ANTIEMETIC PROPHYLAXIS DURING SPINAL ANALGESIA FOR CAESAREAN DELIVERY: A COMPARISON OF ONDANSETRON AND METOCLOPRAMIDE.

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NOVEMBER 2006
DECLARATION

I hereby declare that this work is original. The work has not been presented to any other examining body for a fellowship award nor has it been submitted elsewhere for publication.

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This work is dedicated to:

The Almighty God for his mercy during the period of the residency programme

My parents for their psychological support

My wife and children for their endurance and love
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SUMMARY

This prospective, randomized, placebo controlled, double blind study was performed to compare the effectiveness of ondansetron and metoclopramide in limiting the frequency of intraoperative nausea and vomiting during spinal analgesia for Caesarean delivery.

One hundred and fifty full term parturients, American Society of Anesthesiologists (ASA) physical status I-II requiring elective Caesarean section were randomly assigned into one of three treatment groups. After the umbilical cord clamping, ondansetron 4mg (n=50), metoclopramide 10mg (n=50) or 0.9% saline 2ml (n=50) was administered intravenously depending on the treatment group selected preoperatively.

The patient assessed the presence and degree of nausea while the attending anaesthetist noted the presence and degree of retching and vomiting. The study continued for 2 hours to cover the immediate postoperative period.

The frequency of nausea in the intraoperative post delivery period was 34% with placebo, 6% with metoclopramide and 4% with ondansetron. The frequency of retching or vomiting was 10% with placebo, 2% with both metoclopramide and ondansetron. (P< 0.05). The frequency of nausea, retching or vomiting correlated with the occurrence of hypotension.

For those patients that experienced nausea, the median severity score was reduced from 7.0 for placebo to 5.0 for metoclopramide and 4.5 for ondansetron treated groups on numerical rating scale (NRS). The mean number of vomiting episode was reduced from 2 in the control group to 1 for both metoclopramide and ondansetron groups.
There is a significantly lower frequency of nausea and vomiting and a tendency towards less severe emetic symptoms in the ondansetron and metoclopramide groups compared to the placebo group. Both prophylactic ondansetron and metoclopramide are similarly effective in reducing the frequency of intraoperative emetic symptoms during Caesarean delivery under spinal analgesia.
CHAPTER ONE

INTRODUCTION

Spinal analgesia has a time-honoured place among the options of anaesthetic techniques for Caesarean delivery. It is considered the procedure of choice for elective Caesarean section where there is no contraindication and has been shown to be an easy technique. It provides excellent analgesia, minimizes risk of aspiration of gastric contents and rapid oxygen desaturation, facilitates early maternal-neonatal bonding and breast feeding. Nevertheless, there is the likelihood of some side effects. These side effects include maternal hypotension, bradycardia, nausea and vomiting, hypothermia, shivering, limited duration of action and neonatal acidosis.

Intraoperative nausea and vomiting during Caesarean delivery is distressing to the patient and can disrupt the surgery. In spite of advances in anaesthetic practice, refinement of operative technique and identification of predictive factors, intraoperative nausea and vomiting (IONV) still occur and the description of it as “the big little problem” encapsulates the general perception. The abrupt diaphragmatic contractions may cause extrusion of the abdominal viscera, thereby increasing the risk of visceral injuries. Aspiration of acidic gastric content is an added risk because the patient has a potentially full stomach. The resulting maternal distress may result in delayed neonatal bonding. Therefore, IONV during spinal anaesthesia for Caesarean delivery should be prevented.

The frequency of intraoperative nausea and vomiting (IONV) during regional anaesthesia for Caesarean delivery varies from 36% – 69%. Pan and Moore, reported a frequency of 69% while Chestnut reported a frequency of 36%. This frequency justifies the use of prophylactic antiemetic medication during spinal analgesia for Caesarean delivery.

Emetic symptoms during abdominal surgery under spinal analgesia have multifactorial origin and may be influenced by factors such as arterial hypotension, visceral manipulation, pain, anxiety (psychological), concomitant opiate administration and the use of other emetogenic drugs.

Various antiemetics have been used to control IONV during spinal analgesia for Caesarean delivery. These include droperidol, metoclopramide and ondansetron.
Droperidol is a major tranquilizer and has been demonstrated to be an effective antiemetic in low doses but its haemodynamic and sedative effects limit its use. Metoclopramide is often employed as an antiemetic. It is a dopamine receptor antagonist, selective for the D-2 receptors. It also possesses prokinetic action on the gastrointestinal tract. Ondansetron is a serotonin antagonist that selectively inhibits 5 – hydroxytryptamine (5HT₃) receptor and is devoid of dopamine, histamine, cholinergic and adrenergic receptor activities. It has also been demonstrated to be an effective, well tolerated antiemetic for control of intraoperative nausea and vomiting during spinal analgesia.

The purpose of this research was to compare the antiemetic prophylactic effect of intravenous ondansetron with that of metoclopramide or placebo given after clamping the umbilical cord during spinal analgesia for Caesarean delivery. The drugs were administered after clamping the umbilical cord because the effects of ondansetron on the foetus and newborn are still unknown. Ondansetron and metoclopramide were chosen as the study drugs for the antiemetic prophylaxis because of their minimal maternal side effects.

**AIM AND OBJECTIVES**

**AIM:** To compare the antiemetic effect of intravenous ondansetron and metoclopramide during spinal analgesia for Caesarean delivery.

**OBJECTIVES:**
I. To determine the frequency of intraoperative nausea, retching and vomiting during spinal analgesia for Caesarean delivery.

II. To determine the effects of prophylactic administration of intravenous ondansetron or metoclopramide on the frequency of nausea, retching and vomiting during spinal analgesia for Caesarean delivery.

III. To compare the antiemetic efficacy of prophylactic intravenous ondansetron and metoclopramide during spinal analgesia for Caesarean delivery.

**HYPOTHESES**

*Null Hypothesis:* There is no statistically significant difference in the antiemetic efficacy of prophylactic intravenous ondansetron and metoclopramide.

*Alternate Hypothesis:* There is a statistically significant difference in the antiemetic efficacy of prophylactic intravenous ondansetron and metoclopramide

(P < 0.05 is considered significant).

**SIGNIFICANCE OF THE STUDY**

I. To confirm or refute other studies which have demonstrated significant reduction in emetic symptoms following antiemetic prophylaxis during
spinal analgesia for Caesarean delivery and to serve as a local reference for other workers.

II. The result of the study will be utilised to formulate policy on antiemetic prophylaxis during spinal analgesia for Caesarean delivery.

III. Prevention of emetic symptoms in the parturient undergoing operative procedure under regional analgesia will enhance maternal satisfaction and early bonding with the neonate.

CHAPTER TWO
LITERATURE REVIEW

The use of spinal analgesia for Caesarean delivery dates back to 1902, after the technique was initially used as a planned anaesthetic for surgery in 1898 by August Bier⁴. Owing to the high incidence of feto-maternal morbidity associated with its use, it enjoyed
a limited and cautious support. It became popular in obstetric practice in the 1940s, when Adriani and associates established a safe and standardized technique ¼. Improved anaesthetic practices have now placed the technique in a prime position in obstetric anaesthesia ½.

The increased understanding of the pathophysiology, prevention and treatment of the adverse effects associated with spinal analgesia played a vital role in its choice for Caesarean delivery. Intraoperative nausea and vomiting is one of these adverse effects. Despite a century of spinal analgesia to facilitate Caesarean delivery, the problem of intraoperative nausea and vomiting is yet to be fully elucidated. This probably reflects the complexity of the problem, inadequate quantification of the phenomena and inadequate antiemetic regime ¼,10. The interests in the antiemetic prophylaxis is an attempt to reduce this problem during Caesarean section facilitated by spinal analgesia and thus improve patients’ safety and satisfaction.

2.1 Physiology of Nausea and Vomiting

Nausea is defined as a subjective unpleasant sensation associated with awareness of the urge to vomit. It is usually felt in the back of the throat and the epigastrium and is accompanied by the loss of gastric tone, duodenal contraction and reflux of intestinal contents into the stomach ¹³.

Vomiting is the forceful expulsion of gastric contents from the mouth and is brought about by the powerful sustained contraction of the abdominal muscles, descent of the diaphragm, and opening of gastric cardia ¹³. When the sustained contraction of the
abdominal wall muscles and the respiratory muscles does not result in expulsion of gastric contents from the mouth, it is referred to as retching.

The act of vomiting involves a sequence of events that is controlled and coordinated by the emetic centre. The emetic centre is generally accepted as an indiscr"e area located in the lateral reticular formation of the medulla. The centre receives a wide range of afferent impulses from receptors located in the chemoreceptor trigger zone (CTZ), vestibular apparatus, cerebellum, higher cortical and brainstem centres, nucleus solitarius, gastrointestinal tract and peripheral pain receptors. (figure A) The neurochemistry of the vomiting centre is complex, however two neurotransmitters are particularly important. These are acetylcholine and histamine neurotransmitters\textsuperscript{14,15}.

The CTZ is a group of cells situated within the area postrema on the floor of the fourth ventricle. The area is highly vascularized and the vessels terminate in fenestrated capillaries surrounded by large perivascular spaces with no effective blood brain barrier (BBB) making it vulnerable to circulating drugs. It is thought that the CTZ has a major impact on the activity of the vomiting centre. The area postrema is extremely rich in dopamine and serotonin (5HT\textsubscript{3}) receptors, in addition to other receptors such as opioid, acetylcholine and adrenergic receptors. Antagonists of these receptors may have important indirect effects on the vomiting centre\textsuperscript{14,15}. Thus antagonists of these neurotransmitters - acetylcholine, histamine, serotonin and dopamine have acquired much interest in the pharmacological treatment of nausea and vomiting.

Emesis is the result of a complex reflex involving the vomiting centre relaying efferents through cranial nerves V, VII, IX, X and XII to the upper gastrointestinal tract and through spinal nerves to the diaphragm and abdominal muscles. It can be divided into two consecutive phases: \textbf{Pre ejection and ejection phases}. The pre ejection or
prodromal phase is characterized by the sensation of nausea. This phase is usually but not invariably followed by ejection phase. The ejection phase comprises of retching and vomiting with oral expulsion of gastrointestinal content. It starts with deep inspiration, reversed peristalsis moving contents from the upper small bowel into the stomach and an increase in salivation. The glottis closes to protect the airway, the breath is held and the gastric sphincter and oesophagus relax. The muscles of the abdominal wall and thorax contract, and the diaphragm descends vigorously, increasing the intra-abdominal pressure, thus the gastric contents are ejected into the oesophagus and out of the mouth.

Figure A.

Physiology of Vomiting Centre
Adapted from Update in Anaesthesia Number 17, 2003

2.2 Factors Associated with Intraoperative Nausea And Vomiting

Emetic symptoms during abdominal surgery under spinal analgesia have a multifactorial origin. These include patient factors, arterial hypotension, hypoperfusion of the central nervous system, pain, psychological changes (anxiety), abrupt visceral movement, concomitant opiate administration, the use of other emetogenic drugs such as ergometrine and patients with pre-operative factors associated with emetic symptoms. In addition, there is a higher predisposition to nausea and vomiting among pregnant patients, as a consequence of increased abdominal pressure and hormonal changes.
Patient Factors.

Patient specific risk factors include female gender, a history of postoperative nausea and vomiting or motion sickness and non-smoking status. These factors are associated with an increased incidence of emetic symptoms\textsuperscript{16}. Other factors including obesity and high level of preoperative anxiety are also associated with an increased incidence of nausea, retching and vomiting\textsuperscript{16}. The increased blood level of catecholamines in anxious patients, acting via the chemoreceptor trigger zone may be a contributing factor \textsuperscript{15,16}. There is a positive correlation between body weight and intraoperative emetic symptoms during Caesarean delivery possibly due to a large residual gastric volume and increased incidence of oesophageal reflux in the obese parturient \textsuperscript{17}.

Abdominal Visceral Manipulation

Surgical manipulation of the uterus, abdominal viscera and peritoneum, even in the presence of adequate sensorimotor blockade may be related to the onset of emetic symptoms during Caesarean delivery in the awake patient. The gut and other pelvic structures such as bladder and the uterus are invested with both vagal and splanchnic afferents that discharge in response to direct mechanical stimulation. These vagal afferents has important role in triggering emetic symptoms by stimulating the vomiting centre \textsuperscript{13,14,15}. In addition to the direct activation of afferents, surgical manipulation of the intestine also induces release of 5-hydroxytryptamine from the enterochromaffin cells. The 5-hydroxytryptamine can cause both direct activation of the 5HT\textsubscript{3} receptors on the vagus and also produce long lasting sensitization to other stimuli, triggering the emetic reflex especially in awake patients \textsuperscript{13,14,18}.

Hypotension

The frequency of emetic complication during spinal anaesthesia for Caesarean section correlated with the presence of arterial hypotension\textsuperscript{19,20}. Hypotension during spinal analgesia for Caesarean delivery is common, rapid in onset and has adverse effects on both mother and foetus. The principal causes of the hypotension are: rapid blockade of sympathetic nerves causing decrease in systemic vascular resistance and cardiac
output and aorto-caval compression by the gravid uterus causing supine hypotensive syndrome. A rapid decline in arterial blood pressure during spinal analgesia is often associated with the onset of nausea heralded by yawning.

Active management of hypotension is important. The use of left uterine displacement to prevent aorto-caval compression is mandatory as soon as the patient is positioned supine. Vasopressors and non-glucose containing intravenous fluids (crystalloid or colloids) are used for prophylaxis and treatment of hypotension during spinal analgesia. Ephedrine has been used as the vasopressor for this role. It is an indirectly acting agent, with both alpha and beta adrenergic agonist effects. It has minimal effect on the uterine blood flow but has potential to cause fetal acidosis. Phenylephrine is now advocated because of the better fetal acid-base status, and similar efficacy in blood pressure control.

Ratra et al also noted that the incidence of nausea and vomiting in these patients was reduced by the administration of 100% oxygen, suggesting hypoxaemia at the vomiting centre may stimulate emesis.

Opioids

Intrathecal administration of opioids with local anaesthetic agents for Caesarean delivery is associated with excellent analgesia but nausea, vomiting and pruritus are frequent side effects. It is thought that the emetic effect of opioid is via an action on opioid receptors (probably μ receptor) known to be present in the area postrema. Also the emetic effects of intrathecal opioid are believed to be related to its rostral spread from the site of injection to the chemoreceptor trigger zone and the vomiting centre. Thus, the incidence of nausea and vomiting may be lower with the more lipophilic agents such as
fentanyl and sufentanil than with the less lipophilic agents such as morphine. The more lipid–soluble agents have less caudal spread than the less lipid soluble opioids 26.

**Emetogenic Drugs**

The use of oxytocic drugs to after the delivery of the baby to aid uterine contraction and facilitate delivery of the placenta may be associated with emetic complications. Administration of bolus intravenous oxytocin causes vasodilatation, which results in hypotension, and reflex tachycardia associated with nausea and vomiting. Ergometrine also has a potent emetic effect in addition to its marked vasopressor effect.

**Pain**

Regional analgesia may be accompanied by visceral pain, which may occur despite apparently adequate dermatomal sensory block 26. Visceral pain or pelvic pain is often associated with the sensation of nausea. Although the exact mechanism of nociceptive–induced nausea is not known, the activation of visceral nociceptors influences activity in the brain stem, both in the nucleus tractus solitarius and reticular formation and this has effect on the vomiting centre 25.

### 2.3 Antiemetic Therapy for Prevention of Intraoperative Nausea and Vomiting

Antiemetic drugs are generally grouped according to the type of receptor on which they act as antagonist. The receptor types involved are the dopamine (D₂),
muscarinic–cholinergic, histamine (H₁) and the 5-hydroxytryptamine (5HT₃) receptors.

The dopamine receptor antagonists include metoclopramide, phenothiazines, butyrophenones and domperidone. The 5HT₃ receptor antagonist include ondansetron, tropisetron, granisetron and dolasetron. Other antiemetic drugs are the antihistamines and the anticholinergics.

I. ONDANSETRON

Ondansetron is a selective 5-HT₃ receptor antagonist. It acts on the 5HT₃ receptors present both peripherally on the vagus nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It has 250 – 1000 times greater affinity for 5HT₃ receptor than other neurotransmitters.

It is thought that its main action is to antagonize 5-HT₃ receptors that are found in high concentration in the chemoreceptor trigger zone, it may also have peripheral effect on the 5-HT₃ receptors located on the vagus nerve in the gastrointestinal tract. Ondansetron has no effect on oesophageal or gastric motility, lower oesophageal sphincteric pressure or small intestinal transit time.

Pharmacokinetic consideration

Ondansetron may be administered either orally or intravenously. Oral bioavailability in man is approximately 60%. Peak plasma concentration occurs at about 1.5 hours after oral administration. Ondansetron is 70 – 75% bound to plasma protein. It is extensively metabolized by hepatic cytochrome-P enzymes. The primary metabolic
pathway is hydroxylation of the indole ring, followed by glucuronide or sulphate conjugation. The elimination half-life is 3 to 4 hours. Approximately 5% is excreted unchanged in the urine.

The I.V preparation is an isotonic aqueous solution containing ondansetron hydrochloride dihydrate 2mg ml$^{-1}$ buffered to pH 3.5 with sodium citrate and citric acid. It has a shelf life of 3 years. It is compatible with 0.9% sodium chloride, 5% glucose and Ringer’s lactate solution. It is administered either by slow I.V injection or by infusion to avoid flushing sensation associated with rapid I.V administration at the site of the injection.

**Usage**

Ondansetron has been used in the prevention and treatment of chemotherapy induced nausea and vomiting and in the prevention and treatment of postoperative nausea and vomiting $^{28}$. It has also been employed as an antiemetic prophylaxis during spinal analgesia $^{6,12}$. The dose ranges from 4mg to 8mg by slow intravenous injection for the prevention and treatment of intraoperative or postoperative nausea and vomiting in adults.

**Side Effects**

The side effects include headache, light-headedness, warm sensation in the epigastrium, flushing sensation at the site of intravenous injection and constipation may occur particularly at higher doses. Occasionally, hepatic impairment may be associated with prolonged use. Occasional association with increased arterial
pressure, reflex bradycardia, asymptomatic, brief prolongation of PR interval and QRS complex of the electrocardiogram have been reported in adults.  

II METOCLOPRAMIDE

Metoclopramide is a benzamide derivative with selective dopamine antagonist activity at D-2 receptors. It was developed in France in the early 1960s and is related structurally to procainamide. It acts centrally by blocking the dopamine D-2 receptors in the chemoreceptor trigger zone (CTZ) and peripherally by enhancing the action of acetylcholine at muscarinic nerve endings in the gut. It has prokinetic action on the gastrointestinal tract, promoting gastric emptying and shortened transit time through the small bowel. It also increases the barrier pressure of the lower oesophageal sphincter.

Pharmacokinetic consideration

Following intravenous administration of metoclopramide, peak plasma level occurs within minutes, and between 45 to 90 minutes after oral administration. It is 20% bound to plasma protein. There is significant first pass effect after oral administration, and bioavailability varies between 30 to 70%. The elimination half-life is 3 to 5 hours. Thirty to forty percent of the drug is eliminated as the sulphate conjugate. About 20% of the drug is eliminated unchanged in the urine. The half-life is therefore prolonged in patient with impaired renal function.

Usage

Metoclopramide has been used to treat nausea and vomiting associated with gastrointestinal disorder, surgical conditions, radiotherapy and cytotoxic drug therapy. It has also been used as an antiemetic during pregnancy, labour and analgesia for Cesarean delivery with no effect on the course of the labour or the foetus. It has been widely employed during obstetric anaesthesia to hasten gastric emptying and reduce risk of
aspiration\textsuperscript{30,31}. A dose of 0.15mg per kg of metoclopramide administered intravenously reduced the incidence of nausea and vomiting during epidural analgesia\textsuperscript{9}.

**Side Effects**

In some patients, metoclopramide may produce sedation, drowsiness, lassitude, galactorrhoea and extrapyramidal reactions. Sedation and drowsiness are mild and transient. The extrapyramidal symptoms (torticollis, facial spasms, trismus, oculogyric crises) are common in patients on concurrent treatment with other dopamine receptor antagonist. The reaction is rapidly abolished by administration of an antimuscarinic agent. Long-term use of metoclopramide has been associated with tardive dyskinesia in the elderly\textsuperscript{29}.

Intravenous administration of metoclopramide may be associated with cardiovascular side effects. These include hypotension, tachycardia and supraventricular ectopic beats. It is recommended that I.V administration should be administered slowly over 1 – 2 minutes.

**Other dopamine antagonists are phenothiazines, butyrophenones and domperidone:**

The phenothiazines are compounds with aliphatic or heterocyclic ring attached to position 10 of a tricyclic ring. They include chlorpromazine and prochlorperazine. They have been used for prevention and treatment of opioid induced emesis.
Prochlorperazine has some antihistamine effect in addition to its effect on the dopamine receptors. Prochlorperazine is more commonly used as an antiemetic than chlorpromazine because the latter is associated with marked sedation and drowsiness. Both chlorpromazine and prochlorperazine can produce extrapyramidal side effects and acute oculogyric crises may occur with high doses and prolonged treatment. The neuroleptic malignant syndrome (catatonia, cardiovascular instability, hyperthermia and myoglobinaemia) has been reported in association with phenothiazines. Prochlorperazine is administered orally or intramuscularly in a dose of 12.5mg every 6 hours.

The butyrophenones are major tranquilizing drugs that possess significant antiemetic activity as a result of their antagonistic properties at the dopamine receptors. They include haloperidol and droperidol. Droperidol has been employed in the management of postoperative emesis in small doses (0.625mg to 1.25mg in adult and 50 – 75μg/kg in children). Higher doses cause significant drowsiness. It has also been associated with unpleasant side effects including extrapyramidal symptoms, hypotension, hypothermia and hallucinations.

Domperidone, a benzimidazole that is structurally similar to droperidol is said to be effective and has fewer central nervous system side effects compared with droperidol. It however may produce cardiac arrhythmia in large doses.

### Anticholinergics:

Anticholinergics act via the central cholinergic receptors located in the vomiting centre. Anticholinergics are the oldest drugs used to treat nausea and vomiting although this was not the original intention. Hyoscine is more potent than atropine as an antiemetic. Hyoscine is most effective against motion sickness, labyrinthine disease, vestibular disorder, after surgery in the posterior fossa and also to counter the emetic effect of opioids. It has also been used as an antisialogogue during anaesthesia for
Caesarean delivery without deleterious effect on the foetus and newborn. The antimuscarinic side effects include sedation, dry mouth, blurred vision and urinary retention. For perioperative use, hyoscine is given in a dose of 0.2mg to 0.4mg intramuscular or subcutaneously. Atropine is administered in a dose of 0.5 to 0.6mg intramuscularly or intravenously in adult patients.

**Antihistamines:**

These groups of drugs act on the vomiting centre antagonising the histamine (H1) receptors. They also have some effect on the dopamine (D2) receptors. They are particularly useful in the prophylaxis and therapy of motion sickness, control of emesis following middle ear surgery and to counter the emetic effects of opioids. They include cyclizine, hydroxyzine, diphenhydramine, promethazine, and prochlorperazine. The side effects include sedation, urinary retention, blurring of vision. The sedative effect of antihistamine is additive with that produced by anaesthetic agents.

Cyclizine is associated with lowest incidence of side effects. Cyclizine, however, is contraindicated in acute myocardial infarction as it can aggravate heart failure. Cyclizine is administered in a dose of 50mg by intravenous or intramuscular route in the adults.

**Other Drugs used as antiemetics**

Borgeat et al. reported the direct therapeutic antiemetic effect of subhypnotic doses of propofol after minor gynaecological, gastrointestinal and orthopaedic surgical procedures. Propofol appears to possess intrinsic antiemetic properties. Prophylactic antiemetic efficacy of propofol at a subhypnotic dose (1.0mg per kg) has been shown to be comparable to 1.25mg droperidol and 10mg metoclopramide in patients undergoing Caesarean section.

**Acupressure**

Acupressure, a non-invasive variant of acupuncture involving constant pressure on the wrist, has been reported as a possible non-pharmacological method to prevent nausea and vomiting. It is based on the belief that an individual well being depends on
the balance of energy in the body as well as the overall energy level. It is hypothesized that energy flows within the body along paths referred to as meridians and that acupressure restore the balance of energy flow by manipulation of these meridians. In acupressure, pressure is exerted on the Neiguan (P6) acupuncture points located on the anterior surface of the wrists, three Chinese finger breaths above the distal skin crease of the wrist joint between the tendons of the palmaris longus and flexor carpi radialis muscle.

Dundee et al found that acupressure results in significant reduction in post-operative emesis. Stein et al reported a reduced incidence of nausea and vomiting during spinal analgesia for Caesarean section following application of acupressure.
CHAPTER THREE

RESEARCH DESIGN

3.1  **Patient Selection**

Study Population

The study population comprised patients scheduled to undergo elective Caesarean sections under spinal analgesia.

Study Location

The study was carried out at the prenatal ward, labour ward, labour ward theatre and the labour ward recovery room of the University College Hospital (UCH), Ibadan and of the Federal Medical Centre (FMC), Abeokuta.

**Sample Size**

The sample size was calculated using the formula for comparative study.

\[
N = \frac{(Z_\alpha + Z_\beta)^2 \left[ (P_1(1-P_1)) + (P_2(1-P_2)) \right]}{d^2}
\]

N = Sample size

At precision of 95%

\(Z_\alpha = \) Critical ratio of significant level of 5% = 1.96

\(Z_\beta = \) Statistical power for one sided test at 90% = 1.28

At prevalence of 69%  Pan and Moore 8  \(P_1 = 0.69\)

At prevalence of 36%  Chestnut 9  \(P_2 = 0.36\)

\(d = \) Difference between the population prevalence rates \((P_1 - P_2)\)
\[ N = \frac{(1.96 + 1.28)^2 \left[(0.69 \times 0.31) + (0.36 \times 0.64)\right]}{(0.33)^2} \]
\[ = 42 \]

Provision of 20% will be made for attrition = 8

The sample size for each group was (42 + 8) = 50 participants.

For the three groups, the calculated sample size was 50 x 3 = 150 participants.

3.2 Sampling Procedure
The patients were divided into three groups by randomization; Group I, Group II and Group III in a double-blind fashion. Randomization was established by balloting, using sealed envelope technique. Each patient was allowed to pick a coded group from a large envelope that contained three types of coded paper; Group I, Group II and Group III. The patients were unaware of the identity of the drug belonging to the coded group chosen.

After picking a code, the study drug was drawn in an unmarked 2ml syringe by the author and handed over to the attending anaesthetist who administered the drug. Both the patient and the attending anaesthetist were unaware of the identity of the study drug. The anaesthetist collected the data as detailed in Appendix 1. However, the author was available throughout the study period including the postoperative care.

3.3 Methodology
The study was a prospective, randomized and placebo controlled, carried out on patients undergoing non-emergent Caesarean section at the labour wards of the
University College Hospital (UCH), Ibadan and the Federal Medical Centre (FMC), Abeokuta, Nigeria.

Approval for the study was obtained from the Ethical review committee of UCH/UI, Ibadan. Written informed consent was obtained from each of the parturients before entry into the study.

One hundred and fifty parturients with full term pregnancy, 18 – 40 years of age, ASA physical status I and II undergoing elective Caesarean section under spinal analgesia were studied.

Exclusion criteria included parturients with contraindications to regional analgesia, refusal of spinal analgesia, significant maternal medical problems, poor obstetric history, obesity, history of motion sickness, hyperemesis gravidarum and parturients on drugs that might influence emetic symptoms such as antiemetics and opioids. Parturients with inadequate spinal analgesia requiring general anaesthesia supplementation and parturients who experience emetic symptoms before administration of the study drug were also excluded.

The patients were randomly allocated to any of the three groups: ondansetron group (Group I) metoclopramide group (Group II) and placebo group (Group III). This was done by balloting, using sealed envelop technique. Based on the coded group chosen, the study drug was drawn in an unmasked 2ml syringe by the author. Both the patient and the attending anaesthetists were unaware of the identity on the study drug to ensure double blinding.

All the patients were seen a day before surgery, assessed, fasted overnight and premedicated with oral ranitidine 150mg at night and 150mg orally 2 hours prior to
surgery. The patients were educated on numerical rating scale (NRS) for assessing the degree of nausea and they were allowed to practice with it. Sedative premedication was avoided because of risk of neonatal respiratory depression. Parturients were transported to the operating room lying on their sides.

In the operating room, monitoring was instituted. Baseline vital signs (parturients pulse rate, blood pressure, respiratory rate, oxygen saturation and fetal heart rate) were taken and recorded. A large bore intravenous cannula (16 Gauge) was inserted into a non-dominant forearm vein. Each patient was prehydrated with 1000mls of Hartmanns solution over 20 – 30 minutes before instituting the spinal anaesthesia. Resuscitative drugs and equipment were ensured before instituting the spinal anaesthesia.

Under aseptic condition, spinal analgesia was instituted with the parturients in the sitting position, using a midline approach through L3/4 lumbar spinal interspace. After identifying the spinal interspace, the skin and the interspinous ligament were infiltrated with 2mls of 1% plain lidocaine. The subarachnoid space was entered with 25 gauge Quincke spinal needle passed through a 19 gauge introducer (Portex, Hythe, Kent, England).

Analgesia was achieved with 2.5ml of 0.5% hyperbaric bupivacaine (12.5mg). After instituting of spinal analgesia, the patients were placed in the supine position with a left lateral tilt for uterine displacement, while a pillow supported the head and shoulder to limit the cephalic spread of the spinal agent.

Oxygen at 3L/min was administered via a nasal catheter. Vital signs (automated non-invasive blood pressure, heart rate, oxygen saturation and respiratory rate) were recorded every 2 minutes for the first 10 minutes and then every 5 minutes for the rest of
the surgery period. The level of sensory block was assessed every 5 minutes after intrathecal injection for 20 minutes using pinprick along the midaxillary lines and the outer aspect of the thigh. Motor block was assessed using Bromage score.

Each patient received additional volumes of Hartmann’s solution during the surgery as determined by the cardiovascular stability and clinical estimation of the blood loss. There was no intraoperative sedation as this may affect the frequency of nausea and vomiting.

Hypotension was defined as a decrease in systolic blood pressure by 20% from the baseline. When it occurred, it was treated promptly by additional fluid infusion and 5mg incremental doses of intravenous ephedrine.

After delivery of the baby and clamping of the umbilical cord, a slow infusion of syntocinon (20 I.U in 500mls of 5% dextrose water) was administered to aid uterine contraction.

Also, after clamping the umbilical cord, the study drug already drawn by the author in an unmarked 2ml syringe was administered intravenously by the attending anaesthetist slowly over 1-2 minutes.

Rescue promethazine, 12.5mg was administered intravenously, if nausea or vomiting occurred and persisted for up to 5 minutes. The study period was continued for 2 hours after the injection of the study drug to cover the period in the operating theatre and the recovery room. Patients were moved to the recovery room after surgery.

3.4 Data Collection

The demographic, obstetric and surgical variables were recorded on a data collection form. Patients were asked for the presence or absence of nausea every 10
minutes after instituting the spinal analgesia. The severity of nausea was assessed using numerical rating scale (NRS). Patients were asked to assess and score the severity of their nausea on the NRS with zero representing no nausea, while 10 represents maximum intolerable nausea. Also, the presence or absence of retching and vomiting were noted by the attending anaesthetist and recorded every 10 minutes as detailed in Appendix I. Adverse effects were monitored, documented and treated accordingly. The Apgar scores of the baby at 1 and 5 minutes were noted.

3.5 **STATISTICAL ANALYSIS**

Data analysis was performed using SPSS® 11.0 computer based statistical software. The results are presented in tables and figures. Comparison of means and proportions was done using chi-square ($X^2$) while ANOVA and t-test were used for continuous variables. A p-value of less than 0.05 was considered significant.
CHAPTER FOUR

RESULTS

A total of 150 healthy parturients, American Society of Anesthesiologists (ASA) I and II status were studied. The patients were randomized into three groups: groups I, group II and group III, representing the ondansetron group (n=50); metoclopramide group (n=50) and placebo group (n=50) respectively. The three study groups were similar with respect to patient’s characteristics (Table 1) and operative management (Table 2) and intraoperative vital signs.(Table 3).

EMETIC SYMPTOMS AFTER INJECTION STUDYDRUGS

Frequency of Emetic Symptoms:

Emetic symptoms occurred in 2 (4%) patients in the ondansetron group, 3 (6%) patients in the metoclopramide group and 17 (34%) patients in the placebo group. (Table 4) This showed that the frequency of emetic symptoms was significantly higher in the placebo group compared with both metoclopramide and ondansetron groups. (P<0.05) However there was no statistically significant difference in the
frequency of emetic symptoms between the ondansetron and the metoclopramide groups. (P=0.471)

**Type of Emetic Symptoms:**

Emetic symptoms experienced after clamping the umbilical cord included nausea, retching and vomiting (Figure 1). Nausea was the most common type of emetic symptom, occurring in all the patients that experienced emetic symptoms. Nausea occurred in 17 (34%) patients in the placebo group, 3 (6%) patients in the metoclopramide group and 2 (4%) patients of the ondansetron group. Retching or vomiting occurred less frequently. All the patients that retched eventually vomited. Retching or vomiting occurred in 5 (10%) patients of the placebo group, 1 (2%) patient of each of the metoclopramide and ondansetron groups. The frequencies of nausea, retching and vomiting were significantly higher in the placebo group compared with both metoclopramide and ondansetron groups (P<0.05). There were no significant difference between the frequencies observed for the metoclopramide and the ondansetron groups.

**Severity of Emetic Symptoms:**

The severity of nausea was expressed as the median nausea score on the numerical rating scale (NRS). The median nausea score were 4.5 in the ondansetron group, 5.0 in the metoclopramide group and 7.0 in the placebo group. (Figure 2) There was no significant difference between the score obtained for ondansetron and metoclopramide treated groups. (P=0.372). However the median nausea score was significantly higher in the placebo group compared with both ondansetron and metoclopramide. (P< 0.05)
The severity of vomiting expressed as the mean number of vomiting episodes was higher in the placebo group compared with both the ondansetron and metoclopramide groups. The mean number of vomiting was 1 in the ondansetron group, 1 in metoclopramide group and 2 in the placebo group. (Figure 3)

**Hypotension and Emetic Symptoms:**

The result showed that 64 patients (42.6%) out of the 150 patients involved in the study had hypotensive episodes during the course of surgery. The mean systolic blood pressures in these hypotensive patients were 90.0±4.6mmHg, 90.6±5.2mmHg and 90.4±4.2mmHg in the ondansetron, metoclopramide and placebo groups respectively. (Table 5) In the patients who had no hypotension, the mean systolic blood pressures were 118±8mmHg, 119±6mmHg and 117.5±8mmHg in the ondansetron, metoclopramide and placebo groups respectively. The frequency of hypotension was comparable among the three study groups. It occurred in 20 (40%) patients in the ondansetron group, 22 (44%) patients in the metoclopramide group and 22 (44%) patients in the placebo group.

Emetic symptoms occurred predominantly in patients who had hypotension compared with the non-hypotensive patients. In the placebo group, emetic symptoms occurred in 15 (68.1%) of the 22 patients who had hypotension, whereas only 2 (7.1%) of the remaining 28 patients in this group without hypotension had emetic symptoms. (Figure 4).

However, the frequency of emetic symptoms was significantly reduced following antiemetic prophylaxis in both the ondansetron and metoclopramide groups. The result further showed that in the metoclopramide group, only 3 (13.6%) of the 22 patients that
had hypotension developed emetic symptoms, and in the ondansetron group, emetic symptoms occurred in only 2 (10%) of the 20 patients that had hypotension. There was no statistically significant difference between the result of the ondansetron and metoclopramide groups.

**Use of Rescue Promethazine**

The result of the study showed that none of the patients in both the ondansetron and metoclopramide groups required rescue promethazine in the course of surgery whereas 5 patients (10%) in the placebo group required the administration of rescue promethazine to treat emetic episodes, which were persistent for up to five minutes.(Table 4).

**Side Effects of Study Drug**

No adverse effects related to the study drugs were observed during the study.

**TABLE 1**

**Patients’ Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>GROUP I (n=50)</th>
<th>GROUP II (n=50)</th>
<th>GROUP III (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONDANSETRON</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.7±3.2</td>
<td>29.9±3.7</td>
<td>29.6±3.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.9±6.9</td>
<td>62.6±6.6</td>
<td>62.2±6.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>153.8±3.7</td>
<td>154.7±3.7</td>
<td>154.6±4.3</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>38.7±0.8</td>
<td>38.6±0.8</td>
<td>38.7±0.9</td>
</tr>
<tr>
<td>Parity</td>
<td>1(0-3)</td>
<td>1(0-3)</td>
<td>1(0-3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Previous</td>
<td>25 (50%)</td>
<td>24 (48%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Caesarean Section</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 2

**Operative conditions**

*Data expressed as mean ± SD. Maximum level of sensory blockade Apgar score expressed as median and range, Type of incision and exteriorized uterus expressed as number and percentage.*

<table>
<thead>
<tr>
<th></th>
<th>GROUP I (n=50) ONDANSETRON</th>
<th>GROUP II (n=50) METOCLOPRAMIDE</th>
<th>GROUP III (n=50) PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum level of sensory block</strong></td>
<td>T₅ (T₄-T₅)</td>
<td>T₅ (T₄-T₅)</td>
<td>T₅ (T₄-T₅)</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Bromage Score</strong></td>
<td>6.0±1.2</td>
<td>5.8±1.0</td>
<td>5.9±0.9</td>
</tr>
<tr>
<td><strong>U-D interval (sec)</strong></td>
<td>72±18</td>
<td>71±6</td>
<td>68±12</td>
</tr>
<tr>
<td><strong>Surgical time (min)</strong></td>
<td>65±9</td>
<td>68±5</td>
<td>69±6</td>
</tr>
<tr>
<td><strong>Type of incision</strong></td>
<td>Midline incision 6 44</td>
<td>Pfannestiel incision 5 45</td>
<td>5 45</td>
</tr>
<tr>
<td></td>
<td>Crystalloid administered (ml)</td>
<td>2150±290</td>
<td>2410±285</td>
</tr>
<tr>
<td><strong>Exteriorised uterus</strong></td>
<td>48</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>20 (40%)</td>
<td>22 (44%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td><strong>Newborn weight (g)</strong></td>
<td>3273±304</td>
<td>3198±241</td>
<td>3086±247</td>
</tr>
<tr>
<td><strong>Apgar Score</strong></td>
<td>8 (7-9)</td>
<td>8 (8-9)</td>
<td>8 (8-9)</td>
</tr>
<tr>
<td><strong>1st Min</strong></td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td><strong>5 Min</strong></td>
<td>8 (7-9)</td>
<td>8 (8-9)</td>
<td>8 (8-9)</td>
</tr>
</tbody>
</table>
I-D Interval  = Skin incision –delivery interval
U-D Interval  = Uterine incision - delivery interval

**TABLE 3**

**INTRA-OPERATIVE VITAL SIGNS**

Data expressed as mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>GROUP I (n=50) ONDANSETRON</th>
<th>GROUP II (n=50) METOCLOPRAMIDE</th>
<th>GROUP III(n=50) PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline vital sign</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>121.9± 7.2</td>
<td>122±6.0</td>
<td>120.7±7.0</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>70.5± 7.4</td>
<td>75.7±7.6</td>
<td>72.1±8.3</td>
</tr>
<tr>
<td>Heart Rate (min)</td>
<td>78±6</td>
<td>80±4</td>
<td>80±5</td>
</tr>
<tr>
<td>Resp. Rate (min)</td>
<td>17±1</td>
<td>17±1</td>
<td>18±1</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>98±1</td>
<td>97±1</td>
<td>97±1</td>
</tr>
<tr>
<td><strong>Postspinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>100.6±6.0</td>
<td>102.4±8.0</td>
<td>102.5±6.0</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>60.0±4.0</td>
<td>62.0±6.0</td>
<td>62.0±4.0</td>
</tr>
<tr>
<td>Heart Rate (min)</td>
<td>90±4</td>
<td>92±4</td>
<td>90±2</td>
</tr>
<tr>
<td>Resp Rate (min)</td>
<td>18±2</td>
<td>18±2</td>
<td>18±2</td>
</tr>
<tr>
<td>SaO₂%</td>
<td>97±1</td>
<td>97±1</td>
<td>97±1</td>
</tr>
<tr>
<td></td>
<td>Post Delivery (After Injectate)</td>
<td>Recovery Room</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td><strong>Mean SBP (mmHg)</strong></td>
<td>108.7±4.4</td>
<td>116.0±7.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.5±4.0</td>
<td>60.0±5.0</td>
<td></td>
</tr>
<tr>
<td><strong>Mean DBP (mmHg)</strong></td>
<td>106±6.4</td>
<td>118.0±6.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.4±4.2</td>
<td>65.0±4.5</td>
<td></td>
</tr>
<tr>
<td><strong>Heart Rate (min)</strong></td>
<td>82±4</td>
<td>82±6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17±2</td>
<td>16±1</td>
<td></td>
</tr>
<tr>
<td><strong>Resp Rate (min)</strong></td>
<td>97±1</td>
<td>97±1</td>
<td></td>
</tr>
<tr>
<td><strong>SaO₂ (%)</strong></td>
<td>97±1</td>
<td>97±1</td>
<td></td>
</tr>
</tbody>
</table>

**Mean SBP= Systolic Blood Pressure**  
**Resp. Rate= Respiratory Rate**  
**Mean DBP= Diastolic Blood Pressure**  
**SaO₂= Oxygen Saturation**

**TABLE 4**

**DISTRIBUTION OF INTRAOPERATIVE EMETIC SYMPTOMS AFTER ADMINISTRATION OF STUDY DRUGS**

Data expressed as number and percentage. Severity of nausea expressed as median and range. Mean number of vomiting expressed as number.

<table>
<thead>
<tr>
<th></th>
<th>GROUP I (n=50) ONDANSETRON</th>
<th>GROUP II (n=50) METOCLOPRAMIDE</th>
<th>GROUP III (n=50) PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emesis Free</strong></td>
<td>48 (96%)</td>
<td>47 (94%)</td>
<td>33 (66%)</td>
</tr>
<tr>
<td><strong>Emetic Symptom</strong></td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Type of Emetic Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Retching</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td><strong>Severity of Nausea (NRS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5 (4-5)</td>
<td>5.0 (5-6)</td>
<td>7.0 (7-10)</td>
</tr>
<tr>
<td><strong>Mean number of vomiting episodes</strong></td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Use of Rescue promethazine</strong></td>
<td>0%</td>
<td>0%</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

NRS= Numerical Rating Scale.
**TABLE 5**

Frequency of Hypotension related to emetic symptoms during spinal anaesthesia for Caesarean section.

Data expressed as number and percentage. Blood pressure and ephedrine dosages expressed as mean ±SD.

<table>
<thead>
<tr>
<th></th>
<th>GROUP I (n=50) ONDANSETRON</th>
<th>GROUP II (n=50) METOCLOPRAMIDE</th>
<th>GROUP III (n=50) PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
<td>20 (40%)</td>
<td>22 (44%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td><strong>Mean SBP</strong></td>
<td>90.0±4.6</td>
<td>90.6±5.2</td>
<td>90.4±4.2</td>
</tr>
<tr>
<td><strong>Mean DBP</strong></td>
<td>50±4.2</td>
<td>48±5.2</td>
<td>50±4.0</td>
</tr>
<tr>
<td><strong>Ephedrine dosage (mg)</strong></td>
<td>5±0</td>
<td>5±0</td>
<td>5±0</td>
</tr>
<tr>
<td><strong>Emetic Symptoms</strong></td>
<td>2 (10%)</td>
<td>3 (13.6%)</td>
<td>15 (68.1%)</td>
</tr>
<tr>
<td><strong>Emesis Free</strong></td>
<td>18 (90%)</td>
<td>19 (86.4%)</td>
<td>7 (31.9%)</td>
</tr>
</tbody>
</table>

Mean SBP= Systolic arterial Pressure

Mean DBP= Diastolic arterial pressure
FIGURE 1
FREQUENCY OF NAUSEA, RETCHING AND VOMITING AFTER ADMINISTRATION OF STUDY DRUGS
FIGURE 2
SEVERITY OF NAUSEA AFTER ADMINISTRATION OF STUDY OF DRUGS

PLACEBO

METOCLOPRAMIDE

ONDANSETRON

MEDIAN SCORE ON (NRS)
FIGURE 3
SEVERITY OF VOMITING AFTER ADMINISTRATION OF STUDY DRUGS

MEAN NUMBER OF EPISODE OF VOMITING

ONDANSETRON  METOCLOPRAMIDE  PLACEBO
FIGURE 4

FREQUENCY OF EMETIC SYMPTOMS IN HYPOTENSIVE PATIENTS
CHAPTER FIVE

DISCUSSION

Nausea, retching and vomiting are important problems in obstetric analgesia. These problems are appreciably high during Caesarean delivery under spinal analgesia especially when no prophylactic antiemetic is provided. These symptoms can be problematic and may interfere with the procedure. The physiological and anatomical changes of pregnancy predispose parturients to emetic sequelae in the first trimester. The aetiology of these emetic symptoms is multifactorial and varies among parturients. The study was designed to compare the effectiveness of ondansetron and metoclopramide as antiemetic prophylaxis during the intra-operative and immediate post-operative period for Caesarean delivery under spinal analgesia.

Only ASA I and 2 patients were recruited for the study because it has been shown that ASA 3 and 4 patients may have pronounced hypotension following spinal analgesia and the incidence of emetic complication during spinal analgesia has been shown to be affected by arterial hypotension. Patients with factors that might influence occurrence of emetic symptoms were also excluded from the study. These include patients with history of motion sickness, gastrointestinal disorders, morbid obesity, severe pregnancy induced hypertension and patients on medications such as opioids, antihistamines and antiemetics.

All the patients studied were prehydrated with 1000ml of Ringers lactate solution before instituting the spinal anaesthesia to prevent arterial hypotension. Spinal induced
hypotension has been shown to be associated with the development of emetic symptoms \(^{23,24}\). Hypotension is the greatest immediate complication of spinal analgesia in obstetric patients.\(^{37,38,39}\) It is common, rapid in onset and has adverse effects on both the mother and foetus. It has an incidence of up to 80% without prophylactic measures\(^{40,41}\). It is primarily due to blockade of preganglionic sympathetic fibres resulting in decreased in systemic vascular resistance and decrease in cardiac output. Spinal induced hypotension is worsened by supine hypotensive syndrome, which is due to aortacaval compression, by the gravid uterus. Arterial hypotension may lead to hypoperfusion and hypoxaemia of the brainstem and this could trigger the vomiting centre and cause emetic symptoms\(^ {24,42}\).

Prevention of the hypotension may be achieved by volume preloading with non glucose containing crystalloid or colloid, use of vasopressor and prevention of aorto-caval compression by left uterine displacement \(^{40,43}\). Crystalloid preloading does not always prevent spinal induced hypotension\(^ {37,38}\). This is also borne out by this study with the incidence of hypotension of 42.6% inspite of preloading with 1000ml of Ringers lactate. Colloid has also been used successfully, \(^{44}\) however Rout and Rocke cautioned against the risk of pulmonary edema and allergy when colloid are used.

In the conscious (non sedated) parturient, a relatively high block is necessary to ensure pain relief and cooperation for Caesarean delivery. In this study, a block of up to T5 was necessary, which also block the sympathetic outflow to that level causing hypotension in all the three groups. Hypotension often heralded by yawning may affect the CTZ. It is therefore necessary to preventive measures against a fall in blood pressure as a first line treatment.
Ephedrine was employed in this study as part of the active management of hypotension. Traditionally, ephedrine has been recommended in this role, but the use of phenylephrine is increasing. Ephedrine does not appreciably affect uterine blood flow. Its position has been challenged because of potential complications that include supraventricular tachycardia, tachyphylaxis and fetal acidosis. The use of phenylephrine is associated with better fetal acid-base status and similar efficacy in blood pressure management. However, phenylephrine is associated with fetal bradycardia and serial dilution for intravenous administration is a source of error. Spinal analgesia was instituted with 2.5ml (12.5mg) of 0.5% hyperbaric bupivacaine as against 15mg usually employed for the general population. This volume (2.5ml) has been shown to offer adequate spinal block with lower incidence of hypotension in obstetric patients. The decreased requirement of anaesthetics for spinal analgesia during pregnancy may be due to several factors including:

- Increased sensitivity of nerve fibres to local anaesthetics due to raised cerebrospinal and plasma concentrations of progesterone during pregnancy.
- Increased venacava pressures secondary to obstruction caused by the gravid uterus

Hyperbaric bupivacaine rather than the isobaric form is favoured in obstetric analgesia because of reports of excessive rostral spread, even total spinal analgesia after the use of isobaric bupivacaine. The same dosage (12.5mg) of 0.5% hyperbaric bupivacaine was used for all the patients in this study. This is based on the report of Norris M.C that in parturients at term, the patients height or weight does not appreciably affect the spread of hyperbaric spinal analgesia.
Ondansetron 4mg and metoclopramide 10mg were chosen as the dosages of the study drugs based on previous studies\textsuperscript{52,53}. Ondansetron 4mg has been shown to be effective in reducing the frequency of nausea and vomiting without inducing side-effect in elective outpatient surgical procedures \textsuperscript{52}. Intravenous administration of 4mg ondansetron has been found to significantly reduce the incidence of vomiting in women undergoing Caesarean section under spinal analgesia \textsuperscript{6}. Claybon also showed that 4mg single dose intravenous ondansetron reduces post-operative nausea and vomiting, was well tolerated and produced minimum side effects \textsuperscript{53}. Pearman had suggested that 8mg of ondansetron may be more effective than 4mg in women at higher risk of manifesting emetic symptoms \textsuperscript{54}. Lussos et al\textsuperscript{7} noted that 10mg metoclopramide produced significant antiemetic prophylactic effect compared to placebo in patients undergoing elective Caesarean section under spinal analgesia\textsuperscript{7}.

The three groups in this study, the ondansetron, metoclopramide and placebo treated groups had comparable patients and operative characteristics. (Table 1 and 2). The data obtained from this study revealed that the frequency of emetic symptoms is high without preventive measures. The frequency of emetic symptoms in the placebo group was 34\%. However, antiemetic prophylaxis with either metoclopramide or ondansetron reduced this frequency to 6\% and 4\% respectively. There was no statistically significant difference between the frequency observed in the ondansetron and metoclopramide groups.

This result follows the pattern of results that had been reported in the previous studies \textsuperscript{8,9,12,55}. Chestnut et al\textsuperscript{8} reported a reduced frequency of emetic symptoms from 36\% to 12\% during spinal analgesia for Caesarean delivery following the administration
of intravenous metoclopramide after the delivery of the foetus. Pan and Moore also documented a reduction from 69% to 31% in emetic symptoms after administration of intravenous ondansetron during Caesarean section under epidural analgesia.

Considering the frequency of 34% in the placebo group, it is not surprising, therefore, that nausea and vomiting decrease patients' satisfaction during spinal analgesia. Patients often rate emetic symptoms as worse as pain. Without preventive measures and adequate treatment, this problem may extend to the postoperative period. Persistent vomiting has been associated with increased risk of aspiration, wound dehiscence, oesophageal rupture, subcutaneous emphysema, dehydration and electrolyte imbalance. Nausea and vomiting also frequently delays discharge from the postanaesthesia care unit.

A statistically significant reduction in the severity of nausea was also observed in both the metoclopramide and ondansetron groups compared to the placebo group. The median severity score was reduced from 7.0 in the placebo to 5.0 and 4.5 in the metoclopramide and ondansetron groups respectively. This agrees with Abouleish et al who reported significant reduction in the severity of nausea following intraoperative administration of 4mg ondansetron during Caesarean section under spinal analgesia.

Nausea has been described as the prodromal phase of vomiting. All the patients who retched or vomited had experienced nausea in this study. Antiemetic prophylaxis reduced the frequency of both the prodromal and the ejection phases. Thus, it is apparent from the above, that both ondansetron and metoclopramide are effective in baseline emetic risk reduction in the intraoperative postdelivery period. Ondansetron has also
been observed to be effective in the treatment of postoperative vomiting by Alon and Himmelseher 58.

The aetiology of intraoperative emesis during spinal analgesia is multifactorial. Patient specific risk factors include age, female gender, history of postoperative nausea and vomiting, history of motion sickness and non-smoking status. Female gender factor is particularly important because it has been noted that women have 3 fold-increased risk of developing emetic symptoms 57. An association between pain and sensation of nausea has been reported in a study of postoperative complications 31. Relief of pain was associated with relief of nausea 31. Manipulation of abdominal viscera, uterus and peritoneum without adequate sensorimotor blockade may also predispose the awake patient to nocioceptive induced nausea 7. In this clinical study, adequate dermatomal level of analgesia (T5) was ensured before surgical incision to prevent nocioceptive induced emetic symptoms.

Intraoperative hypotension is one of the main factors that are associated with onset of emetic symptoms. Most of the episodes of nausea noted in this study coincided with the onset of maternal hypotension. Nausea has been considered a premonitory sign of hypotension. Hypotension is the main cardiovascular side effect of spinal analgesia 59,60. Arterial hypotension may lead to hypoperfusion and hypoxaemia of the brainstem and this could trigger the vomiting centre and cause emetic symptoms.

The result of this study showed that hypotension doubles the risk of emetic symptoms during Caesarean section without preventive management. The frequency of emetic symptoms was increased from 34% to 68% in patients who had hypotension in the placebo group. This correlated with the
findings of previous authors that the incidence of emetic symptoms correlated with the presence of arterial hypotension \textsuperscript{19,20}. Carpenter et al observed that hypotension is associated with a two fold increase in relative risk of intraoperative nausea and vomiting \textsuperscript{23}. Hypotension, as a cause of nausea and vomiting, should always be anticipated and treated promptly.

One of the observations in this study is that antiemetic prophylaxis with either ondansetron or metoclopramide ameliorates this increased frequency of emetic symptoms following hypotension during spinal analgesia. (Figure 4). The frequency of emetic symptoms was reduced from 68.1\% in the placebo group to 13.6\% in the metoclopramide group and 10\% in the ondansetron group among the hypotensive patients.

Routine exteriorisation of the uterus may also be associated with increased episode of emetic symptoms. The data obtained shows that the uterus was exteriorized in 94\% of the patients. This result is comparable to that by Pan and Moore\textsuperscript{8} where the rate of uterine exteriorization was 93\%. Exteriorization of uterus may be associated with traction on the peritoneum, increased surgical manipulation of the uterus and abdominal visceral causing the release of humoral substances including 5HT which may stimulate 5HT\textsubscript{3} receptors on the afferent vagus nerve, triggering the emetic reflex.

The use oxytocic drugs to facilitate uterine contraction after delivery of the baby may predispose the patient to nausea and vomiting. The degree of emesis is dose dependent especially if the oxytoxic drug is administered bolus intravenously.\textsuperscript{22} Intraoperative opioid was also avoided because opioid frequently cause nausea and vomiting\textsuperscript{29}. 

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Small dosages of the drug were administered to avoid the side effects associated with higher dosages. No side effects of ondansetron or metoclopramide were observed during the study. The most commonly reported side effects of ondansetron are headache, flushing at site of injection and constipation. Metoclopramide may be associated occasionally with dizziness, restlessness, sedation and extrapyramidal reactions. The extrapyramidal reactions are mainly dystonia and oculogyric crises.

The significant reduction in emetic symptoms noted in this study, confirms the observation of previous author \(^8,9\), of the beneficial effects of prophylactic ondansetron and metoclopramide in limiting the frequency and severity of nausea, retching and vomiting during Caesarean delivery under spinal analgesia. This will ultimately enhance patient satisfaction, reduces the potential risk of bowel injury and facilitate early neonatal bonding.
CONCLUSION

The frequency of intraoperative emetic symptoms during spinal analgesia for Caesarean delivery is still appreciably high where there is no prophylactic measures. Nausea occurs more frequently than retching or vomiting. The frequency of Nausea is 34% while that of retching or vomiting is 10%.

There is significantly lower frequency of nausea and vomiting and tendency towards less severe emetic symptoms following prophylaxis with ondansetron and metoclopramide.

Both prophylactic ondansetron and metoclopramide are similarly effective in providing prophylactic measures against intraoperative nausea and vomiting.
Subarachnoid block with both motor and sensory blockade up to T5 invariably produces hypotension which significantly affects the frequency of nausea and vomiting during Caesarean delivery. Ondansetron and metoclopramide have been shown to significantly reduce this frequency without side effects. Despite preloading, the patients still developed hypotension. A more effective means of preventing a fall in blood pressure should be used when the study drugs are not easily available.

**LIMITATION OF STUDY**

The period of assessment of the emetic symptoms was for 2 hours, covering the intraoperative and immediate post operative period. Extension of the assessment to cover the entire period of stay in the recovery room could have offered better results.
RECOMMENDATION

Antiemetic prophylaxis should be considered during Caesarean section under spinal analgesia to save parturients the suffering associated with the occurrence of emetic symptoms intraoperatively. This is particularly important in parturients with preoperative emetic risk factors and in parturients that develop hypotension during spinal analgesia.

Whereas metoclopramide could be administered before or after the delivery of the foetus, ondansetron should be administered after delivery of the foetus because the effects of ondansetron on newborn is not yet fully elucidated.

Metoclopramide is favoured because it is less expensive and it is easily available compared with ondansetron.
APPENDIX I

DATA COLLECTION FORM

A.  **BIODATA**

i.  Serial Number in the study -----------------------------------------------

ii. Patient’s Initials -------------------------------------------------------

iii. Age (yr) ----------------------------------------------------------------

iv. Weight (kg) -------------------------------------------------------------

v. Height (cm) --------------------------------------------------------------

vi. ASA classification -------------------------------------------------------

vii. Date -------------------------------------------------------------------

B.  **OBSTETRIC CHARACTERISTICS/HISTORY**

i.  Gestational age (wk) ----------------------------------------------------

ii. Parity -------------------------------------------------------------------

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iii. Previous Caesarean Section --------------------- YES/NO

iv. Newborn weight (g) -----------------------------------------------

v. Apgar score

  1 Minute ........................................................................
  5 Minutes ......................................................................

C.  **SURGICAL VARIABLES**

i. Level of sensory block ---------------------------------------------

ii. Anaesthesia – Incision time (min) ---------------------------------

iii. Skin Incision – Delivery time (min) -------------------------------

iv. Uterine Incision – Delivery time (sec) -----------------------------

v. Surgical time (min) -----------------------------------------------

vi. Blood loss (ml) -------------------------------------------------

vii. Crystalloid administered (ml) ------------------------------------

viii. Type of Incision

  - Midline
  - Pfannestiel

ix. Exteriorisation of uterus (YES OR NO)

x. Hypotension (mmHg) -----------------------------------------------

xi. Ephedrine: Total dose (mg) ----------------------------------------

ASA = American Society of Anesthesiologists Physical Status Classification

**VITAL SIGNS AND OXYGEN SATURATION**

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From baseline to 2 hours.
INTRAOPERATIVE NAUSEA AND VOMITING

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<td>Use of Rescue Antiemetic</td>
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APPENDIX II

ETHICAL CONSIDERATION

STATEMENT OF CONFIDENTIALITY

All information obtained from the patients and the result of this study shall be treated strictly confidential. In case of publication of this research, no personal identifying information will be disclosed.

STATEMENT OF TRANSLATION TO LOCAL LANGUAGE
The language of communication shall be English, but where this is not possible; the assistance of an interpreter to the relevant ethnic language shall be employed.

**BENEFICIENCE TO PARTICIPANTS**

The result of the study will be of help in improving the care for patients during spinal analgesia for Caesarean delivery.

**NON-MALEFICIENCE TO PARTICIPANTS**

The study will not expose the patient to any drug that has not been used safely in the past. The baby will have no added risk.

**VOLUNTARY PARTICIPATION**

The choice to participate in this study shall be voluntary, the patient have the right to withdraw at any stage of the study.
UI/UCH INSTITUTIONAL REVIEW COMMITTEE

CERTIFICATION LETTER

Principal Investigator: Dr. A. I. Rasaki
IRC Protocol No: UI/IRC/04/0161
Protocol Title: ANTIEMETIC PROPHYLAXIS DURING SPINAL ANAESTHESIA FOR CAESAREAN DELIVERY: A COMPARISON OF ONDANSETRON AND METOCLOPRAMIDE.

STATUS: APPROVED

The Joint UI/UCH Institutional Review Committee has reviewed your protocol titled: "Antiemetic Prophylaxis During Spinal Anaesthesia for Caesarean Delivery: A Comparison of Ondansetron and Metoclopramide."

The Proposal is set up to compare the antiemetic prophylaxis of intravenous ondansetron and metoclopramide during spinal analgesia for caesarean delivery. The outcome of the study is to facilitate the formulation of antiemetic prophylaxis to reduce intraoperative nausea and vomiting in this category of patients.

THE RESEARCH PROTOCOL AND CONSENT FORM DESCRIBED ABOVE HAVE BEEN REVIEWED BY THE UI/UCH IRC WITH THE RESULTS AS INDICATED.

Adeyinka G. Falusi
Professor/Chair, UI/UCH IRC
E-mail: uiuchirc@yahoo.com

International Regulations require that any severe drug reaction and unexpected adverse occurrence to subjects during the conduct of this research be reported to the UI/UCH IRC Protocol and Data Management Office promptly. Any changes to this protocol must be submitted for review to the UI/UCH IRC.
APPENDIX III

PATIENT’S INFORMED CONSENT

Dear Patient,

You are being requested to participate in this multicentre research study. In order to decide whether or not you should agree to be part of the study, you should understand enough about the research to make an informed judgment. Once you understand the study, you will be asked to sign this consent form if you wish to participate.

The research study being proposed to you is “Antiemetic prophylaxis during spinal analgesia for Caesarean delivery: A comparison of intravenous Ondansetron and metoclopramide”.

Purpose of the Study

The purpose of this study is to see if there are differences in the ability of ondansetron and metoclopramide to reduce or prevent intraoperative nausea and vomiting during spinal analgesia for Caesarean delivery.

Description of the Research Procedure

You will have your Caesarean delivery under spinal analgesia technique. This involves injecting a drug into the cerebrospinal fluid. The injection is made at the lower back in the midline away from the spinal cord. Onset of analgesia will be signified by numbness in both lower limbs and abdomen. The research drug will be administered intravenously after the delivery of your baby and clamping of the umbilical cord, so the drug does not get to the baby.
You will be allocated by chance to any of three groups. Group 1 will receive intravenous ondansetron, group 2 will receive intravenous metoclopramide, group 3 will receive 0.9% normal saline.

**Statement of Confidentiality**

Your participation in this research is confidential. All information obtained from you and the results shall be treated strictly confidential. In the event of publication of this research, no personal identifying information will be disclosed.

**Benefit**

The result of this study will be of help in improving the care for patient like you under spinal analgesia.

**Risk**

You will not be exposed to any drug that has not been used safely in the past. Your baby will have no added risk.

**Voluntary Participation**

The choice to enter or not to enter this study is yours. You also have the right to discontinue your participation.

**Financial Cost**

There will be no additional charges to you for taking part in this study.

**CONSENT**

I have read this consent form and the research study has been explained to my satisfaction. I hereby consent to participate in the study as titled above; I am also informed of my right to discontinue my participation.
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