderi et al. studied the effects of a multimodal approach to PONV prophylaxis (116). They followed a strategy of aggressive hydration, anxiolysis, oxygen, prophylactic antiemetics (dexamethasone and droperidol at the beginning of surgery, and ondansetron at the end of surgery), total intravenous anaesthesia with propofol and remifentanil, and ketolorac. No nitrous oxide or neostigmine was used. This approach had a 98% response rate, compared to a 76% response rate in patients receiving antiemetic monotherapy, and a 59% response rate in patients receiving a routine anaesthetic plus saline placebo.

2.6.2 TREATMENT OF ESTABLISHED PONV

PONV occurs in patients who did not receive prophylactic antiemetics or in whom prophylaxis failed. These patients should be given antiemetic therapy.
If the patient was given antiemetic prophylaxis, the patient should be treated with a drug from another class. If the patient was not given antiemetic prophylaxis, the first line agent of choice for treatment of established PONV is a low dose 5HT3 antagonist (102,117). The 5HT3 antagonists are the class of agents that have been most extensively investigated for this indication (102,118). The recommended doses are ondansetron 1mg, dolasetron 12.5mg, granisetron 0.1mg and tropisetron 0.5mg (NNT = 4-5). Alternative treatments are dexamethasone 2-4mg, droperidol 0.625 mg, promethazine 6.25-12.5mg or propofol 20mg IV bolus (102). Around one third of patients receiving postoperative opioids for pain relief will have nausea and vomiting (119). Droperidol and ondansentron have been used effectively in this patient population (119).
Repeating the same drug as was given for antiemetic prophylaxis during the first 6 hours from the initial dose, is not effective (120). Rescue medication should be initiated when the patient first complains of PONV. Other causes for nausea and vomiting (2.1), should also be sought while rescue treatment is being given.

2.7 ASSESSMENT OF PONV

Vomiting and retching are symptoms that are relatively simple to evaluate, as they are exhibited as definite coordinated, easily observed activity. Objective assessment of each episode is possible.
Nausea is a highly subjective feeling that may or may not terminate in an episode of vomiting. Despite not having a physical manifestation, it is extremely unpleasant. The degree of the feeling of unpleasantness due to nausea is difficult to assess. It is more accurately assessed by the patient rather than by the observer. One of the most widely used and validated methods of measuring the degree of nausea is the visual analogue scale (VAS). Another method is the verbal descriptive scale, otherwise known as the verbal rating scale.

2.7.1 VISUAL ANALOGUE SCALE

Visual analogue scales have been used extensively in the measurement of subjective sensations (121,122).

The visual analogue scale consists of a card or paper on which a 10cm line is printed, with gradations at each centimetre from zero to ten. Words describing the absence of the symptom in question (e.g. pain or nausea) in front of the zero mark, and words describing the presence of the worst possible intensity of the symptom after the ten mark, are often used to annotate the scale. The patient is required to place a mark on the scale with a pencil or pen, on a single point on the line which most corresponds with the intensity of symptom that the patient feels. The mark is then measured and given a centimetre value (e.g. 3.2 cm). This allows the feeling of severity of a continuous symptom such as nausea to be converted into a numerical value between zero and ten. Each recording of such a value can easily be used in statistical analyses (123). If the patient is adequately counselled in their home language, it can reliably be used in patients from different ethnic backgrounds, assuming the patient population chosen has a similar basic education level. The visual analogue scale to be used in this study is shown in Appendix B (p 106).

There are several disadvantages to using a visual analogue scale for the assessment of any subjective sensation, including nausea. Firstly, it requires the full understanding and cooperation of the patient. It is ineffective in patients who do not understand how to use it, and in those who are unwilling or unable to use this means of assessment. It also requires spatial perception and coordination in order to translate the subjective sensation into another dimension. Secondly, it does not remove subjectivity from the assessment. Patients make their own judgement as to the severity of their symptom. For the same intensity of symptom, there may be a large difference in scores between patients. Lastly, in common with the verbal descriptive scale, it requires an abstractive thinking process by the patient, and not all patients are able to reliably process and describe their symptom in a continuous fashion.

Results from pain studies show that: (a) difficulty in understanding the VAS is most common in older patients; (b) response problems can occur with all scales if patients are unsupervised when completing them; and (c) no scale is associated with more response

problems than any other scale (124-128).
Despite these disadvantages, the visual analogue scale has been shown to be highly reliable and sensitive in pain studies (129). It has also been shown to be reliable in PONV studies, and has gained widespread acceptance as the standard for assessment of nausea in PONV (21).

2.7.2 VISUAL DESCRIPTIVE SCALE

This is also known as the verbal rating scale. It consists of 4-5 word categories describing the severity of the symptom (e.g. "none/mild/moderate/severe/unbearable nausea") (22). Each adjective category is then given a score from zero to four or five. The scores are then used for statistical analysis. This scale was widely used in the assessment of nausea, prior to the validation of a VAS for this purpose. It forces the patient to translate their feeling into words, which may vary between patients. Another obvious disadvantage of this approach is that the patient is required to understand the separate categories. These categories may be shown as words that are not in the patient's home language. This is therefore not a reliable scale when assessing a population comprising of patients from different ethnic backgrounds. It also does not represent a continuum of sensation as opposed to the VAS.

2.8 RISK FACTORS FOR PONV

2.8.1 DETERMINATION OF RISK FACTORS

Potential risk factors have been mentioned in the literature since the beginning of anaesthesia in the 1800's (130). Prior to the 1990's each potential risk factor was determined in isolation, and influence of other potential risk factors was excluded from analysis. Establishing causality between risk factor and the outcome of PONV is difficult due the presence of other known or unknown risk factors. Some anaesthetic risk factors can be controlled (e.g. volatile agent use, opioids), whereas the majority of patient and surgical risk factors are not modifiable.

During the 1990's developments in statistical methods allowed the introduction of multivariate logistic regression analysis into PONV research (131). This allowed for an exponential growth in the understanding and defining of risk factors for PONV.

2.8.2 LOGISTIC REGRESSION ANALYSIS

Logistic regression analysis describes the effect of multiple variables on a single dichotomous dependant variable (i.e. presence or absence of PONV). It allows for the generation of an odds ratio (OR) for each factor being examined (132, 133). An odds ratio is the ratio of the likelihood of an outcome in a group that includes the risk factor being examined to the likelihood of an outcome in a group that excludes the risk factor being examined. This analysis also calculates a 95% confidence interval for the OR, which gives the range of values that is 95% likely to include the true OR in the study population. When the lower limit for the 95% confidence interval for the OR is less than one, then the factor examined is considered to increase the risk of PONV (132,133).

2.8.3 ESTABLISHED RISK FACTORS

The risk factors established thus far can be divided into surgical, anaesthetic and patient risk factors.

2.8.3.1 SURGICAL RISK FACTORS

There have been numerous studies attempting to correlate type of surgery with PONV risk. However, prospective studies using multivariate analysis have only been able to show that the duration of surgery is independently associated with increased PONV risk (5,6,1,134,135). An outpatient study showed that every 30 mins of surgical time increased baseline risk by 60% (5). Certain surgery types that may be thought to increased PONV risk include: intraabdominal (2,5,6,83,84,135-145); laparoscopic (2,5,6,83,84,135-142,145); orthopaedic (2,5,6,83,84,135-142,145); major gynaecological (2,5,6,83,84,135-142,145); ear

nose and throat (2,5,6,83,84,135-142,145); thyroid (139); neurosurgery (2,5,6,83,84,135-142,145); breast (2,5,6,83,84,135-142,145); strabismus surgery (135) and plastic surgery (2,5,6,83,84,135-142,145).

2.8.3.2 ANAESTHETIC RISK FACTORS

Well established anaesthetic risk factors include: use of volatile anaesthetics (83,84,134,146); use of nitrous oxide (10,83); use of high dose (>2.5 mg) neostigmine for neuromuscular blockade reversal (8); use of general inhaled anaesthesia (vs. total intravenous anaesthesia) and use of intraoperative(7,134) or postoperative (1,2,6,131,136,139,147-150) opioids. High fractional inspired concentration of oxygen (>70%), was previously thought to reduce PONV risk (151,152), but this has since been disproved (83,91,92). There appears to be no difference between isoflurane, sevoflurane and enflurane in PONV risk (83,84).

2.8.3.3 PATIENT RISK FACTORS

Much of the data regarding PONV risk factors examines patient related risk factors. Well established risk factors include the following: female gender; non-smoking status; history of PONV and history of motion sickness. Possible risk factors include: better ASA status; migraine; ethnicity and anxiety.

Female gender has an independent effect on the risk for PONV (1,2,5,6,84,131,134,136,138-141,147,148,156). No study has contradicted this finding. The effect is seen only in post-pubescent females (135,157), which may point to a hormonal aetiology. The odds ratio for female gender as a risk factor ranges from 2 to 4 depending on the study, and infers a twofold to fourfold increase in risk (1,2,131,134,136,139,147,148,156). It was previously thought that timing during the menstrual cycle has an effect on risk, but this has since been disproved (158). Patients who don't smoke are at increased risk for PONV (1,2,5,6,134,136,139,156). The aetiology of this is unclear. The odds ratio for non-smoking status is from 1.5 to 2.5. Histories of previous PONV or motion sickness both have a combined odds ratio of 1.8 to 3.1

(1,5,6,84,131,139,140,147,148,156). It is also thought that a history of PONV in the patient's parent or sibling (135), increases the risk for PONV. Age has been shown in some literature to have an effect. A greater than 10% reduction in risk has been shown in adults for every decade of age (5,147). In children, a sharp increase in PONV risk is seen at age 3, and then a decrease of 0.2% to 0.8% is seen for each year until the age of 14 (135).
Possible risk factors include: a better ASA status; patients who suffer from migraines (increased risk for PON only) and anxiety (2,6,136,138). Obesity was previously thought to be a risk factor, but this has since been disproved (159).

2.8.3.3.1 ETHNICITY AS A RISK FACTOR

There is a paucity in the literature investigating ethnicity as a risk factor for PONV. It was reported in a meta-analysis of patients undergoing gynaecological surgery that Chinese or Asian-American patients were more susceptible to PONV (16). A study in a laboratory induced motion sickness setting, showed that a group of Chinese subjects had higher than average incidence of motion sickness (17). Another study in the laboratory, compared inducible motion sickness in Caucasian vs. Chinese patients, and found that motion sickness susceptibility was higher in the Chinese group (18). Although not confined to the postoperative group, a retrospective study of 8855 black and white patients receiving opioids, showed that white patients had more nausea and vomiting than black patients (19).

2.8.4 CLINICAL APPLICATIONS OF RISK FACTORS

2.8.4.1 SCORING SYSTEMS

There have been 8 major scoring systems developed by a number of groups in an attempt to quantify the risk of postoperative nausea, vomiting or both. Only 2 out of the eight systems include anaesthetic and surgical risk factors.
The ability of scoring systems to distinguish between patients who will develop PONV and those that won't (i.e. the accuracy of the scoring system), is most commonly assessed by the

area under the given risk scoring system's receiver operating characteristic (ROC) curve. The ROC curve plots the system's true positive rate (sensitivity) against its false positive rate (1-specificity). The area under the curve is expressed as a value between 0 and 1. An area under the curve of 0.5, means that a scoring system is correct 50% of the time (i.e. it is no better than guessing). An area under the curve of 1 denotes that the scoring system is correct 100% of the time. Due to the fact that most risk factors have low predictive value anyway (OR 1.5 to 3.0) (160), and due to the limitations of risk factor research outlined above, it is not surprising that the scoring systems developed have poor to moderate accuracy. Areas under the ROC curve range from 0.56 to 0.785 which denotes only a 12 to 57% improvement over guesswork. Despite their poor accuracy, use of scoring systems to tailor individual PONV therapy, has shown to significantly decrease the incidence of PONV in high risk patient populations (161,162). This has also simultaneously caused a reduction in PONV prophylactic use; resulting in reduced expense and side-effects in lower risk individuals. Three simplified scoring systems are shown in Table 2.1 below. These are the most common scoring systems in use. Apfel et. als' scoring system (1) is simple to use, and has varying area under the ROC curve accuracy (between 0.58 to 0.71) (130,139,145,147,163). The Eberhart et al scoring system is the only one developed for use in children and has a ROC curve accuracy of 0.72 (135). Koivuranta et al have developed a scoring system that is able to show separate risk for postoperative nausea and postoperative vomiting (6). ROC curve accuracy for this scoring system is 0.66 for PONV, 0.66 for nausea and 0.65 for vomiting (163). Its ROC curve accuracy for children is 0.61 (145).

Table 2.1: Simplified scoring systems for PONV (1,6,135)

Scoring system	Formula	Comments
Apfel et. al	gender[a] + history of PONV or motion sickness[b] + smoking status[c] + anticipated use of opioids[d]	Range of possible scores: 0-4 Risk of PONV by score: 0- 10% 1- 21% 2- 39% 3- 61% 4- 79%
Eberhart et al.	duration of surgery[e] + age 3 yr[f]+strabismus surgery[g] + history of PV in child or of PV/PONV in a parent or sibling[h]	Range of possible scores: 0–4. Only scoring system developed for children. Developed for vomiting only. Risk of PV by score (137): 0- 9% 1- 10% 2- 30% 3- 55% 4- 70%
Koivuranta et al.	gender[i] + history of PONV[j] + duration of surgery > 60 min[k] + smoking[l] + history of motion sickness[m]	Range of possible scores: 0–5 Risk of postoperative nausea, vomiting, respectively, by score (134): 0- 17%, 7% 1- 18%, 7% 2- 42%, 17% 3- 54%, 25% 4- 47%, 38% 5- 87%, 61%

Key to formulas in above table:

Apfel et. al: a: male =0, female = 1; b: no=0, yes=1; c:smoker =0, non-smoker=1; d:no=0,yes=1.

Eberhart et al.: e: no= 0, yes=1; f: no = 0, yes=1; g: no = 0, yes= 1; h: no =0, yes= 1.

Koivuranta et al.: i: male=0, female = 1; j: no= 0, yes =1; k: no = 0, yes = 1; l: no = 1, yes= 0; m: no = 0,yes = 1.

One semi simplified scoring system elaborated by Van den Bosch et al. requires a nomogram and is shown in Table 2.2 (138). It is not simple to use and has a ROC accuracy of 0.72 (138).

Table 2.2: Semi-simplified scoring system for PONV risk (138)

Scoring system	Formula	Comments
Van den Bosch et al.	sex[a] + history of PONV or motion sickness[b] + smoking status[c] + surgery type[d] + anaesthetic technique[e] + age[f]	Range of possible scores: 0–61. Risk of PONV by point score: 2- 10%, 12- 20%, 19- 30%, 25- 40%, 31- 50%, 31- 50%, 36- 60%, 42- 70%,49- 80%, 59- 90%

Key to the formula in above table:

a: male=0, female=6; b: no=0, yes=10; c: no=8, yes= 0; d: lower abdominal or middle ear=8, other=0; e: propofol=0, isoflurane= 9; f: 15–19 yr= 20, 20–24 yrs =19,25–29 yr =17, 30–34 yr =16, 35–39 yr=14, 40–44 yr=13, 45–49 yr=11, 50–54 yr =10, 5–59 yr = 9, 60–64 yr=7, 65–69 yr=6, 70–74 yr =4, 75–79 yr =3, 80–84 yr =1, >85 yr =0

Four weighted scoring systems have also been developed but are not used often due to their complexity. These systems have been developed by Palazzo and Evans (131), Sinclair et al. (5), Apfel et al. (156), and Koivuranta et al. (6). The simplified risk scoring systems have shown to have greater accuracy than these more complex weighted scoring systems (139,147,164). Their description in Table 2.3 below is included for completeness.

Table 2.3: Weighted scoring systems for PONV risk (5,6,131,156)

Scoring system	Formula	Comments
Apfel et al	- 0.92 +1.28 x gender[a] -0.029 x (age in yr) - 0.74 x smoking status[b] + 0.63 x history of PONV or motion sickness[c] + 0.26 x (duration of anaesthesia in hours)	Only developed for vomiting
Koivuranta et al.	- 2.21+ 0.93 x gender[d]+0.82 x history of PONV[e]+0.75 x duration of surgery > 60 min[f] + 0.61 x smoking status[g] +0.59 x history of motion sickness[h]	
Palazzo and Evans	- 5.03 + 2.34 x postoperative opioids[i] + 3.97 x history of PONV[j] +2.4 x gender[k]+ 078 x history of motion sickness[l] - 3.2 X female with previous PONV[m]	
Sinclair et. al	- 5.97- 0.14 x (age in yr/10) - 1.03 x gender[n] - 0.42 x smoking status[o] +1.14 x history of PONV[p] + 0.46 x (duration of surgery in 30-min increments)+ 2.36 x general anaesthesia[q] + 1.48 x ENT surgery[r] +1.77 x ophthalmological surgery[s] +1.90 x plastic surgery[t] +1.2 x gynaecological surgery except dilatation and curettage[u] + 1.04 x orthopaedic surgery on knee[v] + 1.78 x orthopaedic surgery on shoulder[w] + 0.94 x orthopaedic surgery elsewhere[x]	Only scoring system developed for outpatients

Key to formulas in above table:

Apfel et al.: a: male=0, female=1; b: no= 0, yes=1; c: no= 0, yes=1.

Koivuranta et al.: d: male=0, female=1; e: no=0, yes=1; f:no=0, yes =1; g: no=1, yes=0; h:no=0, yes=1.

Palazzo and Evans: i:no=0, yes=1; j:no=0, yes=1; k: male=0, female=1; l: no=0, yes=1; m:no=0, yes=1.

Sinclair et al.: n: female= 0, male=1;o: no=0, yes=1; p: no=0, yes=1; q: no=0, yes=1; r:no=0,yes=1; s: no=0, yes=1; t: no=0, yes=1; u:no=0, yes=1; v: no= 0, yes= 1; w:no= 0, yes=1; x: no=0, yes=1

There is no "gold standard" scoring system based on accuracy. The main developments have been in ease of use, rather than improvement of accuracy. Koivuranta et. al and Apfel et al came to the conclusion that omitting constants and coefficients derived from logistic regression modelling, only minimally affected the accuracy of risk assessment. They also concluded that inclusion of more, rather than a few risk factors, does not significantly increase accuracy.

Comparisons between all scoring systems suggest that for inpatients, the Koivuranta et al. simplified scoring system (6), is the most accurate, but not much more accurate than the Apfel et al. simplified scoring system (1). The Eberhart et al. simplified scoring system is the preferred choice for use in children (135). It should be noted that these scoring systems are at best moderately accurate in predicting the risk of PONV.

A scoring system based on Koivuranta and Apfel simplified systems, categorises patients in three groups: low to moderate, moderate to high, and high-risk patient groups (13). Therapeutic modalities are also suggested for each risk group. Patients who have a history of PONV on one occasion, or two of the following other risk factors: female gender; postoperative opioid use; history of motion sickness or non-smoking status; fall into a low to moderate risk group. Single agent prophylaxis is suggested for this group. Patients falling into a moderate to high-risk group are those who have a history of PONV on one occasion and one other risk factor, or three separate risk factors. Dual agent prophylaxis is suggested for this patient group. Patients that fall into a high-risk group are those who have a history of PONV on more than one occasion and one other risk factor. These patients are best treated with a multimodal approach. This system is outlined in Table 2.4 below.

Table 2.4: A simplified scheme for risk stratification (13)

	Low to Moderate Risk	**Moderate to High Risk**	**High Risk**
Criteria	**A** on one occasion or 2 factors from **B**	**A** on one occasion PLUS > 1 factor from **B** OR >3 factors from **B**	**A** on more than one occasion PLUS > 1 factor from **B**
Prophylaxis	One Agent	Dual Agent	Multimodal (anti emetic drugs and changing modifiable risk factors)

A: History of PONV

B: Female gender, postoperative opioid use, history of motion sickness, non-smoker, expected surgery greater than 30 mins duration

2.8.4.2 IMPLICATIONS OF RISK DETERMINATION

Contemporary literature has reinforced the multifactorial nature of PONV, and has lead to the development of a multimodal approach to the prevention and treatment of PONV (116,146). Application of these findings to the treatment and prevention of PONV has led to the promotion of a "decision-tree" approach. Patients are divided into risk categories (low, moderate, high, extremely high) based on the number or nature of their risk factors, or their score from a formula (144,165,166). There is a growing consensus, that PONV prophylaxis is not cost-effective in low risk patient groups (<10 or <20% expected risk), and that it is most effective in moderate, high, or extremely high-risk (with >70% expected risk) patient groups (77,83,165,167). These patients should be treated with combinations of drugs from different classes (82) and additional nonpharmacological measures (e.g. acupuncture) (76).

2.8.4.3 LIMITATIONS OF RISK FACTOR RESEARCH

Risk factor research using newer statistical methods has shed much light on this aspect of PONV. There are still numerous risk factors, which have not as yet been properly investigated. However, there continue to be limitations, which need to be borne in mind when conducting risk factor research. Firstly studies have focused on readily discernible clinical factors. Molecular biological and genetic patient characteristics have not been examined. Sweeney has highlighted the expression and activity of selected cytochrome P 450 hepatic enzymes (CYP450) as a potential risk factor for PONV (174). CYP450 metabolises many drugs, including widely used anaesthetic and analgesic drugs and antiemetics (56,175). Patients can be categorised into "poor", "intermediate", "extensive" or "ultrarapid" metabolisers of the drugs, based on CYP450 activity (176). CYP450 can be stimulated or suppressed by various environmental influences. Sweeney has postulated that the tar in cigarette smoke, which contains polycyclic aromatic hydrocarbons, induce CYP450 activity and hence result in the protective effect of cigarette smoking on the risk of PONV. Other compounds such as alcohol, erythromycin, cimetidine, terfenadine, cabbage, brussel sprouts, cauliflower and red pepper also affect CYP450. These have not been investigated as potential PONV risk factors. Gender and racial differences have also been documented in CYP450 expression.

A second limitation of PONV risk factor research is the difficulty of controlling for more subtle factors, particularly in smaller or single-centre studies. An example of this is the fact that the unusual proficiency of anaesthetists or surgeons, may mask the emetogenic nature of a procedure, that may be otherwise, where less skilled practitioners were involved (177).
A third limitation is the variation between outcome measures between studies. Some studies consider nausea and vomiting as separate outcomes, whereas others consider them as a single combined outcome. Methods of measuring these outcomes differ between studies. For example, one study (134) used the administration of rescue antiemetics as the sole criteria for the presence of PONV. In some centres, heavy nursing or anaesthesiology workloads may lead to under observation of emetic episodes (5).
A fourth limitation is the difficulty in separating true from surrogate risk factors (131,160).

This results from an incomplete understanding of the pathophysiology behind PONV. Deficiency of our knowledge of the molecular and biochemical mechanisms behind PONV, can lead to incorrect conclusions and confusing association with causality. For example, gynaecological procedures may be a surrogate risk factor for the true risk factor of female gender. Duration of surgery may be a surrogate for duration of anaesthesia, or vice versa. These limitations need to be kept in mind when conducting PONV risk factor research.

CHAPTER 3 - METHODOLOGY

The methodology that was used for the study is discussed in this chapter. A description of the study design is followed by a discussion about the study location and sampling method. The chapter is concluded by a brief discussion about the data management, analysis, and the ethical considerations of the study.

3.1 STUDY DESIGN

The study was designed as a contextual, prospective, inception cohort study. This epidemiological study design was chosen to answer the research question and complete the aims of the project best. The concept is best explained by defining each of the separate three terms.

The term "prospective" provides the temporal context of the data collection. This means that we enrolled patients before conducting the study, and collected data as events happened during a pre-defined data collection period. (178)

The term "controlled" means that aspects of the study were constrained so as to attempt to eliminate bias introduced by other factors that are known to influence the endpoint of the study (i.e. PONV). This assures that the data collected will be reliable enough to statistically analyse and interpret. (178)

A cohort study is by definition observational. Two cohorts of people were identified. They were then followed over time after exposure to general anaesthesia, to see who developed PONV and who did not. The time factor is important to note. At the beginning of the study neither the patients nor the researcher knew who was going to get the disease. This effectively avoided recall bias. (178)

The term "inception" means that the patents in both cohorts were assembled because they were patients at the study hospital.

3.2 STUDY PERIOD

Although the data collection period was initially expected to take 6 months, due to researcher availability and suitable patient availability, the research period extended over 20 months (from 30/03/2009 to 30/11/2010).

3.3 STUDY SITE AND CONTEXT OF THE STUDY

The study was conducted at the Johannesburg Hospital. The Johannesburg Hospital is a busy, 1088 bed tertiary, state funded hospital. It provides level 2 and level 3 services, and is the main teaching hospital for the University of the Witwatersrand, Faculty of Health Sciences (179). A wide range of surgical procedures is performed in the theatre facilities available. The patient demographic undergoing surgery at this hospital allowed us to be able to sample both cohorts from one site.

The recruitment of patients was done in the surgical wards of the hospital. The study was conducted within the post anaesthetic care unit and the wards of the Johannesburg Hospital. Data collection during the early PONV period (0-2 hours) was conducted in the post anaesthesia care unit. Data collection was conducted in the wards for the late PONV period (2-24 hours).

3.4 STUDY POPULATION

The study sample was drawn from patients attending the Johannesburg Hospital for elective surgery. Only adult patients able to give informed consent were chosen, from two ethnically different groups, as described below.

3.5 STUDY SAMPLE

Two cohorts were required in order to fulfil the research objectives and study aim. To show statistical significance, 82 patients were required in each group. The aim was to recruit 100 patients into each group to attempt to account for unexpected eventualities. However, after a revised power calculation in consultation with a statistician, it was decided that a smaller number could be recruited. In total 89 patients were recruited (59 in the black cohort, and 30 in the non-black cohort). This was due to researcher availability and time constraints.

The cohorts were chosen to differ from each other in ethnicity. The black South African cohort (Group A), was of South African ethnic origin. The non-black South African cohort (Group B), was of non-African South African ethnic origin. Patients of mixed ethnicity were included in the non-black group. All the patients chosen were in the moderate to high-risk, or high-risk category for PONV. This risk assessment was performed during the patient interview prior to recruitment, and is summarised in Table 3.1.
Patients who have a history of PONV on one occasion, or two of the following other risk factors: female gender; postoperative opioid use; history of motion sickness or non-smoking status; fell into a low to moderate risk group. Patients falling into a moderate to high-risk group were those who had a history of PONV on one occasion and one other risk factor, or three separate risk factors. Patients that fell into a high-risk group were those who had a history of PONV on more than one occasion and one other risk factor.

Table 3.1: Scheme for risk stratification(13)

	Low to Moderate Risk	**Moderate to High Risk**	**High Risk**
Criteria	**A** on one occasion or 2 factors from **B**	**A** on one occasion PLUS > 1 factor from **B** OR >3 factors from **B**	**A** on more than one occasion PLUS > 1 factor from **B**

A: History of PONV

B: Female gender, postoperative opioid use, history of motion sickness, non-smoker, expected surgery greater than 30 mins duration

The sampling method used was non-random, convenience sampling (178). Inclusion and exclusion criteria were delineated in order to limit bias and to aid answering the study question.

Inclusion criteria:

Patients were included in the study if they were:

- 18-70 years old
- undergoing elective surgery
- receiving general anaesthesia of at least 30 minutes duration (no maximum duration was specified)
- at moderate to high risk for PONV (See Table 3.1)
- classed as ASA 1-3
- able to give informed consent.

Exclusion criteria:

Patients were excluded from the study if they were:

- expected to undergo total intravenous anaesthesia or regional anaesthesia
- undergoing emergency surgery
- unable to give informed consent
- unable to understand the visual analogue scale (VAS).

Surgeons usually book theatre lists on the day before the surgery. These lists are present in the theatre. Patient name, age, location, procedure type and expected duration are recorded on the list. An anaesthetist is assigned to each theatre list by the Department of Anaesthesia. A list of anaesthetists responsible for each theatre list is available within the Department of Anaesthesia well in advance. The theatre lists were reviewed on the day before surgery, and patient details were obtained for patients that were eligible for inclusion in the study. These patients were approached for recruitment and informed consent in the surgical wards. After obtaining consent, the anaesthetist responsible for the anaesthesia of the recruited patient was contacted. The anaesthetist was informed about the participation of the patient in the study, and was given a document detailing the

standardisation required for the study. There was no blinding in the study, and the patient identity and group allocation was known throughout. Patients were also assigned a group letter (A or B), and a number.

Anaesthesia was standardised in several aspects. Firstly, standardised dual agent prophylaxis was given to all patients recruited into the trial. This was a combination of ondansetron and dexamethasone, at their recommended doses for this indication as per the South African Medicines Formulary. Secondly, no nitrous oxide was used and the inhalational agent used for maintenance was isoflurane. Thirdly, propofol was the induction agent for the anaesthetic. Propofol is the induction agent most in use for elective general anaesthesia at the study hospital. Finally only a single dose of neostigmine was given to reverse the neuromuscular blocker. The remainder of the anaesthetic was up to the individual anaesthetist.

3.6 METHODS FOR MEASURING OUTCOMES

The investigator approached the patient in the post anaesthesia care unit after surgery. The presence of nausea was determined after confirmation that the patient was alert and oriented. Any episode of vomiting reported by the anaesthetist or nursing staff in the area was noted. The patient was assessed as alert and oriented if a modified Aldrete score of at least 9 out of 10 and a Glasgow Coma Scale score of at least 14 out of 15 was achieved (see Appendix C, p 107). The patient was assessed for nausea using the visual analogue scale (VAS) (see Appendix B, p 106).

This visual analog scale was created after an extensive literature search and is based on a description of a VAS validated for use in PONV research (21). It was printed on paper, and at each point of data collection a blank scale was used. Patients had an in depth explanation about the use of the VAS prior to taking consent for participation in the study. If use of the scale was not understood, the patient was not enrolled in the study.

Patients were also asked a "yes/no" question about feeling nausea. This was in the patient's

home language. The 11 official languages in South Africa are English, Afrikaans, isiNdebele, isiXhosa, isiZulu, Sepedi, Sesotho, Setswana, SiSwati, Tshivenda and Xitsonga.

Incidents of vomiting and complaints of nausea may have occurred in between questionnaires. Although these reports were specifically sought out by the investigator at the next planned questionnaire time point, there was no allocated section on the questionnaire for additional complaints of nausea (see Appendix A, p 104), and the investigator added additional notes as was necessary to each questionnaire. Administration of rescue anti-emetic, as recorded on the patient medication chart, was also noted.

3.6.1 TIMING OF DATA COLLECTION

Time intervals to assess degree of PONV were 0 hours (defined by first assessment of the patient as having a modified Aldrete recovery score of 9 out of 10 and a Glasgow Coma Scale score of 14 out of 15), 15 mins, 90 mins, 180 mins, and 24 hours. These assessment time intervals have been validated in previous studies for PONV (21).

3.7 QUALITY CONTROL

Strict adherence to inclusion and exclusion criteria ensured appropriate selection of patients. Deviations from the anaesthesia standardisation as determined by examination of the anaesthesia record resulted in the patient being excluded from the study. Missed interviews, incomplete data collection or illegible data collection forms, also resulted in the patient being excluded from the study. These measures limited poor quality data being collected for analysis.

3.8 DATA ANALYSIS AND MANAGEMENT

The following variables were recorded: times and results of VAS nausea assessment and "yes/no" nausea questions; number and times of vomiting events; timing, dose and type of

antiemetic; patient age; risk factor profile (gender, non-smoking status, previous history of PONV or motion sickness) and type of surgery. Data collected was digitised weekly. Paper datasheets were kept in a safe location. A person other than the investigator, who did the data collection, crosschecked digitised data with paper datasheets monthly.
The data was analysed and processed after the data collection period, and the following information was reported for each group: female gender, age(years), non-smoking status, history of PONV, history of motion sickness, duration of anaesthesia (min), type of surgery and surgical techniques, postoperative opioids, number of patients with 0-4 risk factors according to Apfel (1) and calculated mean risk for PONV.

A logistic regression analysis was then performed examining the influence of race as a risk factor for PONV (131,132). A calculation of relative risk and associated confidence interval was also performed(133).

3.9 ETHICAL CONSIDERATIONS

The patients in the study sample were extensively advised about their rights if they decided to participate in the study. This included withdrawal at any stage of the study should they feel against continuing participation, with the understanding that withdrawal would not prejudice their continued care. They were also informed that they would not receive monetary remuneration for their participation in the study. This study did not involve experimental treatments or placebos. It also did not withhold antiemetic prophylaxis or treatment. The prophylaxis administered was based on well-established and proven regimes (50). Denial of prophylaxis or treatment in moderate to high-risk patient groups cannot be justified (21). Therefore, study patients were at no additional risk from receiving less than the established standard of care. Patients were enrolled once they fully understood their rights, their purpose in the study, and were able to sign the informed consent form.
The Human Research Ethics Committee and the Post Graduate Committee from the University of the Witwatersrand extensively reviewed the study. The Johannesburg Hospital superintendent was also required to approve the study before it could be conducted.
The above measures protected the rights and health of the study participants.

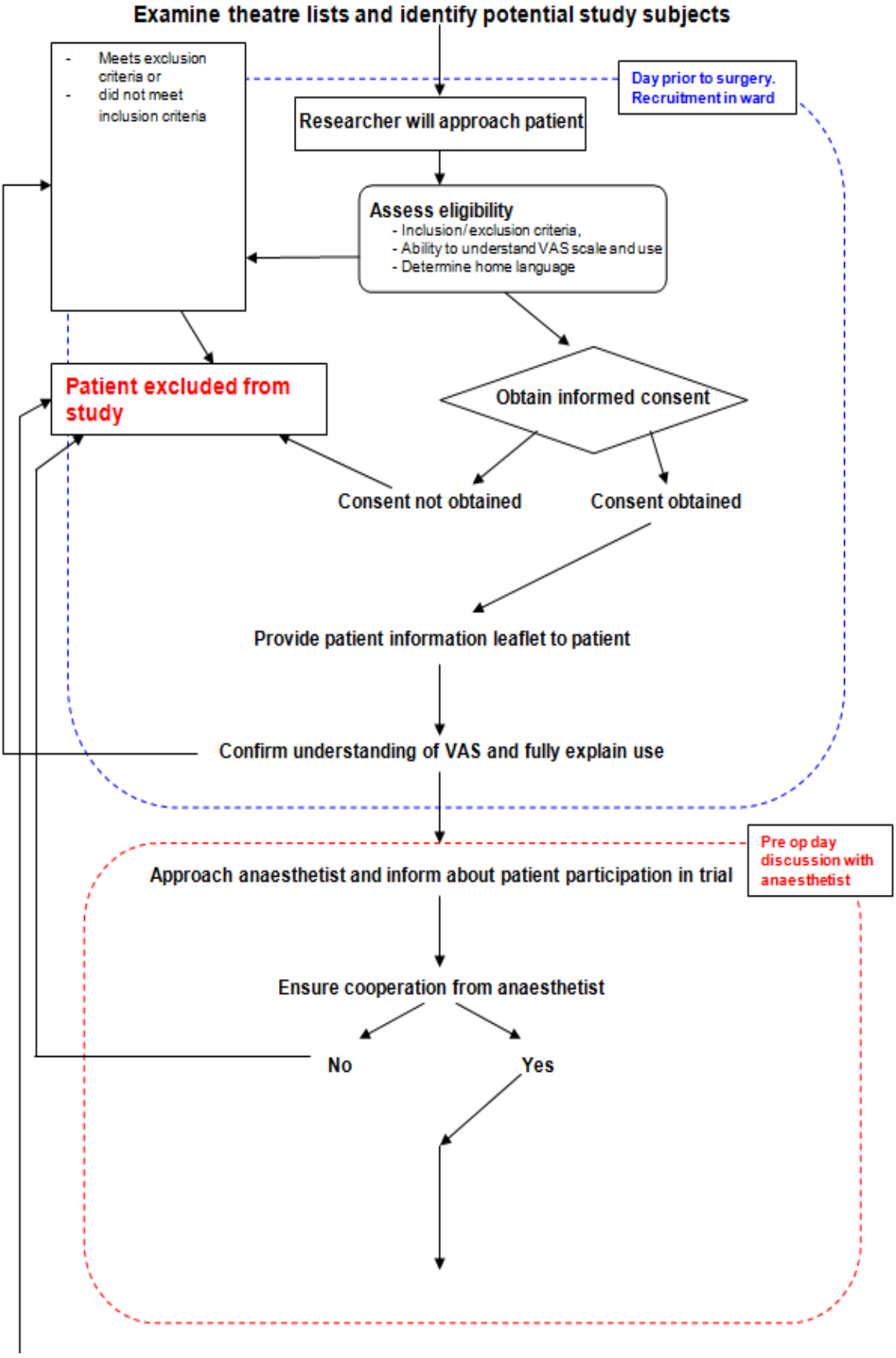
3.10 COSTING AND ACQUISITION OF STUDY MATERIALS

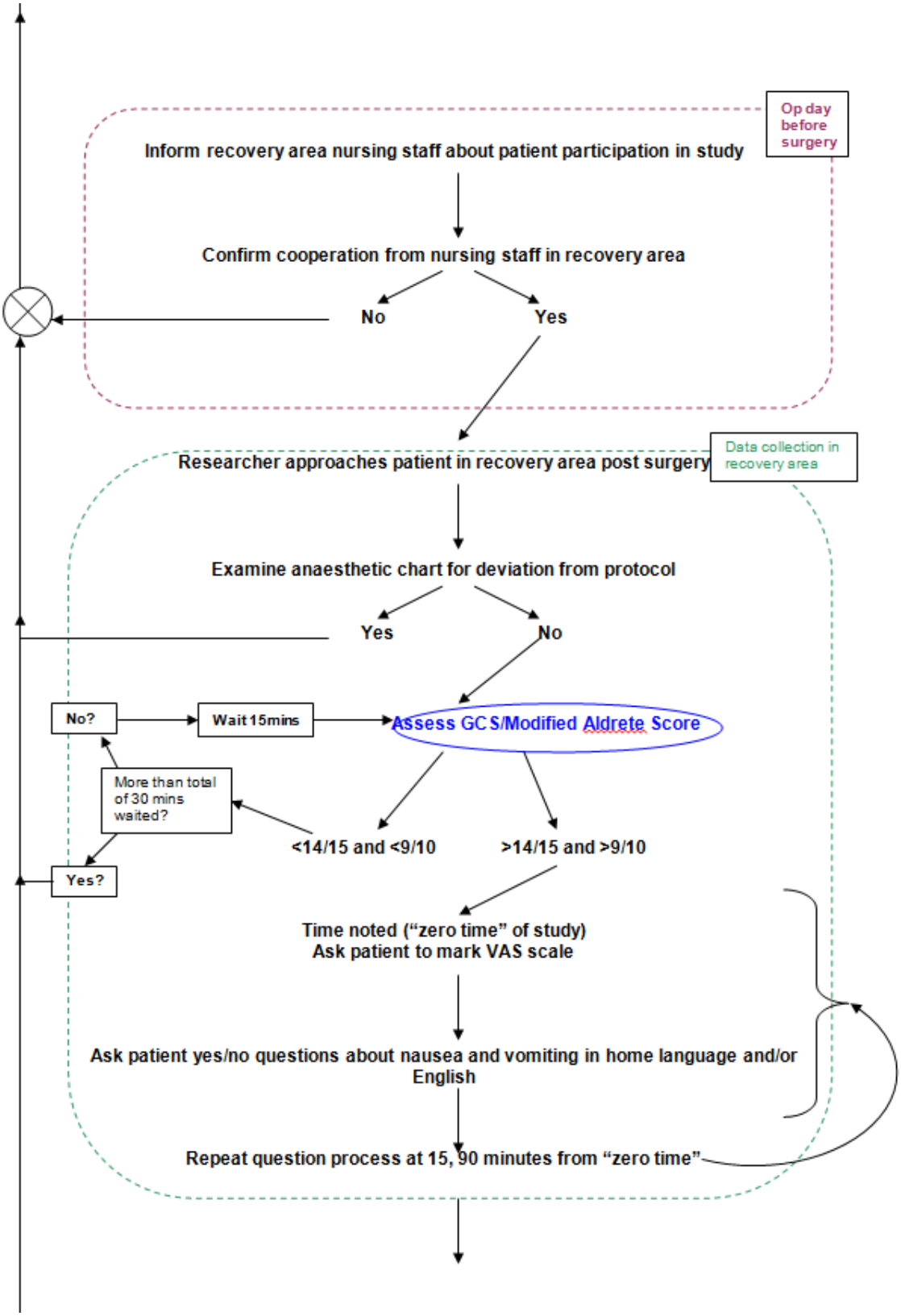
The antiemetic prophylactic drugs used were ondansetron and dexamethasone. Grant funding (Jan Pretorius fund) from the South African Society of Anaesthesiologists was obtained to purchase ondansetron for purposes of the study. The total funding received was R10 000.00 . Dexamethasone was widely available in the hospital and is used widely for PONV prophylaxis in high-risk patient groups.
Questions to be targeted to patients (see Appendix A, p 104) were translated into the 11 official South African languages by the Wits Language School at no cost.

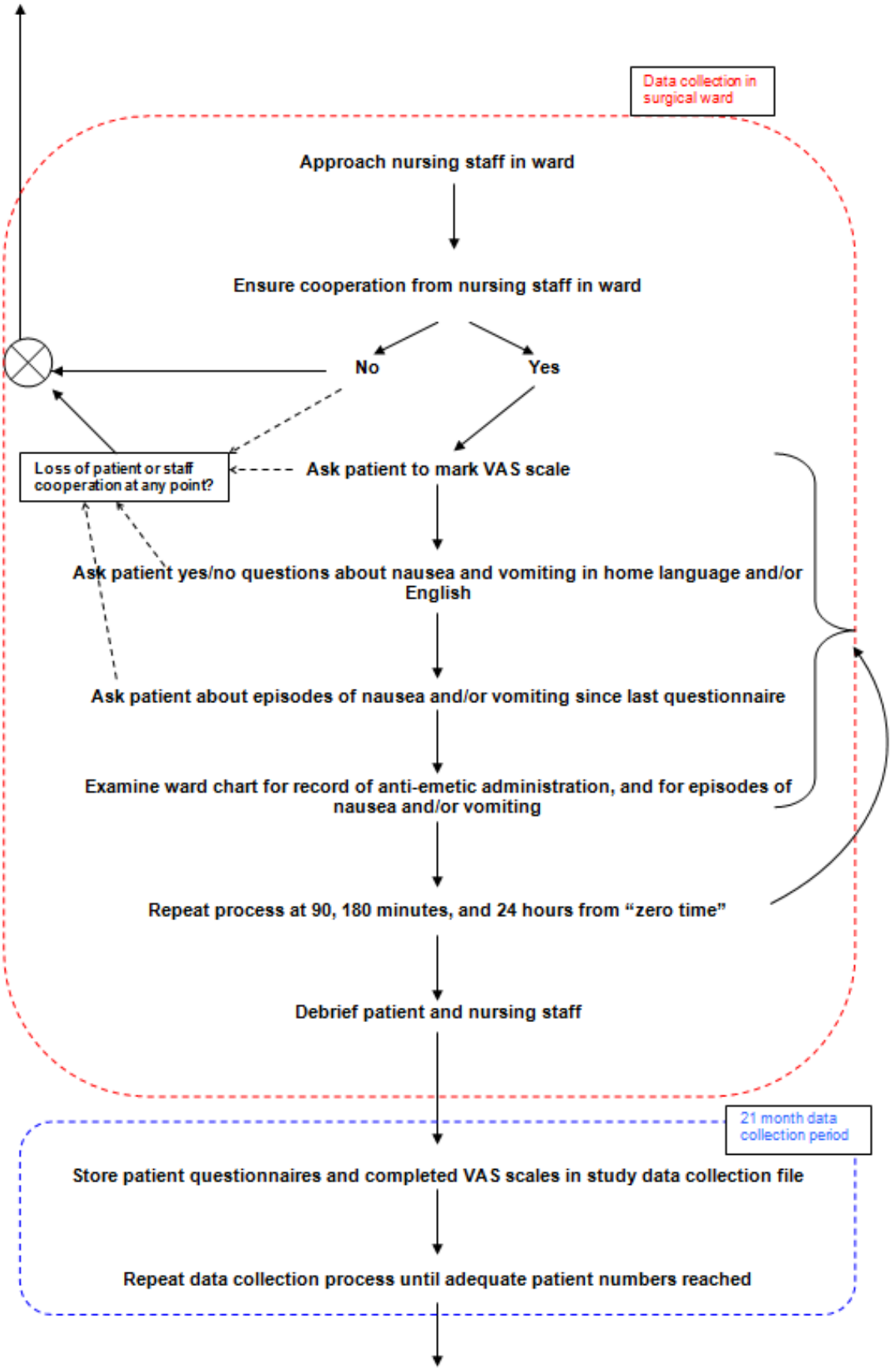
3.11 ORIENTATION OF NURSES AND ANAESTHETISTS

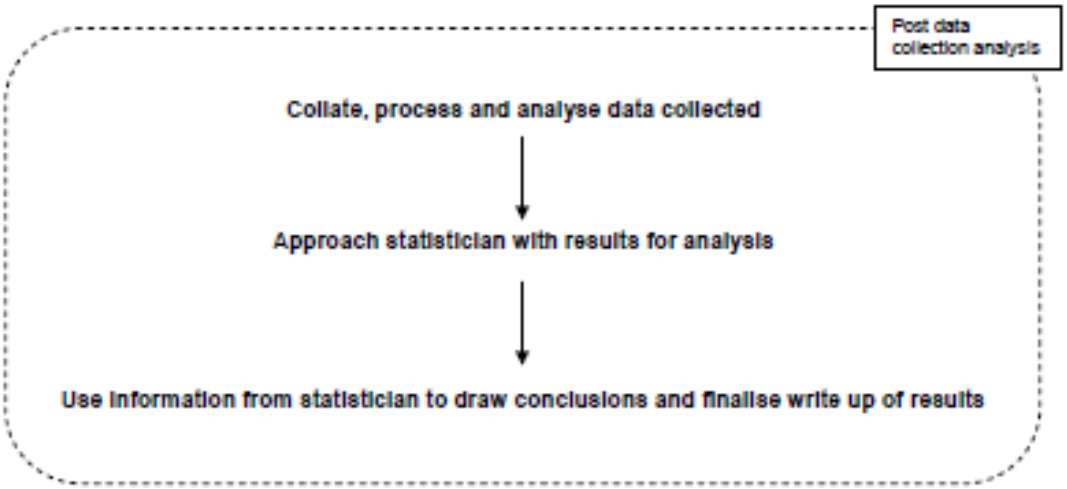
Anaesthetists, recovery room nurses and surgical ward nurses were approached prior to the commencement of patient recruitment and data collection. They were given a talk about the purpose of the study, and their participation in it.

3.12 FLOW CHART FOR STUDY DESIGN




Op day before surgery
Inform recovery area nursing staff about patient participation in study
Confirm cooperation from nursing staff in recovery area
No
Yes
Data collection in recovery area
Researcher approaches patient in recovery area post surgery
Examine anaesthetic chart for deviation from protocol
Yes
No
No?
Wait 15mins
Assess GCS/Modified Aldrete Score
More than total of 30 mins waited?
<14/15 and <9/10
>14/15 and >9/10
Yes?
Time noted ("zero time" of study)
Ask patient to mark VAS scale
Ask patient yes/no questions about nausea and vomiting in home language and/or English
Repeat question process at 15, 90 minutes from "zero time"


Data collection in surgical ward
Approach nursing staff in ward
Ensure cooperation from nursing staff in ward
No
Yes
Loss of patient or staff cooperation at any point?
Ask patient to mark VAS scale
Ask patient yes/no questions about nausea and vomiting in home language and/or English
Ask patient about episodes of nausea and/or vomiting since last questionnaire
Examine ward chart for record of anti-emetic administration, and for episodes of nausea and/or vomiting
Repeat process at 90, 180 minutes, and 24 hours from "zero time"
Debrief patient and nursing staff
21 month data collection period
Store patient questionnaires and completed VAS scales in study data collection file
Repeat data collection process until adequate patient numbers reached


Post data collection analysis
Collate, process and analyse data collected
Approach statistician with results for analysis
Use information from statistician to draw conclusions and finalise write up of results

CHAPTER 4 - RESULTS

4.1 INTRODUCTION

This chapter consists of the presentation of results and statistical methods. The results are presented using the aims and objectives set out in Chapter 1. This is followed by a comparison of demographic data, and statistical methods. The chapter is then concluded with a short summary of important findings.

Initially, it was expected that at least 80 patients would be included in each group resulting in a total of 160-200 patients. However, due to time constraints, the recruiting period was shortened. A statistician was consulted and a repeat power calculation was performed based on the ethnic demographic that presented for surgery in the theatres under study (over a one year period, 3496 patients underwent surgery in these theatres; 901[25.7%] of these were non-black). The repeat calculation suggested that 104 black patients and 36 non-black patients would be needed. However, eventually only 63 black patients and 31 non-black patients were recruited, giving a total of 94 patients. There were 5 exclusions; due to protocol violation in 2 cases; cancellation of surgery in 2 cases and loss to follow-up in 1 case. This left 59 patients in the black patient group, and 30 patients in the non-black patient group. A statistician was re-consulted, and it was decided that although not ideal, these numbers would be adequate to answer the question of the study.

4.2 AIM AND OBJECTIVES

4.2.1 AIM

An initial cursory identification of non-black ethnicity as a risk factor was performed using the Spearman ranked linear correlation. This was followed by performed a multiple regression analysis at each time interval to confirm non-black ethnicity as a risk factor. Finally, the degree of increased risk associated with non-black ethnicity, and also the degree

of risk protection associated with black ethnicity was examined by calculating the relative risk ratios.

4.2.1.1 LINEAR CORRELATION OF ETHNICITY AND NAUSEA

The dependence of the presence of nausea and vomiting on ethnicity, of the whole study population, at different time intervals was analysed by using Spearman's ranked linear correlation.

The presence of nausea was statistically dependent on non-black ethnicity at the 0, 15 and 90 minute time intervals. The presence of vomiting from 0 to 24 hours was statistically dependent on non-black ethnicity.

The incidence of postoperative nausea(PON) was significantly increased in the non-black population group during the first 3 time points (i.e. 0, 15 and 90 minutes), but there was no difference in the incidence of PON at the 180 minute and 24 hour time points. This may be due to lower opioid requirement and treatment of nausea in the ward during this late 2-24 hour time period. Table 4.1 describes the Spearman coefficients and p-values in more detail below.

Table 4.1: Spearman ranked analysis for the dependence of the presence of nausea and vomiting on ethnicity

Variable	R Value	P value
Nausea at 0 min	-0.22	0.036
Nausea at 15 min	-0.44	0.000012
Nausea at 90 min	-0.24	0.020
Nausea at 180 min	-0.09	0.366
Nausea at 24 hours	0.16	0.121
Vomiting 0-24 hours	-0.23	0.024

4.2.1.2 RISK FACTORS FOR NAUSEA AT 0 MINUTES

Multiple regression analysis was performed looking for risk factors for nausea at each time interval.

At the 0 minute time interval, it was found that the procedure type and non-black ethnicity were risk factors for nausea, with p values of 0.004 and 0.009 respectively. Although detected as a risk factor, procedure type and its lack of effect on PONV have been previously described, are examined in closer detail in section 5.4.

Other known risk factors of PONV such as anaesthetic duration, non-smoking status, history of PONV, history of motion sickness and female gender were not found to be significant risk factors at this time point although non-smoking status trended toward significance (p=0.06).

4.2.1.3 RISK FACTORS FOR NAUSEA AT 15 MINUTES

At the 15 minute time interval it was found once again that non-black ethnicity was a risk factor for nausea with a p value of 0.000014. Non-smoking status was also significantly associated with nausea with a p value of 0.0053.

As in the findings for the 0 minute time interval, risk factors such as history of PONV or motion sickness, female gender and anaesthetic duration were not found to be correlated to the risk of nausea.

4.2.1.4 RISK FACTORS FOR NAUSEA AT 90 MINUTES

At the 90 minute time interval, non-black ethnicity, procedure type (discussed in section 4.3), non-smoking status and history of PONV were found to be risk factors for nausea with p values of 0.000019, 0.0031, 0.0024 and 0.014 respectively.

4.2.1.5 RISK FACTORS FOR NAUSEA AT 180 MINUTES

At the 180 minute mark no risk factors correlated to the presence of nausea, although non-black ethnicity trended toward significance with a p value of 0.055.

4.2.1.6 RISK FACTORS FOR NAUSEA AT 24 HOURS

Since there was no nausea recorded at the 24 hour mark throughout the population, there was no variance in the nausea variable. This made the data at the 24 hour mark unsuitable for multiple regression analysis.

4.2.1.7 RISK FACTORS FOR NAUSEA BETWEEN 0 AND 24 HOURS

Multiple regression analysis was performed for the whole study period of 0 to 24 hours. Non-black ethnicity, non-smoking status, history of PONV and procedure type(discussed in section 4.3) were identified as risk factors for nausea with p values of 0.000003, 0.0019, 0.045, and 0.0054 respectively.
Once again, the known risk factors: female gender; history of motion sickness and anaesthetic duration were not identified as risk factors for PON in this study.

4.2.1.8 RISK FACTORS FOR VOMITING BETWEEN 0 TO 24 HOURS

The risk factors for postoperative vomiting between 0 and 24 hours were examined. Non-black and non-smoking status were identified as risk factors with p values of 0.0044 and 0.037 respectively.

4.2.1.9 SUMMARY TABLE OF MULTIPLE REGRESSION RESULTS

The multiple regression analysis data is summarised in Table 4.2 below.

Table 4.2: Summary of risk factor identification using multiple regression analysis

	Nausea at 0 mins	**Nausea at 15 minutes**	**Nausea at 90 minutes**	**Nausea at 180 minutes**	**Nausea between 0-24 hours**	**Vomiting between 0-24 hours**
Risk factors (p value)	Procedure type (0.004) Non-black ethnicity (0.009)	Non-black ethnicity (0.000014) Non-smoking status (0.0053)	Procedure type (0.0031) Non-black ethnicity (0.000019) Non-smoking status (0.0024) History of PONV (0.014)	Nil	Procedure type (0.0054) Non-black ethnicity (0.000003) Non-smoking status (0.0019) History of PONV (0.045)	Non-black ethnicity (0.0044) Non-smoking status (0.037)

4.2.1.10 RELATIVE RISK RATIO

The total number of nausea or vomiting events and total number of observations over the 24 hour study period were used to calculate the relative risk ratio and confidence interval.

The relative risk is a measure of the strength of association between the risk factor and the disease. In this case the risk factor non-black ethnicity and the disease is PONV. If the relative risk is greater than one, it means that the presence of non-black ethnicity increases the incidence of nausea.

The relative risk is calculated by dividing the incidence of nausea in the non-black group by the incidence of nausea in the black group.

This is calculated with the aid of the following box plot:

	Risk factor	No Risk factor	
Disease present	A	B	A+B
Disease absent	C	D	C+D
	A+C	B+D	

The relative risk is given by the formula:

$$RR = \frac{\left(\frac{A}{A+C}\right)}{\left(\frac{B}{B+D}\right)}$$

A 95% confidence interval also has to be calculated in order to give an idea of how the risk is distributed. The higher the lower limit of this confidence interval above 1, the more significant the relative risk result. Similarly, if the higher limit of the confidence interval is closer to the lower limit, that is if the confidence interval range is smaller, the more significant the result. This implies that there is not much risk variation among the range of results, and the conclusion is more significant. In order to do this, a standard error of log relative risk (SElogR) has to be calculated.

The SElogR is given by the formula:

$$SElogR = \sqrt{\left(\left(\left(\frac{1}{A}\right) - \left(\frac{1}{A+C}\right)\right) + \left(\left(\frac{1}{B}\right) - \left(\frac{1}{B+D}\right)\right)\right)}$$

The lower and upper limits of the confidence interval are given by the equation:

$$CI = \log \mathrm{RR} \pm \mathrm{SElogR} * 1.96$$

Using the above equations and box plot, the relative risk ratios and confidence intervals were calculated for the influence of ethnicity on nausea and vomiting over the study period.

4.2.1.10.1 RELATIVE RISK OF NAUSEA

	Non-black	Black	Totals
PON (0-24 hrs)	49	40	89
No PON (0-24 hrs)	101	255	356
Totals	150	295	

Using the above box plot, it was calculated that the relative risk ratio of nausea in patients who were non-black was 2.40, with a 95% confidence interval of 1.67 to 3.48.

4.2.1.10.2 RELATIVE RISK OF VOMITING

	Non-black	Black	Totals
POV (0-24 hrs)	4	1	5
No POV (0-24 hrs)	146	294	440
Totals	150	295	

Using the above box plot, it was calculated that the relative risk ratio of vomiting in patients who were non-black was 7.86, with a 95% confidence interval of 0.88 to 69.76.

4.2.2 OBJECTIVES

4.2.2.1 DOCUMENT THE INCIDENCE OF NAUSEA

The number of patients experiencing nausea in the non-black patient group at 0 minutes was 14; at 15 minutes was 21; at 90 minutes was 11; at 180 minutes was 3 and at 24 hours was 0. The respective proportion of patients who felt nauseous at these time intervals was 46.7%; 70%; 36.7%; 10% and 0%.

The number of patients experiencing nausea in the black patient group at 0 minutes was 13; at 15 minutes was 14; at 90 minutes was 10; at 180 minutes was 3; and at 24 hours was 0. The respective proportion of patients who felt nauseous at these time intervals was 22%; 23.7%; 16.9%; 5.08% and 0%.

The above data is summarised in the Table below:

Table 4.3 The incidence of nausea at predetermined time intervals

Time of observation	Number of non-black patients (%), Total=30	Number of black patients (%), Total = 59
0 minutes	14(46.7%)	13(22%)
15 minutes	21(70%)	14(23.7%)
90 minutes	11(36.7%)	10(16.9%)
180 minutes	3(10%)	3(5.08%)
24 hours	0(0%)	0(0%)

The data was further processed to examine nausea events: early (0-2 hours), late (2-24 hours) and total (0-24 hr) postoperative periods.
The number of observations of nausea in the non-black patient group during the 0-2 hour time interval was 46 out of a total of 90 observations. The number of observations of nausea in this group during the 2-24 hour time interval was 3 out of a total of 60

observations. The number of total nausea events in this group was 49 out of a total of 150 observations.

The number of observations of nausea in the black patient group during the 0-2 hour time interval was 37 out of a total of 177 observations. The number of observations of nausea in this group during the 2-24 hour time interval was 3 out of a total of 118 observations. The number of total nausea events in this group was 40 out of 295 observations.

This data is summarised in Table 4.4.

Table 4.4: The number of nausea events during predetermined time intervals

Time Interval	Number of events - non-black patients (Total observations/%)	Number of events - black patients (Total observations/%)
0-2 hours	46 (90/51.1%)	37(177/20.9%)
2-24 hours	3 (60/5%)	3 (118/2.5%)
0-24 hours	49 (150/32.7%)	40 (295/13.5%)

4.2.2.2 DOCUMENT THE INCIDENCE OF VOMITING

The number of patients who experienced episodes of vomiting in the non-black patient group at 0 minutes was 0; at 15 minutes was 2; at 90 minutes was 1; at 180 minutes was 1 and at 24 hours was 0.

The number of patients who experienced episodes of vomiting in the black patient group at 0 minutes was 0; at 15 minutes was 1; at 90 minutes was 0; at 180 minutes was 0 and at 24 hours was 0.

The above data is summarised in Table 4.5 below.

Table 4.5: The incidence of vomiting at predetermined time intervals

Time of observation	Number of non-black patients (%), Total = 30	Number of black patients (%), Total = 59
0 minutes	0 (0%)	0 (0%)
15 minutes	2 (6.6%)	1 (1.7%)
90 minutes	1 (3.3%)	0 (0%)
180 minutes	1 (3.3%)	0 (0%)
24 hours	0 (0%)	0 (0%)

The data was also further processed into early (0-2 hours), late (2-24 hours) and total postoperative periods.

The number of episodes of vomiting in the non-black patient group was 3 out of a total of 90 observations between the 0-2 hour period; 1 out of a total of 60 observations between the 2-24 hour period and 4 out of 150 observations over the total period.

The number of episodes of vomiting in the black patient group was 1 out of a total of 177 observations between the 0-2 hour period; 0 out of a total of 118 observations between the 2-24 hour period and 1 out of 295 observations over the total period. This data is summarised in Table 4.6.

Table 4.6: The number of vomiting events during predetermined time intervals

Time Interval	Number of vomiting Events - non-black patients (Total observations/%)	Number of vomiting Events - black patients (Total observations/%)
0-2 hours	3 (90/3.3%)	1 (177/0.56%)
2-24 hours	1 (60/1.67%)	0 (0/0%)
0-24 hours	4 (150/2.67%)	1 (295/0.33%)

4.2.2.3 DOCUMENT THE USE OF RESCUE ANTIEMETICS

Rescue antiemetics were used if the patient complained of nausea to the nursing staff independent of the study. The standard of care within the institution is administration of intramuscular prochlorperazine of 12.5 to 25mg. The type of drug used for rescue therapy could not be standardised as each of the surgical wards have variable stock levels of prochlorperazine and occasionally antiemetics other than prochlorperazine have to be used to treat PONV (for example metoclopramide).

The total dosage of prochlorperazine administered was recorded over a 24 hour period. Complete postoperative antiemetic prescription and administration records were only obtained for 22 out of 59 patients in the black group, and 14 out of 30 patients in the non-black group. This was due to administrative problems and lost records in the wards.

Patients in the non-black group were given a total dose of 225mg of prochlorperazine which equates to a mean of 16.07mg per patient.

Patients in the black group were given a total dose of 450mg of prochlorperazine which equates to a mean of 20.45mg per patient.

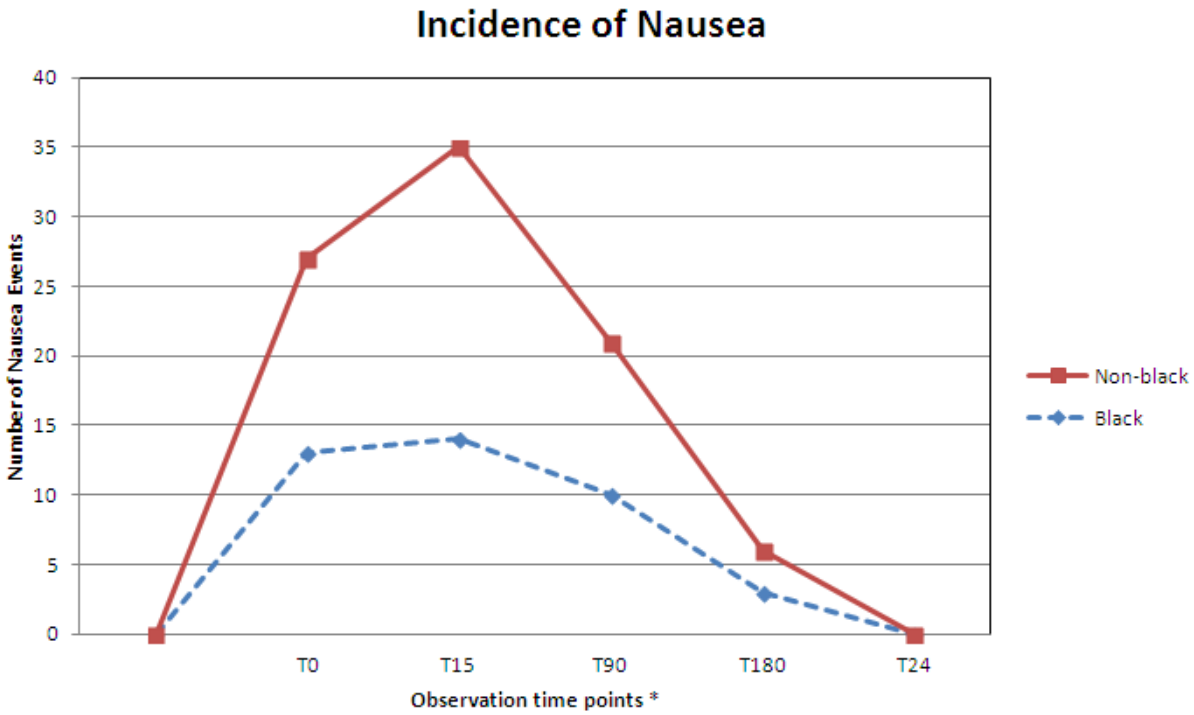
4.2.2.4 COMPARE THE INCIDENCE OF NAUSEA

With the exception of the T24 (24 hours) time point, where there was no recorded nausea in any patient in both groups, the number of events of nausea were greater at all other time points in the non-black group. This is displayed in Figure 4.1.

Comparison of the incidence of nausea was carried out using the Chi-Squared test with 1 degree of freedom. Significance was defined as $p<0.05$. The difference between the incidences of nausea at T0 (0 minutes) was significant with a p value of 0.01687; at T15 (15 minutes) was significant with a p value of 0.00002; at T90 (90 minutes) was significant with a

p value of 0.038 and at T180 (180 minutes) was not significant with a p value of 0.382. The incidence of nausea at T24 (24 hours) could not be compared, as there were no events at this time point in either group. These results are summarised in Table 4.7.

Similarly when the groups were stratified into 0-2 hours, 2-24 hours and 0-24 hour time intervals, patients in the non-black group had significantly more nausea than those in the black group at 0-2 and 0-24 hours, with a p values of 0.00000046 and 0.0000019 respectively. When comparing the incidence of nausea in the 2-24 hour period, there was no significant difference shown with a p value of 0.3904. These results are shown and summarised in Figure 4.2 and Table 4.8 below.



* T0= 0 minutes, T15= 15 minutes, T90= 90 minutes, T180= 180 minutes, T24= 24 hours

Figure 4.1: The incidence of nausea at each time interval for both groups

Table 4.7: Comparison of the incidence of nausea at each time point using the Chi-Squared test with 1 degree of freedom

Time point	P value
T0 (0 minutes)	0.01687 *
T15 (15 minutes)	0.00002 *
T90 (90 minutes)	0.038 *
T180 (180 minutes)	0.382
T24 (24 hours)	Could not be calculated

* significant ($p<0.05$)

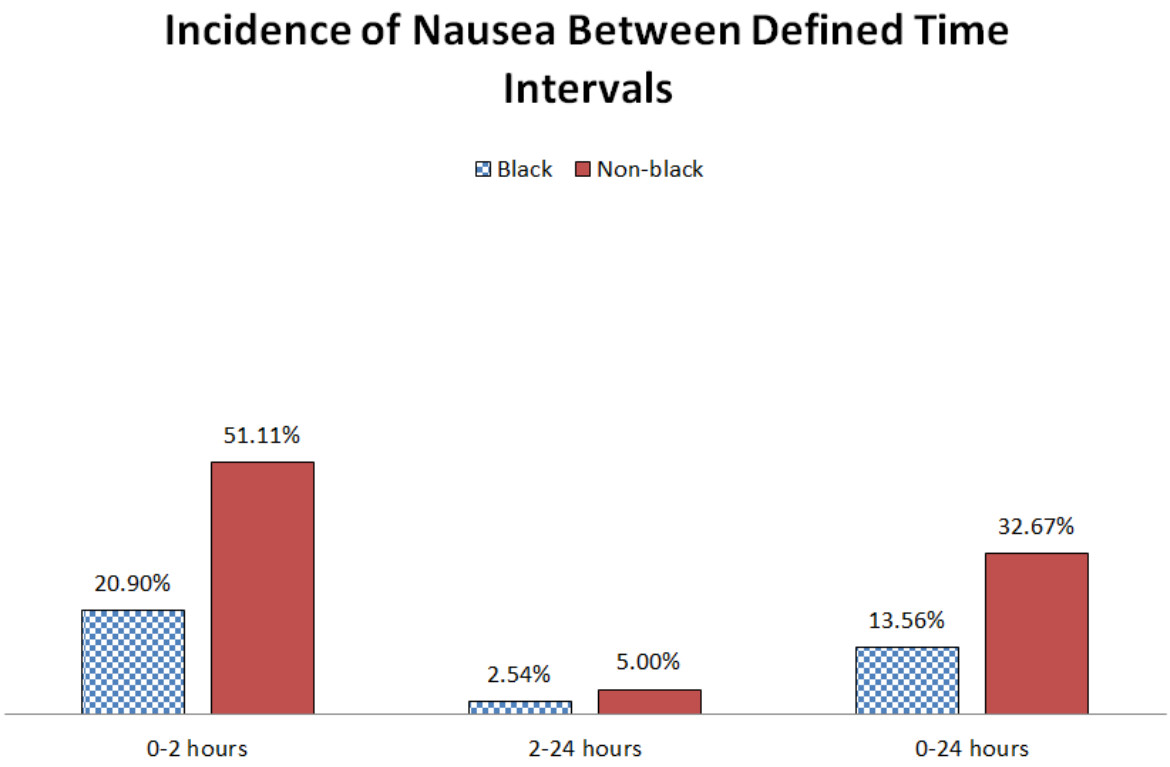


Figure 4.2: Comparison of the incidence of nausea at each time interval

Table 4.8: Comparison of the incidence of nausea during predefined time intervals using a Chi-Squared test with 1 degree of freedom

Time Interval	P value
0-2 hours	0.00000046*
2-24 hours	0.3904
0-24 hours	0.00000190 *

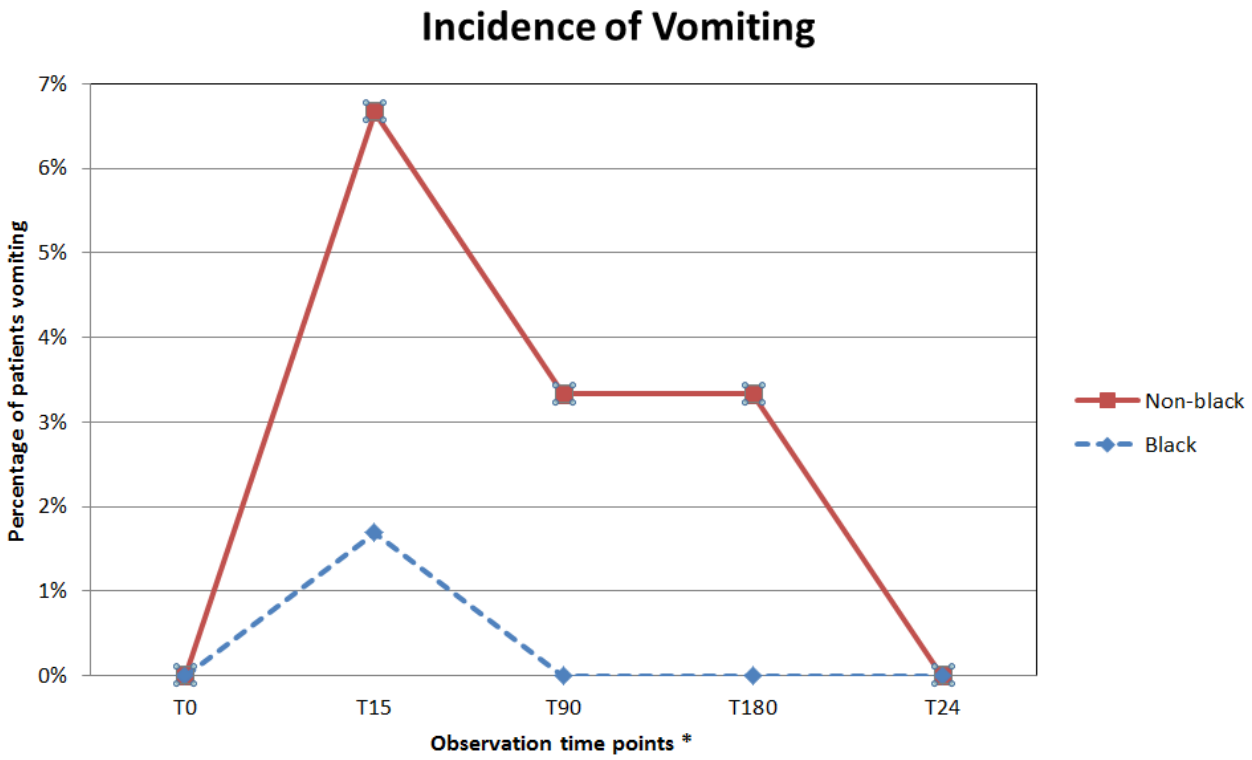
* significant (P<0.05)

4.2.2.5 COMPARE THE INCIDENCE OF VOMITING

The incidence of vomiting was greater in the non-black patient group at 15 minutes (T15), 90 minutes (T90) and 180 minutes (T180). This is displayed in Figure 4.3 below.

The data was compared using the Chi-Squared test with 1 degree of freedom. Significance was defined as P<0.05. Since the number of vomiting events for both groups at 0 minutes (T0) and 24 hours (T24) were 0, these time points could not be tested. Although the incidence of vomiting at T15, T90 and T180 was greater in the non-black group, this was not significant as shown by p values of 0.2193, 0.1585 and 0.1585 respectively. These results are summarised in Table 4.9.

However, when the vomiting event counts were stratified into time periods of 0-2 hours, 2-24 hours and 0-24 hours, different results were obtained. The incidence of vomiting during the total 0-24 hours time period was significantly more in the non-black group with, with a p value of 0.0277. During the 0-2 hours and 2-24 hours period the difference in incidence remained insignificant with p values of 0.0784 and 0.1596 respectively. These results are shown and summarised in Table 4.10 and Figure 4.4.



* T0= 0 minutes, T15= 15 minutes, T90= 90 minutes, T180= 180 minutes, T24= 24 hours

Figure 4.3: The incidence of vomiting at each time point for both groups

Table 4.9: Comparison of the incidence of vomiting at each time point using the Chi-Squared test with 1 degree of freedom

Time point	P Value
T0 (0 minutes)	Could not be calculated
T15 (15 minutes)	0.2193
T90 (90 minutes)	0.1585
T180 (180 minutes)	0.1585
T24 (24 hours)	Could not be calculated

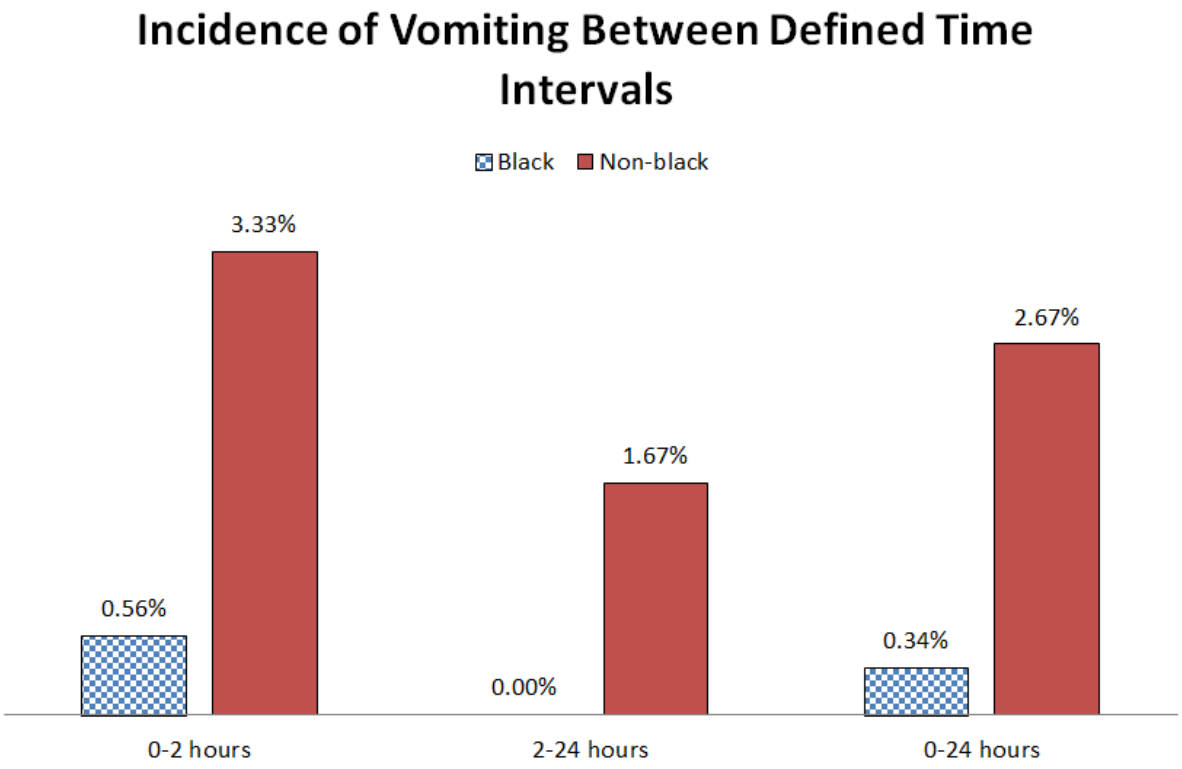


Figure 4.4 The incidence of vomiting between time intervals for both groups

Table 4.10: Comparison of the incidence of vomiting during predefined time intervals using a Chi-Squared test with 1 degree of freedom

Time Interval	P value
0-2 hours	0.0784
2-24 hours	0.1596
0-24 hours	0.0277 *

* significant (P<0.05)

4.2.2.6 COMPARE THE USE OF RESCUE ANTIEMETICS

As mentioned previously in 4.2.2.3, complete records for postoperative antiemetic use were only available for 22 out of 59 patients in the black group, and 14 out of 30 patients in the non-black group.

This data was analysed using the Mann-Whitney U test for two continuous independent samples. Although the mean dose of prochlorperazine given in the black group (20.45mg) was higher than that given in the non-black group (16.07mg), this was not statistically significant with a p value of 0.305.

4.3 DEMOGRAPHIC AND BASELINE DATA

As shown in Table 4.13 below, the groups were very similar. There were however significant differences in the following variables: history of PONV (p=0.035), non-smoking status (p=0.07), procedure type(p=0.0358), atracurium dosing(p=0.04) and rocuronium(p=0.02) dosing. Despite differences in individual risk factors for PONV; i.e. history of PONV and non-smoking status, the average Apfel scores(156) between the two groups were not different, therefore the PONV risk categories in the two groups were the same (moderate to high risk). The distribution of procedure types is shown below in Figure 4.4 and Figure 4.5.

Table 4.13: Summary table and comparison of baseline variables

Variable	All (89)	Black (59)	Non-black (30)	P value	Test
Age (yrs)	40.6 ± 11.8 42 [19-73]	38.7 ± 10.03 41 [19-60]	44.36 ± 14.23 45 [20-73]	P=0.052	MW U
Anaesthetic time (mins)	120.9 ± 67.19 110 [40-560]	120.38 ± 72.7 100 [40-560]	122.13 ± 55.88 115 [50-278]	P=0.77	MW U
ASA (1-5) (Median (Mode) [Range])	1(1) [1-3]	1(1) [1-3]	1(1) [1-2]	P=0.67	P-Chi Sq
Gender (N, m/f)	17/72	11/48	6/24	P=0.87	P- Chi Sq
Hx of PONV (N (%))	16 (17.9%)	7 (13.4%)	9 (30%)	**P=0.035**	P-Chi Sq
Hx of MS (N, %)	27 (30.3%)	16 (27.1%)	11 (36.6%)	P=0.35	P-Chi Sq
Non Smokers (N, %)	81 (91%)	58 (98.3%)	23 (76.6%)	**P=0.0007**	P-Chi Sq
Procedure Type	See Figure 4.5 and 4.6 below			**P=0.0358**	P- Chi Sq
Apfel Score average		3.18	3.23	P>0.1	MWU
Fluids- Crystalloid (ml)	1069.1 ± 402.01 1000 [200-3000]	1097.45 ± 403.58 1000 [400-3000]	1013.33 ± 399.77 1000 [200-1800]	P=0.64	MW U
Fluids- Colloid (ml)	57.86 ± 175.63 0 [0-1000]	78.81 ± 203.25 0 [0-1000]	16.66 ±91.28 0 [0-500]	P=0.09	MWU
FiO2 (Fraction)	0.54 ± 0.06 0.55 [0.4-0.8]	0.54 ± 0.06 0.54 [0.4-0.8]	0.54 ± 0.05 0.55[0.45-0.69]	P=0.76	MWU
Neostigmine (mg)	2.19 ± 0.82 2.5 [0-2.5]	2.20 ±0.81 0[0-2.5]	2.16 ± 0.86 2.5[0-2.5]	P=0.84	MWU
Propofol (mg)	158.53 ± 49.82 150 [60-400]	157.9 ± 43.96 150 [100-300]	159.66 ± 60.54 150 [60-400]	P=1	MWU

Fentanyl (ug)	100 ± 81.53 100 [0-300]	98.30 ± 76.54 0[100-300]	103.3± 91.85 100[0-300]	P=0.98	MWU
Morphine (mg)	8.01 ± 4.44 8.5 [0-24]	8.33 ± 4.6 9 [0-24]	7.38 ± 4.05 7.5 [0-16]	P=0.52	MWU
Sufenta (ug)	0.44 ± 4.2 0 [0-40]	0	1.33 ± 7.3 0 [0-40]	P=0.16	MWU
Alfentanil (ug)	52.80 ± 219.55 0 [0-1000]	67.79 ± 253.55 0[0-1000]	23.3 ± 127.8 0 [0-700]	P=0.48	MWU
IV paracetamol (g)	0.78 ± 0.41 0 [0-1]	0.77 ± 0.41 0 [0-1]	0.8 ± 0.4 0 [0-1]	P = 0.83	MWU
Remifentanil(average ng/kg/hr)	54.77 ± 110.90 0 [0-650]	64.83 ± 124.92 0 [0-650]	35 ± 74.16 0 [0-250]	P =0.45	MWU
Midazolam (mg)	0.07 ± 0.376 0 [0-3]	0.10 ± 0.44 0 [0-3]	0.03 ± 0.18 0 [0-1]	P=0.50	MWU
Ketorolac (mg)	6.74 ± 12.59 0 [0-30]	7.11 ± 12.87 0 [0-30]	6 ± 12.205 0 [0-30]	P=0.69	MWU
Atracurium (mg)	32.13 ± 20.81 35 [0-75]	35.84 ± 19.25 40 [0-75]	24.83 ± 22.14 30 [0-70]	**P=0.04**	MWU
Rocuronium (mg)	4.49± 16.23 0[0-100]	1.694± 9.12 0 [0-50]	10±24.21 0 [0-100]	**P=0.02**	MWU
Cisatracurium (mg)	0.23 ± 1.38 0 [0-10]	0.05 ± 0.39 0 [0-3]	0.6 ± 2.29 0 [0-10]	P=0.216	MWU
Vecuronium (mg)	0.13 ± 1.27 0 [0-12]	0	0.4 ± 2.19 0 [0-12]	P=0.168	MWU
Augmentin (g)	1.09 ± 0.73 1.2 [0-2.4]	1.15±0.77 1.2 [0-2.4]	0.96±0.66 1.2 [0-2.4]	P=0.24	MWU
Kefzol (g)	0.20±0.504 0 [0-2]	0.186±0.43 0[0-2]	0.23±0.62 0[0-2]	P=0.79	MWU

* MWU- Mann Whitney U, P-Chi Sq - Pearson Chi Squared, N-number, MS-motion sickness, ml-milliliters, FiO2 - fraction of

inspired oxygen, mg-milligrams, ug-micrograms, g-grams, ng-nanograms, kg-kilogram, hr-hour.

** Continuous variables are given as Mean ± Standard Deviation, Median[Range]

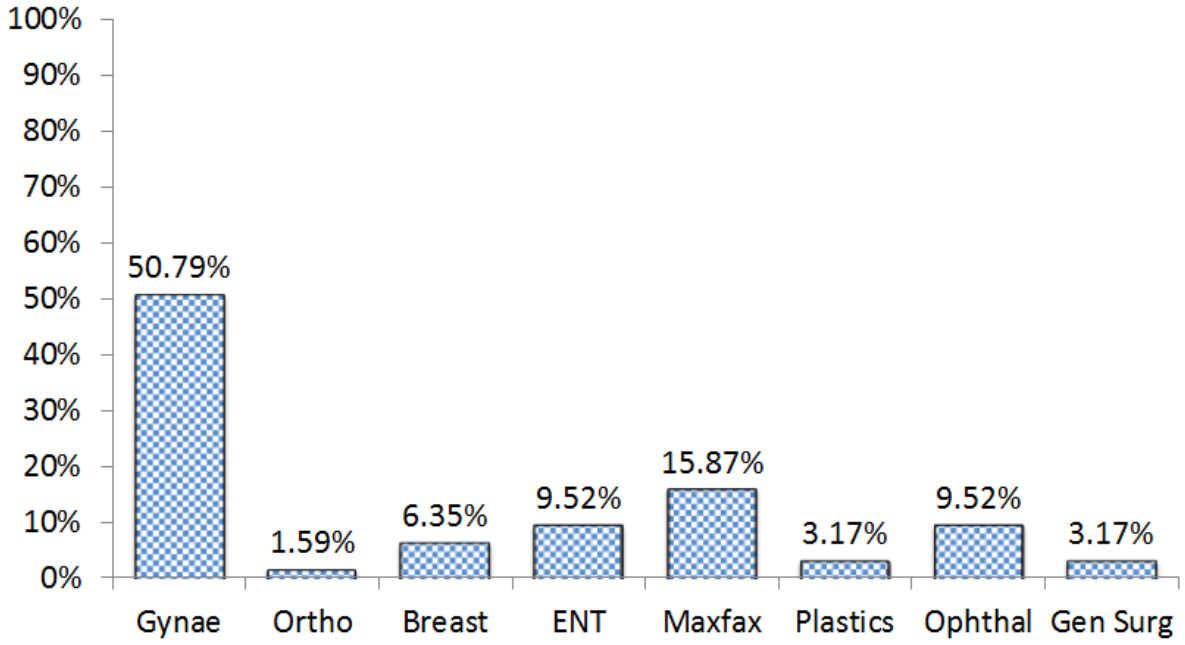


Figure 4.5: Distribution of surgical procedures in black patients

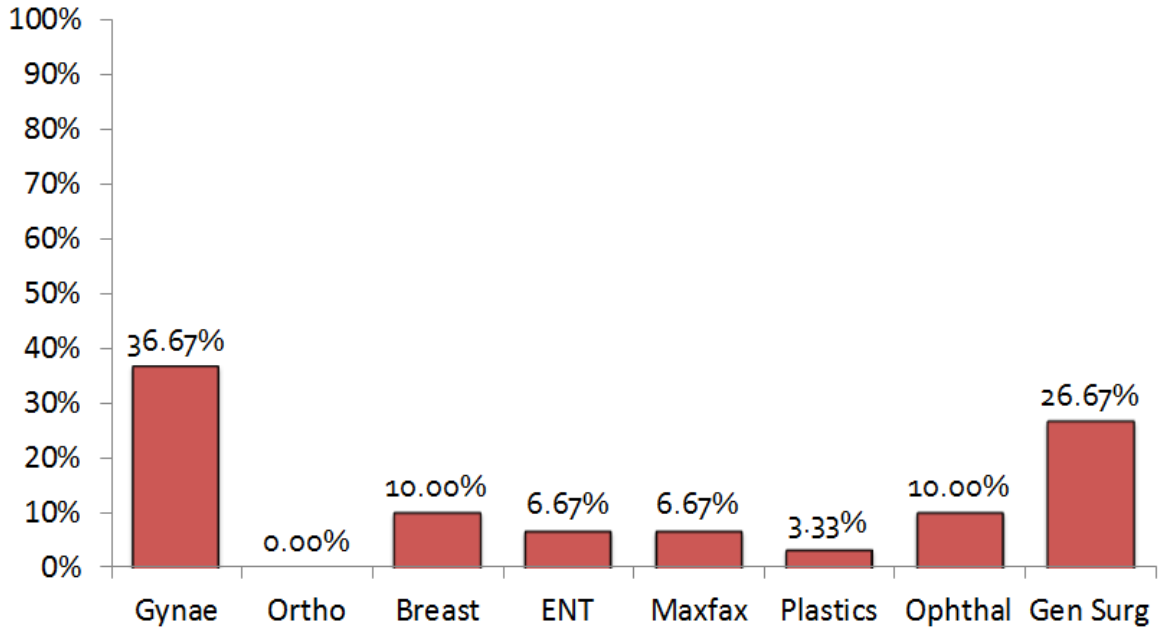


Figure 4.6: Distribution of surgical procedures in non-black patients

* Gynae= gynaecology; Ortho= orthopaedics; ENT= ear, nose and throat; Maxfax= maxillofacial; Opthal=ophthalmology; Gen surg= general surgery

4.4 APPROACH TO DATA ANALYSIS

4.4.1 QUALITY OF DATA

The quality of data was checked using descriptive statistics and normality analysis. Data cleaning had no unwarranted effects on the quality of the data.

Means, modes, ranges, standard deviations and variances as appropriate were calculated for all groups of variables. The majority of the data fitted the normal distribution pattern, with only a minority of data being non-normally distributed. Non-normally distributed data were not adjusted into a normal distribution.

4.4.2 RANDOMISATION CHECK

No formal randomisation procedure was used. The method of sampling was convenience based. However, the non-random sampling was considered to be successful, since background and substantive variables were shown to be equally distributed across both groups as is shown in 4.3.

4.4.3 ANALYSES

Various statistical tests were used to analyse the data (see 4.5 below). Nominal and ordinal variables were analysed using numbers and percentages. These values were also cross tabulated (for the Chi-squared test). Standard deviations, means and variances were calculated for continuous variables. In addition the Mann Whitney U test was used to compare these variables.

4.5 DATA ANALYSIS

4.5.1 SOFTWARE USED

Statistica for Windows version 10 and 11 were used for descriptive statistics, univariate and multivariate analyses.

4.5.2 TESTS USED

The following tests were used to analyse the data. A p value of less than 0.05 was taken as being significant.

The Pearson Chi-Squared test was used to analyse discrete and categorical data. One degree of freedom was used.
The Mann-Whitney U test was used to analyse continuous data. A Spearman's linear rank correlation coefficient was measured to determine the dependence of the presence of PONV on ethnic origin. Multiple regression analysis was also used to analyse if PONV was dependent on ethnic origin. The independent variable was assigned as ethnic origin, whilst the dependent or explanatory variables were the known risk factors for PONV: female gender; non-smoking status; history of postoperative nausea and vomiting.

Relative risk ratios and associated confidence intervals were calculated for the identified risk factor of ethnicity.

4.6 SUMMARY

The results of the study were presented in this chapter. Although the intended sample number was not achieved, it was decided in conjunction with a statistician that data analysis should proceed, as there would be enough data in order to answer the questions of the study. Various statistical methods were used in order to analyse the different categories of

data. Mann Whitney U and Pearson Chi-Squared tests were used to compare different categories of data. Linear correlation, multiple regression and relative risk calculation were used to ascertain if ethnicity is indeed a risk factor for PONV.

The aims and objectives of the study were achieved, and the results will be discussed in detail in the following chapter.

CHAPTER 5 - DISCUSSION

This chapter contains a discussion revolving around the results detailed in chapter 4.

5.1 INCIDENCE OF NAUSEA

The cumulative incidence of nausea in the non-black patient group between 0 and 24 hours was significantly higher (32.7%) than in the black patient group(13.5%).

The Apfel score (1) predicted a 39% risk of PONV for both groups. The incidence of nausea in the non-black group mirrors international literature(2), however the Apfel score grossly overestimated the predicted incidence of nausea in the black patient group. There is no international literature to date on the incidence of postoperative nausea (PON) in different ethnic groups. The data from our study is different from a non-controlled prospective observational study examining a population drawn from a similar population group in South Africa, which showed a higher overall incidence of PONV; 45% in the non-African group, and 22% in the African group (14). This trial was non-controlled, and some patients did not receive antiemetic prophylaxis which may explain the higher overall incidence. It is worth noting however, that the risk of nausea in that study doubled in the non-African group, which is similar to the risk increase seen in our study.

On examination of the distribution of nausea events, it can be seen that the incidence in the non-black group is higher than that of the black group at all time points, except for 24 hours (when both groups had a zero incidence). This is illustrated in Figure 4.1.

If the data is divided into early (0-2 hours) and late (2-24 hours) periods, the difference in incidence of nausea between the two groups is only present in the early period ($p=0.00000046$). Although the incidence is still higher in the non-black group during the late period, the difference is non-significant ($p=0.3904$). Despite this non-significant result, the incidence is still almost double in the non-black group (2.54% vs. 5%) during the late period. This is illustrated in Figure 4.2. The reason for this reduction in significant difference in

nausea risk is difficult to illicit, and could be due to the amount of postoperative opioid received. Only 22 (66 observations in total) records of prescribed opioids were available in the black group, and 14 records (42 observations in total) in the non-black group. Out of those 66 total observations in the black group, there were 19 records(28.7%) of received opioids in the 2-24 hour period, and out of the 42 observations of patients in the non-black group, there were only 10 records (23.8%) of opioid received in the same period. Although this difference in opioid requirement is non-significant taken independently (p=0.56), there was more opioid requirement in the black group. This increased opioid requirement may have been enough to cause a relative increase in nausea incidence in the black patient group resulting in a non-significant nausea difference in the late period.

5.2 INCIDENCE OF VOMITING

The incidence of vomiting was significantly higher (p=0.027) in the non-black population group during the entire 0-24 hour period (2.67% vs. 0.34%).

There were only 5 vomiting events throughout the entire study group, with no events being recorded at 0 minutes and 24 hours.

Examining the early and late postoperative periods separately, there is no difference in the incidence of vomiting between the two patient groups, however, the difference in the early period tended towards significance (p=0.078).

As is for the case with the incidence of nausea, there was less of a significant difference in the incidence of vomiting in the late period versus the early postoperative period, although there was no vomiting at all recorded in the black patient group during this time.

The reason for the reduced difference in vomiting between the two patient groups in the late period, is most likely due to a lowering of the incidence of vomiting in the non-black group during the late period. This may be as a result of the lower postoperative opioid requirement by the non-black group (as discussed in 5.1).

The incidence of vomiting during the different time periods and the total study period is shown graphically in Figure 4.4.

5.3 ETHNICITY AS A RISK FACTOR

Both linear correlation and multiple regression analysis showed that ethnicity is a risk factor for PONV. Black South African patients had reduction of PONV risk as compared with non-black South Africans.

As described in detail in 4.2.1.1, the Spearman ranked coefficient analysis was used to test for linear correlation between ethnicity and PONV.

It was found that there was a correlation between non-black ethnicity and the presence of nausea at the 0, 15 and 90 minute time points (p=0.036, 0.000012, 0.020 respectively). It was also found that there was a correlation between non-black ethnicity and vomiting between 0-24 hours. As shown for the comparison of nausea (5.1), non-black ethnicity could not be identified as a risk factor for nausea if the late postoperative is examined independently.

Multiple regression analysis also showed similar results, with non-black ethnicity being identified as a risk factor for nausea at 0, 15, 90 minutes and 0-24 hours (p values of 0.009, 0.000014, 0.000019, 0.000003 respectively). Using the same analysis it was also shown that non-black ethnicity was a risk factor for vomiting between 0-24 hours (p=0.0044).

On examining the relative risk ratios, non-black ethnicity was found to be a significant risk factor for nausea with a relative risk ratio of 2.40 (95 % CI, 1.67-3.48). This is similar to the result found in Rodseth et als' study where the odds ratio was found to be 2.1 (95% CI, 1.5-2.82) (14).

Despite a high relative risk ratio of 7.86 for vomiting, the 95% confidence interval for this

calculation was wide (0.88 to 69.76), which reduces the significance of the risk increase. This result was most likely due to the very low numbers of vomiting events for both groups. Examining relative risk ratio for postoperative nausea risk reduction, the black patient group was protected against postoperative nausea, with a relative risk of 0.41 (95% CI, 0.28-0.60).

This data shows that non-black ethnicity is a risk factor for PONV, although the strength of the association is more significant for early postoperative nausea (than for late postoperative nausea), and for postoperative vomiting.

Previous laboratory studies have shown that Chinese ethnic origin is a risk factor for induced motion sickness (16,17).
However, there is little work done on examining this effect in the perioperative setting. In this regard, the little that is published is conflicting. A meta-analysis examining risk factors for PONV in gynaecological surgery found that there is an increased risk in patients of British origin as opposed to patients of German origin (17). A large retrospective study with 8855 patients examining the effect of gender, age and race on the side effects of short term opioid administration, found that black patients had less nausea and vomiting than white patients with an OR of 1.4 (CI 1.1-1.7) (18). A recent non-controlled prospective observational study examining the same study question in Durban, South Africa showed that non-black ethnic origin was associated with a much higher risk of PONV, OR 2.1 (95% CI, 1.5-2.82) (14). However, there is other retrospective work that has shown no effect of ethnicity on the risk of PONV (148).
Examining this conflicting literature, it is apparent that only Rodseth et als' (14) trial was designed to specifically answer the question of whether ethnicity is a risk factor. The data in our prospective study add further support to this argument.

5.3.1 POSSIBLE EXPLANATIONS FOR THE EFFECT OF ETHNIC ORIGIN ON PONV

PONV has been seen as the result of multifactorial interactions. The main factors resulting in differing risk profiles for PONV may be variations in: afferent stimuli, psychology, receptors and drug metabolism. These may have varying effects between ethnic groups due to

genetic, sociocultural or psychological factors.

5.3.1.1 GENETIC FACTORS

There are numerous pharmacogenetic factors that have been identified as risk factors for PONV. Genetic polymorphisms in the cytochrome P450 system, particularly the number of alleles of CYP2D6, affect the efficacy of 5HT3 receptor antagonists (56,174,175,176). Variations of 5-HT3A/B receptor genes (HTR3A/HTR3B) have been shown to be associated with the individual risk of developing POV (180).

Opioid efficacy is affected by genetic polymorphisms of the OPRM1 A118G mu-opioid receptor gene (181). This may imply that the more efficacious an opioid, the higher the risk of PONV, however this has been refuted in a study by Zhang et al (182).

Other receptor polymorphisms such as the dopamine D2 receptor Taq 1A polymorphism (183) have also been associated with PONV.

A genome wide association study used pooled DNA and found that at least one single nucleotide polymorphism was associated with PONV susceptibility (184).

5.3.1.2 SOCIOCULTURAL AND PSYCHOLOGICAL FACTORS

Although cultural factors affecting PONV have not been investigated in the literature, there is work done on cultural differences in the perception of pain. In a quantitative review on the differences in experimental pain response, the researchers found differences between ethnic and cultural groups (185). They suggest that cultural group attitudes toward pain may differ, and each group may have differing degrees of pain expectancy and acceptance resulting in differences in measured clinical pain. This could also potentially be applied to explain ethnic group differences in PONV.

Other factors that could also be used to explain the ethnic variation in PONV incidence are mentioned in the same pain study and they include: pain sensitivity, language,

expressiveness, medication practices and beliefs, socioeconomic status, chronic stress, socialisation of pain expression, and environmental factors. Psychological factors mentioned include pain coping strategies, mood and hyper vigilance.
Unfortunately there is no literature that directly investigates the possible sociocultural and psychological factors that influence the incidence of PONV. Using literature investigating another subjective sensation such as pain, may provide insight into the psychopathology of PONV.

5.4 BASELINE DEMOGRAPHICS

As examined in detail in 4.3, the study groups were similar in all variables except for history of PONV, non-smoking status, procedure type, atracurium dosing and rocuronium dosing.

As mentioned previously, despite the difference in history of PONV and non-smoking status, the mean Apfel score(156) was similar; which, in addition to history of PONV and non-smoking status, takes into account female gender and perioperative opiate use. Therefore, the difference in history in PONV and non-smoking status between the two groups did not change their baseline risk of PONV.

The procedure type was different, with the majority of black patients undergoing gynaecological surgery (51%), followed by maxillofacial surgery (16%). The majority of non-black patients also underwent gynaecological surgery (36%), followed by general surgery (27%). It is controversial as to whether the type of surgery is a risk factor for PONV. Previous work has shown that the type of surgery is a risk factor (5), but more recently it has been shown that the duration of surgery is more of a risk factor than the type of surgery itself (1,134), with the possible exception of strabismus surgery in paediatric patients (135). Therefore, the difference in procedure types between the two groups is unlikely to have changed their baseline risk of PONV.

There was a difference in the amount of muscle relaxant (atracurium and rocuronium) use between the two groups. Non-depolarising muscle relaxants have not been shown to be

independent risk factors for PONV. Controversy exists regarding neostigmine use as a risk factor for PONV. Previous work has shown that neostigmine increases the risk of PONV in a dose dependent manner (8). However, a recent meta-analysis suggests that neostigmine may not be implicated at all as a risk factor for PONV (186).
Despite the different amounts and types of muscle relaxants used in this study, the neostigmine doses for both groups were similar, therefore the baseline risk of PONV was unlikely to have been influenced.

The additional risk factor of perioperative opioid use was not added to the data since every patient in the study received opioids. The amount of intraoperative opioid between the two groups was similar.

5.5 LIMITATIONS OF THIS STUDY

5.5.1 STUDY DESIGN

This study was a non-blinded non-randomised prospective non-placebo controlled trial with a convenience sampling method. The use of placebo for antiemetic prophylaxis was considered unethical and unnecessary to answer the study question. It may have improved the strength of the trial to have a randomised patient selection method, but due to researcher availability a non-randomised convenience sampling method was selected. It was impossible to blind such a study since the patients had to be interviewed by an investigator after surgery. The strengths of this study design were that the intraoperative period was controlled, and every patient received the same combination of anti-emetic prophylaxis. To improve on the study, although requiring more resources, the postoperative period could also have been controlled.

5.5.2 STUDY METHODOLOGY

The patients recruited into the study had a wide range of first languages. In order to prevent

communication difficulties after recruitment, patients were only recruited if they understood the visual analogue scale and other questions on the study questionnaire adequately. This may have introduced a selection bias, as only patients with a certain level of education and possibly a certain level of socioeconomic status were recruited into the trial. If there was difficulty in questioning the patient after surgery, translated questions were available to use in order to facilitate communication.

Only one researcher was available to interview the patients postoperatively. This resulted in reliance on nursing records, as was initially planned in the protocol. Unfortunately, the accuracy of the nursing records with regard to postoperative opioid and antiemetic administration was questionable, and only those records which were meticulously completed were included in the study. This resulted in an incomplete assessment of patients' postoperative opioid and antiemetic use.

Patients of mixed ethnicity were to be included in the non-black patient group. The potential limitation of this strategy was that the data from the non-black group would be skewed in an unknown manner with regard to the risk of PONV. However, there were no patients of mixed ethnicity available to recruit as potential subjects for the study, and therefore this limitation was not realised.

5.5.3 DATA ANALYSIS

The number of patients ultimately recruited was much lower than that planned, once again due to researcher availability and time constraints, but also due to a low rate of admission of eligible patients (most of the patients presenting to this tertiary academic hospital met multiple exclusion criteria and were not recruited). This affected the power of the study, but after numerous consultations with statisticians, it was decided that the final numbers were adequate in order to answer the questions of the study.

CHAPTER 6 - SUMMARY, IMPLICATIONS, RECOMMENDATIONS AND CONCLUSION

This chapter concludes the thesis and includes a summary of the study, followed by practice implications, future research recommendations and a conclusion.

6.1 SUMMARY OF THE STUDY

6.1.1 PROBLEM STATEMENT

PONV is a multifactorial and complex phenomenon that is extremely unpleasant and potentially costly. Prophylactic measures are only cost effective, and less harmful in patients at high risk for PONV. Anecdotally, black South African patients were considered to have a lower incidence of PONV. There has been little prospective work done on assessing ethnicity as a risk factor for PONV in South Africa.

6.1.2 AIM

To compare the effect of ethnicity on the incidence of PONV in moderate to high risk black versus non-black South African patients undergoing general anaesthesia.

6.1.3 OBJECTIVES

To determine and compare the incidence of PONV in moderate to high risk black and non-black South African patients.

6.1.4 METHODOLOGY

A prospective, controlled observational study was carried out. After ethics approval and informed consent, 95 patients at high risk for PONV undergoing surgery under general anaesthesia were enrolled onto the study over a period of 20 months. 89 patients fulfilling

the inclusion criteria were divided according to race into two cohorts. Ondansetron and dexamethasone were used as PONV prophylaxis after induction of general anaesthesia. Propofol was used as the induction hypnotic with isoflurane to maintain anaesthesia. Nitrous oxide, ketamine and droperidol were avoided. Use of analgesics was unrestricted, but neuraxial and nerve plexus regional anaesthesia were avoided. A maximum of 2.5mg of neostigmine was given to reverse neuromuscular blockade. Nausea and vomiting were assessed by means of a visual analogue scale and questionnaire in the recovery room and ward. Time intervals to assess degree of PONV were 0 hours (defined by first assessment of a modified Aldrete recovery score of at least 9 out of 10 and Glasgow Coma Scale score of 14 out of 15), 15 minutes, 90 minutes, 180 minutes, and 24 hours. Reports of incidents of vomiting and complaints of nausea between interviews were obtained from patients through questioning.

6.1.5 RESULTS

There were 59 black participants and 30 non-black participants. There were 17 males and 72 females. There were no differences in the black and non-black groups with regard to gender, past history of motion sickness, past history of post operative nausea and vomiting, ASA status, smoking and anaesthetic time ($p>0.05$). There was a significant difference in the distribution of surgical procedures in the black and non-black participants (Mann Whitney U test, $p= 0.02$), although this did not affect the final result.

On univariate analysis there were significant correlations between black South African ethnicity and nausea at all time intervals and also vomiting. Using multivariate regression analysis, non-black South African ethnicity was identified as a risk factor for PONV. It was found that black South African patients were protected against PON, with a RR of 0.41 (95% CI, 0.28-0.60).

6.2 IMPLICATIONS OF THIS STUDY

PONV is a distressing and potentially costly complication of general anaesthesia (3,4). The use of anti-emetic drugs is associated with cost, and a number of potential side effects.

Therefore, scoring systems have been developed in order to assess the risk of PONV in patients preoperatively (1,6,12). According to this risk stratification, patients will be given either no prophylaxis, or single/multiple agent prophylaxis.

We have shown in this study that black South African patients are protected against PONV, and have a lower risk than that predicted by existing scoring systems. These scoring systems were developed in the northern hemisphere, predominantly in affluent countries, and may not be appropriate for use in South Africa. The use of a scoring system may result in over-estimation of PONV risk in our patient population, and this may result in excess cost and side-effects from the inappropriate administration of anti-emetic prophylaxis. A modified scoring system needs to be developed for use in South Africa that includes black South African ethnicity as a protective factor.

Since ethnic groups have discrete genetic origins, a lower incidence of PONV may reflect the existence of a unique genetic polymorphism in the South African black patient. Identification of this polymorphism could improve our understanding of the molecular mechanisms underlying PONV. Sociocultural and psychological issues may also play a role in the risk of PONV in the black South African population.

6.3 FUTURE RESEARCH SUGGESTIONS

Further work needs to be done to confirm the reduction of risk of PONV in black South African patients. A larger powered study is necessary in order to achieve this aim. This trial should also have a prospective controlled design.

Other trials should examine variation in genetic polymorphisms in this population group, perhaps examining the number of CYP2D6 alleles, or the presence of mu-opioid receptor polymorphisms, and correlating those with the risk of PONV.

Psychological and socioculturual factors also need to be examined. This may be achieved by extending an incidence/risk factor study, such as this one, into the private sector. The

private sector in South Africa serves the more affluent members of the population who have different living circumstances, social stressors and educational status than patients that seek health care in state facilities. This may show that black South Africans who have a higher socioeconomic and education level, have a similar risk of PONV to that of non-black South Africans.

6.4 CONCLUSION

In this study we found that black South African ethnicity reduced the risk of PONV as compared with non-black South African ethnicity. We found that non-black South Africans had a similar risk of PONV to that published in international literature and predicted by the Apfel score, whereas the risk of PONV in similar Apfel scored black South African patients was much lower.

APPENDIX A - STUDY QUESTIONNAIRE

Post operative nausea and vomiting study questionnaire:

Date (dd/mm/yyyy):

Time of induction of anaesthesia (hhmm):

Time of return of airway reflexes (hhmm):

Time of entry into recovery area (hhmm):

Home Language:

1- English, 2- Afrikaans, 3- isiNdebele, 4- isiXhosa, 5- isiZulu, 6 – Sepedi, 7- Sesotho, 8- Setswana, 9 – siSwati, 10 – Tshivenda, 11 – Xitsonga

Assessment of nausea:

(Read questions off appropriate language card or show patient question on card)

0 minutes: **Date(dd/mm/yyyy):** **Time (hhmm):**

GCS (Min 15/15): E: **V:** **M:** **Total GCS/15:**

"Do you feel nauseous?" Yes No

Nausea Score (1-10) on visual analog scale:

Episode of vomiting? Yes No

Rescue antiemetic received? Yes No

Time(hhmm): Drug Name: Dose:

15 minutes: **Date(dd/mm/yyyy):** **Time(hhmm):**

"Do you feel nauseous?" Yes No

Nausea Score (1-10) on visual analog scale:

Episode of vomiting since previous assessment? Yes No

Rescue antiemetic received? Yes No

Time(hhmm): Drug Name: Dose:

90 minutes: **Date(dd/mm/yyyy):** **Time(hhmm):**

"Do you feel nauseous?" Yes No

Nausea Score (1-10) on visual analog scale:

Episode of vomiting since previous assessment? Yes No

Rescue antiemetic received? Yes No

Time(hhmm): Drug Name: Dose:

180 minutes: **Date(dd/mm/yyyy):** **Time(hhmm):**

"Do you feel nauseous?" Yes No

Nausea Score (1-10) on visual analog scale:

Episode of vomiting since previous assessment? Yes No

Rescue antiemetic received? Yes No

Time(hhmm): Drug Name: Dose:

24 hours: **Date(dd/mm/yyyy):** **Time(hhmm):**

"Do you feel nauseous?" Yes No

Nausea Score (1-10) on visual analog scale:

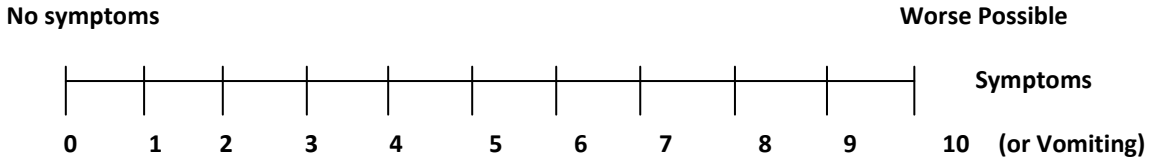
Episode of vomiting since previous assessment? Yes No

Rescue antiemetic received? Yes No

Time(hhmm): Drug Name: Dose:

APPENDIX B - VISUAL ANALOGUE SCALE

How bad is your nausea now? Place a vertical mark on the line below to indicate how bad you feel your nausea is now.



APPENDIX C – Modified Aldrete and Glasgow coma scale scores

MODIFIED ALDRETE RECOVERY SCORE

Activity		Points
Able to move, voluntarily or on command	Four extremities Two extremities No extremities	**2** **1** **0**
Respiration	Able to breathe deeply and cough freely Dyspnoea, shallow or limited breathing Apnoea	**2** **1** **0**
Circulation	BP within 20mmHg of preop BP within 20-50mmHg of preop BP more than 50mmHg of preop level	**2** **1** **0**
Consciousness	Fully awake Arousable on calling Unresponsive	**2** **1** **0**
Oxygen Saturation	Saturation > 92% Needs oxygen to maintain sats >90% Saturation <90% with oxygen	**2** **1** **0**

Nine or more points are required for recovery to be confirmed

GLASGOW COMA SCALE

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to pain	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible	Slurred speech, muttering	Confused, disoriented	Oriented, converses normally	N/A
Motor	No movements	Extension to pain (decerebrate)	Abnormal flexion to pain (decorticate)	Flexion/ withdrawal to painful stimuli	Localises painful stimuli	Obeys commands

APPENDIX D - PATIENT INFORMATION LEAFLET

Patient Information Leaflet: Post operative nausea and vomiting study

My name is Dr A Alli I am a doctor in the Department of Anaesthesia of this hospital.

1. You are invited to consider taking part in a research study. Your participation in this study is entirely voluntary.
2. Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risk, discomfort, and precautions, and your right to withdraw from the study at any time. This information leaflet is to help you to decide if you would like to participate. You should fully understand what is involved before you agree to take part in the study.
3. If you have any questions, do not hesitate to ask me. You should not agree to take part unless you are satisfied with all the procedures involved.
4. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.
5. If you have a personal doctor, you may discuss with or inform him/her of your possible participation in this study. If you wish, I can also notify your personal doctor in this regard.
6. **Purpose of this study and study procedures:**
    - You have been diagnosed with a surgical problem that requires surgery under general anaesthesia. Due to the nature of the surgery, and the length of anaesthesia, you are at risk for developing nausea and vomiting after awaking from general anaesthesia.
    - You will be assigned to one of two patient groups. This will be dependent on your past medical history as well as your ethnic origin.
    - **The purpose of the study is to assess your risk for nausea and vomiting after general anaesthesia.**
    - We will inform the anaesthetist responsible for administering your anaesthetic about your participation in this study. He or she will follow the study guidelines regarding aspects of the anaesthetic. This is so that all the participants in the study receive a similar anaesthetic. I want to assure you, that despite the study guidelines regarding the anaesthetic, you are at no additional risk of complications from general anaesthesia. As part of the anaesthetic you will receive medication that will reduce the risk of post-operative nausea and vomiting. This is standard medication and is not different to what patients that are not involved in this study would receive.
    - Either myself or one of the other investigators involved in this study will assess you as you enter the recovery area after your procedure. We will ask you standard questions. These will assess if you are nauseous. Once you have been taken to the surgical ward, we will observe you and ask you the same questions in intervals over a period of 24 hours. You will also be monitored by nursing staff, and recordings of the times that you feel like vomiting or actually vomit, will be made.
    - The amount of time required for your participation will be approximately 24 hours.
7. **Right as a Participant in this Study:**
    - **Your decision to participate in this study is entirely voluntary. You may withdraw from the study at any time without stating a reason.**
    - **If you disagree to be a participant in this study, this will not affect your medical treatment at all.**
    - **If you decide to participate in the study, but change your mind at a later stage, we will remove all your information from the study and this will not impact on the care you will receive.**
    - **Your health information will be treated as completely confidential, and will only be available to the researchers involved in this study. Your name will not appear in any of the documentation of any kind in this study.**
    - There may be no benefit to you from participation in the study. Your participation in this study will contribute to medical knowledge that may help other patients that, like you, are at risk for post operative nausea and vomiting. It will also not harm you in any way

8. **Ethics:**
    - The clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and is awaiting written approval. The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2000), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

Before you decide whether you will participate or not, do you have any questions?

The 24-hour telephone number through which you can reach me or another authorized person is 082 718 4989.

If you want any information regarding your rights as a research participant, or have any complaints regarding this research study, you may contact Prof. Cleaton-Jones, Chairperson of the **University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717-2301**

The University of the Witwatersrand, Human research Ethics Committee (HREC), might also inspect the information. They will utilize these records only in connection with carrying out their obligations relating to this clinical study.

Please indicate below, whether you want me to notify your personal doctor or your specialist of your participation in this study:

- **Yes**, I want you to inform my personal doctor/specialist of my participation in this study.
- **No,** I do not want you to inform my personal doctor/specialist of my participation in this study.
- **I do not have** a personal doctor/specialist

APPENDIX E - CONSENT FORM

CONSENT FORM

I hereby confirm that I have been informed by the study doctor _____ about the nature, conduct, benefits and risk of clinical study, **The effect of race on the incidence of post operative nausea and vomiting in moderate to high risk patients in South Africa: A prospective observational study**

I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.

I understand that some information about me will be collected (my age, gender, weight, smoking status, history of motion sickness or previous post operative nausea and vomiting, the surgical diagnosis and the type of surgery, details of the anaesthesia), and I understand that all my information will be given a special code so that no one will be able to trace it back to me. I understand that my name and hospital number will be kept separate from my information, and will be locked away. I understand that my participation is entirely voluntary and that I can pull out of the study at any time.

I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT

_____

Printed Name Signature/Mark of Thumbprint Date and Time

STUDY DOCTOR

_____

Printed Name Signature Date and Time

TRANSLATOR/OTHER PERSON EXPLAINING INFORMED CONSENT_____(DESIGNATION)

Printed Name Signature Date and Time

WITNESS (If applicable)

Printed Name Signature Date and Time

APPENDIX F - ETHICS CLEARANCE LETTER

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Alli

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M071102**
PROJECT	The Effect of Ethnicity of the Incidence of Post-Operative Nausea and Vomiting in Moderate to High Risk Ethnic SA Patients: a Controlled Observtional Study
INVESTIGATORS	Dr A Alli
DEPARTMENT	Department of Anaesthesia
DATE CONSIDERED	07.11.30
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application

DATE 08.01.23 **CHAIRPERSON** .....

(Professor PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr B Naik

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX G - PERMISSION FROM THE STUDY HOSPITAL'S MANAGEMENT

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Office of the Chief Executive Officer
Charlotte Maxeke Johannesburg Hospital
Tell: 011 488 3792
Fax: 011 488 3753
Email: lindiwe.mngomezulu@gauteng.gov.za
Date: 27th March 2013

Dr. Ahmad Alli
MMed Student
University of Witwatersrand

Dear Dr. All

RE: RETROSPECTIVE APPROVAL FOR THE PREVIOUSLY APPROVED STUDY ON: "THE EFFECT OF RACE ON THE INCIDENCE OF POST OPERATIVE NAUSEA AND VOMITING IN MODERATE TO HIGH RISK PATIENTS IN SOUTH AFRICA"

Approval is granted to Dr. Ahmad Alli to undertake research on: **"the effect of race on the incidence of post operative nausea and vomiting in moderate to high risk patients in South Africa"** at Charlotte Maxeke Johannesburg Academic Hospital.

Thank you;

Ms. G. Bogoshi
Chief Executive Officer

1

REFERENCES

1. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999; 91: 693–700.
2. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. Anesthesia and Analgesia 1994; 78: 7–16.
3. Gold BS, Kitz DS, Lecky JH, Neuhaus JM. Unanticipated admission to the hospital following ambulatory surgery. Journal of the American Medical Association 1989; 262: 3008–10.
4. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10 811 patients. British Journal of Anaesthesia 2000; 84: 6–10.
5. Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? Anesthesiology 1999; 91: 109–18.
6. Koivuranta M, Laara E, Snare L, Alahuhta S. A survey of postoperative nausea and vomiting. Anaesthesia 1997; 52: 443–9.
7. Sukhani R, Vazquez J, Pappas AL, Frey K, Aasen M, Slogoff S. Recovery after propofol with and without intraoperative fentanyl in patients undergoing ambulatory gynecologic laparoscopy. Anesthesia and Analgesia 1996; 83: 975–81.
8. Tramer MR, Fuchs-Buder T. Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. British Journal of Anaesthesia 1999; 82: 379–86.
9. Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. British Journal of Anaesthesia 2002; 88: 659–68.
10. Tramer M, Moore A, McQuay H. Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. British Journal of Anaesthesia 1996; 76: 186–93.
11. Gan Et Al, Society for ambulatory anaesthesia. Society for Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting. Anesthesia and Analgesia 2007; 105; 1615-28
12. Palazzo M., Evans R. Logistic Regression Analysis Of Fixed Patient Factors For Postoperative Sickness: A Model For Risk Assessment. British Journal of Anaesthesia, 1993, Vol. 70, No. 2 135-140
13. Habib AS, Tong J. Evidence-based management of postoperative nausea and vomiting: a review. Canadian Journal of Anaesthesia, 2004, Vol 51, No. 4, 326-341
14. Rodseth RN, Gopalan PD, Cassimjee HM, Goga S. Reduced incidence of postoperative nausea and vomiting in black South Africans and its utility for a modified risk scoring system. Anesthesia and Analgesia 2010:110: 1591-1594
15. Haigh CG, Kaplan LA, Durham JM, Dupeyron JP. Nausea And Vomiting After Gynaecological Surgery: A Meta-Analysis Of Factors Affecting Their Incidence. British Journal of Anaesthesia, 1993, Vol 71, No. 4, 517-522
16. Stern, R.M., Hu, S., LeBlanc, R., Koch, K.L. Chinese hypersusceptibility to vection-induced motion sickness. Aviation and Space Environment Medicine. 1993. Volume 64, 827–830.

17. Klosterhalfen, S., Kellermann, S., Pan, F., Stockhorst, U., Hall, G., Enck, P. Effects of ethnicity and gender on motion sickness susceptibility. Aviation and Space Environment Medicine 2005. Med. 76, 1051–1057.
18. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom B. Side effects of opioids during short term administration: Effect of age, gender, and race. Clinical Pharmacology and Therapeautics 2003, Volume 74, No. 2, 102-112
19. Knapp MR, Beecher HK. Postanesthetic nausea, vomiting and retching. Journal of the American Medical Association 1956: 160: 376–385.
20. American Association of Anesthesiologists web site, <http://www.asahq.org/aboutASA.htm>, accessed 27 July 2008.
21. Apfel CC, Roewer N, Korttila K. How to study postoperative nausea and vomiting. Acta Anaesthesiologica Scandinavia 2002; 46: 921–928
22. Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM. Assessment of postoperative nausea using a visual analogue scale. Acta Anaesthesiologica Scandinavia 2000: 44: 470–474.
23. Smith GFR. Post-operative vomiting. British Journal of Anaesthesia 1934;11:132–139
24. Morton HJV, Wylie WD. Anaesthetic deaths due to regurgitation or vomiting. Anaesthesia 1951;6:190–205
25. Edwards G, Morton HJV, Pask EA, et al. Deaths associated with anaesthesia. A report on 1000 cases. Anaesthesia 1956;11:194–220
26. Didier EP, Barila TG, Slogum HC, et al. An evaluation of antiemetic drugs in the control of postoperative nausea and vomiting. Surgical Forum 1954;5:707–712
27. Dent SJ, Ramachandra V, Stephen CR. Postoperative vomiting: incidence, analysis, and therapeutic measures in 3000 patients. Anesthesiology 1955;16:564–572
28. Burtles R, Peckett BW. Postoperative vomiting. Some factors affecting incidence. British Journal of Anaesthesia 1957;29:114–123
29. Dyrberg V, Johansen SH. Pre-anaesthetic medication with chlorpromazine. Acta Anaesthesiologica Scandinavia 1958;2:133–147
30. Lind B, Breivik H. Metoclopramide and perphenazine in the prevention of postoperative nausea and vomiting. British Journal of Anaesthesia 1970;42:614–617
31. Raeder JC, Mjaland O, Aasbo V, et al. Desflurane versus propofol maintenance for outpatient laparoscopic cholecystectomy. Acta Anaesthesiologica Scandinavia 1998;42:106–110
32. Hammas B, Thorn SE, Wattwil M. Superior prolonged antiemetic prophylaxis with a four-drug multimodal regimen—comparison with propofol or placebo. Acta Anaesthesiologica Scandinavia 2002;46:232–237
33. Bunce KT, Tyers MB. The role of 5-HT in postoperative nausea and vomiting. British Journal of Anaesthesia 1992;69:60S–62S
34. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytryptamine. British Journal of Anaesthesia 1994;73:395–407
35. Tramer MR, Reynolds DJ, Moore RA, et al. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology 1997;87:1277–1289
36. Andersen R, Krohg K. Pain as a major cause of postoperative nausea. Canadian Anaesthetists' Society Journal 1976;23:366–369
37. Aasboe V, Raeder JC, Groegaard B. Betamethasone reduces postoperative pain and nausea after ambulatory surgery. Anesthesia and Analgesia 1998;87:319–323

38. Wang JJ, Ho ST, Lee SC, et al. The prophylactic effect of dexamethasone on postoperative nausea and vomiting in women undergoing thyroidectomy: a comparison of droperidol with saline. Anesthesia and Analgesia 1999;89:200–203
39. Liu K, Hsu CC, Chia YY. The effect of dose of dexamethasone for antiemesis after major gynecological surgery. Anesthesia and Analgesia 1999;89:1316–1318
40. Zarate E, Mingus M, White PF, et al. The use of transcutaneous acupoint electrical stimulation for preventing nausea and vomiting after laparoscopic surgery. Anesthesia and Analgesia 2001;92:629–635
41. Riding JE. Post-operative vomiting. Proceedings of the Royal Society of Medicine 1960;53:671–677
42. Belleville WJ, Irwin DJ, Howland WS. Postoperative nausea and vomiting. IV: factors related to postoperative nausea and vomiting. Anesthesiology 1960;21:186–193
43. Purkis IE. Factors that influence postoperative vomiting. Canadian Anaesthetists' Society Journal 1964;11:335–353
44. Janhunen L, Tammisto T. Postoperative vomiting after different modes of general anaesthesia. Annales chirurgiae et gynaecologiae Fenniae 1972;61:152–159
45. Palazzo MG, Strunin L. Anaesthesia and emesis. I: etiology. Canadian Anaesthetists' Society Journal 1984;31:178–187
46. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162–184
47. Hornby PJ. Central neurocircuitry associated with emesis. American Journal of Medicine 2001; 111 Suppl. 8A: 106-2S
48. Miller AD. Central mechanisms of vomiting. Digestive Diseases and Sciences 1999; 44 (8 Suppl.): 39-43S
49. Habib AS, Gan TJ. Pharmacotherapy of postoperative nausea and vomiting. Expert Opinion in Pharmacotherapy 2003; 4 (4): 457-73
50. Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. Canadian Journal of Anaesthesia 2004; 51(4): 326-41
51. Saito R, Takano Y, Kamiya HO. Roles of substance P and NK(1) receptor in the brainstem in the development of emesis. Journal of Pharmacological Sciences 2003; 91 (2): 87-94
52. Kojima Y, Takahashi T, Fujina M, et al. Inhibition of cholinergic transmission by opiates in ileal myenteric plexus is mediated by kappa receptor: involvement of regulatory inhibitory G protein and calcium N-channels. Journal of Pharmacology and Experimental Therapeutics 1994;268 (2): 965-70
53. Tsuchida D, Fukuda H, Koda K, et al. Central effect of mu-opioid agonists on antral motility in conscious rats. Brain Research 2004; 1024 (1-2): 244-50
54. Scuderi PE. Pharmacology of antiemetics. International Anesthesiology Clinics 2003; 41 (4): 41-66
55. Janicki PK. Cytochrome P450 2D6 metabolism and 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. Medical Science Monitor 2005; 11 (10): RA322-328
56. Candiotti KA, Birnbach DJ, Lubarsky DA, et al. The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? Anesthesiology 2005; 102 (3): 543-9

57. Habib AS, Gan TJ. Food and drug administration black box warning on the perioperative use of droperidol: a review of the cases. Anesthesia and Analgesia 2003; 96 (5): 1377-9

58. White PF, Song D, Abrao J, et al. Effect of low-dose droperidol on the QT interval during and after general anesthesia:a placebo-controlled study. Anesthesiology 2005; 102 (6):1101-5

59. Charbit B, Albaladejo P, Funck-Brentano C, et al. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. Anesthesiology 2005; 102 (6): 1094-100

60. Scuderi PE. You (still) can't disprove the existence of dragons. Anesthesiology 2005; 102 (6): 1081-241. Kris M, Gralla R, Tyson L, et al. Controlling delayed vomiting: double-blind randomized trial comparing placebo, alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. Journal of Clinical Oncology 1989;7:108–14.

61. Rich W, Abdulhayoglu G, Di Saia PJ. Methylprednisolone as antiemetic during cancer chemotherapy: a pilot study. Gynecologic Oncology 1980;9:193–8.

62. Harris AL. Cytotoxic-therapy-induced vomiting is mediated via enkephalin pathways. Lancet 1982;1:714–6.

63. Young S. Mechanism of decline in rat brain 5-hydroxytryptamine after induction of liver tryptophan pyrrolase by hydrocortisone: roles of tryptophane catabolism and kynurenine synthesis. British Journal of Pharmacology 1981;74:695.

64. Frederikson M, Hursti T, Furst C, et al. Nausea in cancer chemotherapy is inversely related to urinary cortisol excretion. British Journal of Cancer 1992;65:779–80.

65. Sagar S. The current role of anti-emetic drugs in oncology: a recent revolution in patient symptom control. Cancer Treatment Reviews 1991;18:95–135.

66. Henzi I, Walder B, Martin R. Dexamethasone for the prevention of post operative nausea and vomiting: A quantitative systematic review. Anesthesia and Analgesia 2000;90:186-94

67. Gan TJ, Ginsberg B, Glass PS, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 1997; 87 (5): 1075-81

68. Maxwell LG, Kaufmann SC, Bitzer S, et al. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: a double-blind, prospective, randomized, controlled study. Anesthesia and Analgesia 2005; 100 (4): 953-8

69. Joshi GP, Duffy L, Chehade J, et al. Effects of prophylactic nalmefene on the incidence of morphine-related side effects in patients receiving intravenous patient-controlled analgesia. Anesthesiology 1999; 90 (4): 1007-11 51.

70. Taguchi A, Sharma N, Saleem RM, et al. Selective postoperative inhibition of gastrointestinal opioid receptors. New England Journal of Medicine 2001; 345 (13): 935-40

71. Grant IS, Mackenzie N. Recovery following propofol ("Diprivan") anaesthesia–a review of three different anaesthetic techniques. Postgraduate Medical Journal 1985;61(suppl 3):133–137

72. Mackenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. British Journal of Anaesthesia 1985;57:725–731

73. DeBalli P. The use of propofol as an antiemetic. International Anesthesia Clinics 2003.

74. Grotenhermen F, Muller-Vahl K. The therapeutic potential of cannabis and cannabinoids. Deutsches Artzeblatt International 2012; 109(29-30):495-501

75. Apfel CC, Kinjo S. Acustimulation of P6: an antiemetic alternative with no risk of drug induced side-effects. British Journal of Anaesthesia 2009; 102(5): 585-587.

76. Lee A, Fan LT. Stimulation of the wrist acupuncture point P6 for prevention of postoperative nausea and vomiting. Cochrane Database of Systemic Reviews 2009 April 15; (2):CD003281.

77. Gan TJ, Meyer T, Apfel CC, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesthesia and Analgesia 2003; 97 (1): 62-71

78. Thompson HJ. The management of post-operative nausea and vomiting. Journal of Advanced Nursing 1999; 29:1130–1136.

79. Orhan-Sungur M, Kranke P, Sessler D, Apfel CC. Does supplemental oxygen reduce postoperative nausea and vomiting? A meta-analysis of randomized controlled trials. Anesthesia and Analgesia 2008; 106(6): 1733-1738.

80. Heidari SM, Talakoub R, Yaraghi Z. Comparing the preventive effect of midazolam and midazolam-dexamethasone on postoperative nausea and vomiting in elective middle ear surgery. Advanced Biomedical Research 2012; 1:9.

81. Apfel CC, Meyer A, Orhan-Sungur M, Jalota L, Whelan RP, Jukar-Rao S. Supplemental intravenous crystalloids for the prevention of postoperative nausea and vomiting: quantitative review. British Journal of Anaesthesia 2012; 108(6): 893-902.

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

83. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zemak C, Danner K, Jokela R, Pocock SJ, Trenkler S, Kredel M, Biedler A, Sessler DI, Roewer N; IMPACT Investigators. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. New England Journal of Medicine 2004;350:2441–51

84. Apfel CC, Kranke P, KatzMH, Goepfert C, Papenfuss T, Rauch S, Heineck R, Greim CA, Roewer N. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. British Journal of Anaesthesia 2002;88:659–68

85. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone?Meta-analyses of randomized trials. Anesthesiology 2005;103:1296–304

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

87. Gan TJ, Joshi GP, Zhao SZ, Hanna DB, Cheung RY, Chen C.Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid related adverse effects. Acta Anaesthesiologica Scandinavica 2004;48:1194–207

88. Elia N, Tramer MR. Ketamine and postoperative pain—a quantitative systematic review of randomized trials. Pain 2005;113:61–70

89. Ho KM, Ismail H, Lee KC, Branch R. Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta analysis. Anaesthesia and Intensive Care 2005;33:41–53

90. Cheng CR, Sessler DI, Apfel CC. Does neostigmine administration produce a clinically important increase in postoperative nausea and vomiting? Anesthesia and Analgesia 2005;101:1349–55

91. Orhan-Sungur M, Sessler DI, Kranke P, Apfel CC. Supplemental oxygen does not reduce postoperative nausea and vomiting: a systematic review of randomized controlled trials. Anesthesiology 2005;103:A626

92. Kranke P, Morin A, Apfel C, Schwemmer U, Roewer N, Eberhart L. A qualtitative systematic review on supplemental perioperative oxygen to reduce the incidence of postoperative nausea and vomiting. European Journal of Anaesthesiology 2005;22(suppl 34):4, A-14

93. Sun R, Klein KW, White PF. The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. Anesthesia and Analgesia 1997;84:331–6

94. Wilson AJ, Diemunsch P, Lindeque BG, Scheinin H, Helbo Hansen HS, Kroeks MV, Kong KL. Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting. British Journal of Anaesthesia 1996;76:515–8

95. Mikawa K, Takao Y, Nishina K, Shiga M, Maekawa N, Obara H. Optimal dose of granisetron for prophylaxis against postoperative emesis after gynecological surgery. Anesthesia and Analgesia 1977;85:652–6

96. D'Angelo R, Philip B, Gan TJ, Kovac A, Hantler C, Doblar D, Melson T, Minkowitz H, Dalby P, Coop A. A randomized, double-blind, close-ranging, pilot study of intravenous granisetron in the prevention of postoperative nausea and vomiting in patients abdominal hysterectomy. European Journal of Anaesthesiology 2005;22:774–9

97. Chen X, Tang J, White PF, Wender RH, Quon R, Sloninsky A, Naruse R, Kariger R, Webb T, Norel E. The effect of timing of dolasetron administration on its efficacy as a prophylactic antiemetic in the ambulatory setting. Anesthesia and Analgesia 2001;93:906–11

98. Tramer MR, Reynolds DJM, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a qualitative systematic review of randomized placebo-controlled trials. Anesthesiology 1997;87:1277–89

99. Graczyk SG, McKenzie R, Kallar S, Hickok CB, Melson T, Morrill B, Hahne WF, Brown RA. Intravenous dolasetron for the prevention of postoperative nausea and vomiting after outpatient laparoscopic gynecologic surgery. Anesthesia and Analgesia 1997;84:325–30

100. Kranke P, Apfel CC, Greim CA, Roewer N. Methodological problems arising from "serial publishing" on the effectiveness of granisetron in PONV. British Journal of Anaesthesia 1999; 82(3): 481-3.

101. Carlisle JB. A meta-analysis of prevention of postoperative nausea and vomiting: randomised controlled trials by Fujii et al. compared with other authors. Anaesthesia 2012; 67(10): 1076-90.

102. Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: a quantitative systemic review. BMC Anesthesiology 2001;1:2. http://www.biomedcentral.com/1471-2253/1/2, Accessed July 2008.

103. Wang JJ, Ho ST, Tzeng JI, Tang CS. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesthesia and Analgesia 2000;91:136–9

104. Domino KB, Anderson EA, Polissar NL, Posner KL. Comparative efficacy and safety of ondansetron, droperidol, and metoclopramide for preventing postoperative nausea and vomiting: a meta-analysis. Anesthesia and Analgesia 1999;88:1370–9

105. Fortney JT, Gan TJ, Graczyk S, Wetchler B, Melson T, Khalil S, McKenzie R, Parrillo S, Glass PS, Moote C, Wermeling D, Parasuraman TV, Duncan B, Creed MR. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. Anesthesia and Analgesia 1998;86:731–8

106. Henzi I, Sonderegger J, Tramer MR. Efficacy, dose response, and adverse effects of droperidol for prevention of postoperative nausea and vomiting. Canadian Journal of Anaesthesia 2000;47:537–51

107. Buttner M, Walder B, von Elm E, Tramer MR. Is low-dose haloperidol a useful antiemetic?: a meta-analysis of published and unpublished randomized trials. Anesthesiology 2004;101:1454–63

108. Kranke P, Morin AM, Roewer N, Eberhart LH. Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. Acta Anaesthesiologica Scandinavia 2002;46:238–44

109. Kranke P, Morin AM, Roewer N, Wulf H, Eberhart LH. The efficacy and safety of transdermal scopolamine for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesthesia and Analgesia 2002;95:133–43

110. Bailey PL, Streisand JB, Pace NL, Bubbers SJ, East KA, Mulder S, Stanley TH. Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. Anesthesiology 1990;72:977–80

111. Semple P, Madej TH, Wheatley RG, Jackson IJ, Stevens J.Transdermal hyoscine with patient-controlled analgesia. Anaesthesia 1992;47:399–401[

112. Harris SN, Sevarino FB, Sinatra RS, Preble L, O'Connor TZ, Silverman DG. Nausea prophylaxis using transdermal scopolamine in the setting of patient-controlled analgesia. Obstetrics and Gynecology 1991;78:673–7

113. Habib AS, Gan TJ. Combination therapy for postoperative nausea and vomiting–a more effective prophylaxis? Ambulatory Surgery 2001;9:59–71

114. Eberhart LH, Morin AM, Bothner U, Georgieff M. Droperidol and 5-HT3-receptor antagonists, alone or in combination, for prophylaxis of postoperative nausea and vomiting. A meta-analysis of randomised controlled trials. Acta Anaesthesiologica Scandinavia 2000;44:1252–7

115. Gan TJ. Postoperative nausea and vomiting—can it be eliminated? Journal of the American Medical Association 2002;287:1233–6

116. Scuderi PE, James RL, Harris L, Mims GR. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. Anesthesia and Analgesia 2000;91:1408–14

117. Habib AS, Gan TJ. The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: a preliminary report. Journal of Clinical Anesthesia 2005;17:62–5

118. Meyer TA, Roberson CR, Raab MH, Davis J, McLeskey CH. Dolasetron versus ondansetron for the treatment of postoperative nausea and vomiting. Anesthesia and Analgesia 2005;100:373–7

119. Culebras X, Corpataux JB, Gaggero G, Tramer MR. The antiemetic efficacy of droperidol added to morphine patient-controlled analgesia: a randomized, controlled multicenter dose-finding study. Anesthesia and Analgesia 2003;97:816–21

120. Kovac AL, O'Connor TA, Pearman MH, Kekoler LJ, Edmondson D, Baughman VL, Angel JJ, Campbell C, Jense HG, Mingus M, Shahvari MB, Creed MR. Efficacy of repeat intravenous dosing of ondansetron in controlling postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled multicenter trial. Journal of Clinical Anesthesia 1999;11:453–9

121. Freyd M. The graphic rating scale. Journal of Educational Psychology 1923: 43:83–102.

122. Aitken RCB. Measurement of feelings using visual analogue scales. Journal of the Royal Society of Medicine 1969: 62: 989–993.

123. Dexter F, Chestnut DH. Analysis of statistical tests to compare visual analog scale measurements among groups. Anesthesiology 1995: 82: 896–902.

124. Kremer E, Atkinson JH, Ignelzi RJ. Measurement of pain:patient preference does not confound pain measurement. Pain 1981: 10: 241–248.

125. Ahles TA, Ruckdeschel JC, Blanchard EB. Cancer-related pain. II. Assessment with visual analogue scales. Journal of Psychosomatic Research 1984: 28: 121–124.

126. Joyce CRB, Zutshi DW, Hrubes V, Mason RM. Comparison of fixed interval and visual analogue scales for rating chronic pain. European Journal of Clinical Pharmacology 1975: 8: 415–420.

127. Linton SJ, Gotestam KG. A clinical comparison of two pain scales: correlation, remembering chronic pain and a measure of compliance. Pain 1983: 17: 57–65.

128. Seymour RA. The use of pain scales in assessing the efficacy of analgesics in postoperative dental pain. European Journal of Clinical Pharmacology 1982: 23: 441–444.

129. Huskisson EC. Measurement of pain. Lancet 1974: 2: 1127–1131.[136]

130. Raeder J. History of postoperative nausea and vomiting. International Anesthesiology Clinics 2003;41:1–12.

131. Palazzo M, Evans R. Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment. British Journal of Anaesthesia 1993;70:135–40.

132. Lee J. An insight on the use of multiple logistic regression analysis to estimate association between risk factor and disease occurrence. International Journal of Epidemiology 1986;15:22–9.

133. Schechtman E. Odds ratio, relative risk, absolute risk reduction, and the number needed to treat-which of these should we use? Value Health 2002;5:430–5.

134. Junger A, Hartmann B, Benson M, et al. The use of an anesthesia information management system for prediction of antiemetic rescue treatment at the postanesthesia care unit. Anesthesia and Analgesia 2001;92:1203–9

135. Eberhart LH, Geldner G, Kranke P, et al. The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients. Anesthesia and Analgesia 2004;99:1630–7.

136. Stadler M, Bardiau F, Seidel L, et al. Difference in risk factors for postoperative nausea and vomiting. Anesthesiology 2003;98:46–52.

137. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. British Journal of Anaesthesia 1992;69:24S–32S.

138. Van den Bosch JE, Moons KG, Bonsel GJ, Kalkman CJ. Does measurement of preoperative anxiety have added value for predicting postoperative nausea and vomiting? Anesth and Analgesia 2005;100:1525–32.

139. Apfel CC, Kranke P, Eberhart LH, et al. Comparison of predictive models for postoperative nausea and vomiting. British Journal of Anaesthesia 2002;88:234–40.

140. Apfel CC, Greim CA, Haubitz I, et al. The discriminating power of a risk score for postoperative vomiting in adults undergoing various types of surgery. Acta Anaesthesiologica Scandinavia 1998;42:502–9.

141. Fabling JM, Gan TJ, Guy J, et al. Postoperative nausea and vomiting: a retrospective analysis in patients undergoing elective craniotomy. Journal of Neurosurgical Anesthesiology 1997;9:308–12.

142. Gan TJ, Ginsberg B, Grant AP, Glass PS. Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology 1996;85:1036–42.

143. Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. British Journal of Anaesthesia 1999;83:104–17.

144. Fabling JM, Gan TJ, El-Moalem HE, et al. A randomized, double-blinded comparison of ondansetron, droperidol, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy. Anesthesia and Analgesia 2000;91:358–61.

145. Eberhart LH, Morin AM, Guber D, et al. Applicability of risk scores for postoperative nausea and vomiting in adults to paediatric patients. British Journal of Anaesthesia 2004;93:386–92.

146. Habib AS, White WD, Eubanks S, et al. A randomized comparison of a multimodal management strategy versus combination antiemetics for the prevention of postoperative nausea and vomiting. Anesthesia and Analgesia 2004;99:77–81.

147. Pierre S, Benais H, Pouymayou J. Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. Canadian Journal of Anaesthesia 2002;49:237–42.

148. Toner CC, Broomhead CJ, Littlejohn IH, et al. Prediction of postoperative nausea and vomiting using a logistic regression model. British Journal of Anaesthesia 1996;76:347–51.

149. Moiniche S, Romsing J, Dahl JB, Tramer MR. Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. Anesthesia and Analgesia 2003;96:68–77

150. Polati E, Verlato G, Finco G, et al. Ondansetron versus metoclopramide in the treatment of postoperative nausea and vomiting. Anesthesia and Analgesia 1997;85:395–9.

151. Goll V, Akca O, Greif R, et al. Ondansetron is no more effective than supplemental intraoperative oxygen for prevention of postoperative nausea and vomiting. Anesthesia and Analgesia 2001;92:112–7.

152. Greif R, Laciny S, Rapf B, et al. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology 1999;91:1246–52.

153. Joris JL, Poth NJ, Djamadar AM, et al. Supplemental oxygen does not reduce postoperative nausea and vomiting after thyroidectomy. British Journal of Anaesthesia 2003;91:857–61

154. Purhonen S, Niskanen M, Wustefeld M, et al. Supplemental oxygen for prevention of nausea and vomiting after breast surgery. British Journal of Anaesthesia 2003;91:284–7.

155. Purhonen S, Turunen M, Ruohoaho UM, et al. Supplemental oxygen does not reduce the incidence of postoperative nausea and vomiting after ambulatory gynecologic laparoscopy. Anesthesia and Analgesia 2003;96:91–6.
156. Apfel CC, Greim CA, Haubitz I, et al. A risk score to predict the probability of postoperative vomiting in adults. Acta Anaesthesiologica Scandinavia 1998;42:495–501.
157. Rowley MP, Brown TC. Postoperative vomiting in children. Anaesthesia and Intensive Care 1982;10:309–13.
158. Gratz I, Allen E, Afshar M, et al. The effects of the menstrual cycle on the incidence of emesis and efficacy of ondansetron. Anesthesia and Analgesia 1996;83:565–9.
159. Kranke P, Apefel CC, Papenfuss T, et al. An increased body mass index is no risk factor for postoperative nausea and vomiting. A systematic review and results of original data. Acta Anaesthesiologica Scandinavia 2001;45:160–6.
160. Apfel CC, Roewer N. Risk assessment of postoperative nausea and vomiting. International Anesthesiology Clinics 2003;41:13–32.
161. Biedler A, Wermelt J, Kunitz O, et al. A risk adapted approach reduces the overall institutional incidence of postoperative nausea and vomiting. Canadian Journal of Anaesthesia 2004;51:13–9.
162. Pierre S, Corno G, Benais H, Apfel CC. A risk score-dependent antiemetic approach effectively reduces postoperative nausea and vomiting: a continuous quality improvement initiative. Canadian Journal of Anaesthesia 2004;51:320–5.
163. van den Bosch JE, Kalkman CJ, Vergouwe Y, et al. Assessing the applicability of scoring systems for predicting postoperative nausea and vomiting. Anaesthesia 2005;60:323–31.
164. Eberhart LH, Hogel J, Seeling W, et al. Evaluation of three risk scores to predict postoperative nausea and vomiting. Acta Anaesthesiologica Scandinavia 2000;44:480–8.
165. Watcha MF. The cost-effective management of postoperative nausea and vomiting. Anesthesiology 2000;92:931–3.
166. White PF, Watcha MF. Postoperative nausea and vomiting: prophylaxis versus treatment. Anesthesia and Analgesia 1999;89:1337–9.
167. Habib AS, Gan TJ. Combination antiemetics: what is the evidence? Internal Anesthesiology Clinics 2003;41:119–44.
168. Chimbira W, Sweeney BP. The effect of smoking on postoperative nausea and vomiting. Anaesthesia 2000;55:540–4.
169. Hough M, Sweeney B. The influence of smoking on postoperative nausea and vomiting. Anaesthesia 1998;53:932–3.
170. Riley TR 3rd, Chinchilli VM, Shoemaker M, Koch K. Is nausea associated with chronic hepatitis C infection? American Journal of Gastroenterology 2001;96:3356–60.
171. Chou FH, Lin LL, Cooney AT, et al. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. Journal of Nursing Scholarship 2003;35:119–25.
172. Haug TT, Mykletun A, Dahl AA. The prevalence of nausea in the community: psychological, social and somatic factors. General Hospital Psychiatry 2002;24:81–6.
173. Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. Anesthesia and Analgesia 1990;70:160–7.
174. Sweeney BP. Why does smoking protect against PONV? British Journal of Anaesthesia 2002;89:810–3.

175. Kaiser R, Sezer O, Papies A, et al. Patient-tailored antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. Journal of Clinical Oncology 2002;20:2805–11.

176. Brockmoller J, Kirchheiner J,Meisel C, Roots I. Pharmacogenetic diagnostics of cytochrome P450 polymorphisms in clinical drug development and in drug treatment. Pharmacogenomics 2000; 1:125–51.

177. Everett LL. Can the risk of postoperative nausea and vomiting be identified and lowered during the preoperative assessment? International Anesthesiology Clinics 2002;40:47–62.

178. Dawson B, Trapp RG. Lange Basic and Clinical Biostatistics, 4th Edition 2004, McGraw-Hill publishers.

179. University of the Witwatersrand, Faculty of Health Sciences web site. http://www.wits.ac.za/academic/health. Accessed 14/03/2013.

180. Rueffert H, Thieme V, Wallenborn J, Lemnitz N, Bergmann A, Rudlof K, Wehner M, Olthoff D, Kaisers UX. Do variations in the 5-HT3A and 5-HT3B serotonin receptor genes (HTR3A and HTR3B) influence the occurrence of postoperative vomiting? Anesthesia and Analgesia 2009; 109(5): 1442-7.

181. Chou WY, Wang CH, Liu PH, Liu CC, Tseng CC, Jawan B. Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. Anesthesiology 2006; 105(2):334-7.

182. Zhang W, Yuan JJ, Kan QC, Zhang LR, Chang YZ, Wang ZY. Study of the OPRM1 A118G genetic polymorphism associated with postoperative nausea and vomiting induced by fentanyl intravenous analgesia. Minerva Anesthesiologica 2011; 77(1):33-9.

183. Nakagawa M, Kuri M, Kambara N, Tanigami H, Tanaka H, Kishi Y, Hamajima N.Dopamine D2 receptor Taq IA polymorphism is associated with postoperative nausea and vomiting. Journal of Anesthesia 2008;22(4):397-403.

184. Janicki PK, Vealey R, Liu J, Escajeda J, Postula M, Welker K. Genome-wide Association study using pooled DNA to identify candidate markers mediating susceptibility to postoperative nausea and vomiting. Anesthesiology 2011;115(1):54-64.

185. B Rahim-Williams, JL Riley III, AK Williams, RB Fillingim. A Quantitative Review of Ethnic Group Differences in Experimental Pain Response: Do Biology, Psychology, and Culture Matter? Pain Medicine 2012; 13(4): 522–540.

186. Cheng C, Sessler DI, Apfel CC. Does Neostigmine Administration Produce a Clinically Important Increase in Postoperative Nausea and Vomiting? Anesthesia and Analgesia 2005; 101(5):1349-1355.