Incidence of intraoperative nausea and vomiting during spinal anaesthesia for caesarean section

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Table of contents **Page**

DECLARATION

I, ...*Bridget Magni* ....., hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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List of abbreviations

$5HT_3$	Serotonin
BP	Blood pressure
CS	Caesarean section
CTZ	Chemotactic trigger zone
HxPONV	History of post-operative nausea and vomiting
IONV	Intraoperative nausea and vomiting
IVI	Intravenous
KZN	KwaZulu-Natal, province of South Africa
MAP	Mean arterial blood pressure
NVP	Nausea and vomiting of pregnancy
PONV	Post-operative nausea and vomiting
SBP	Systolic blood pressure
UCT	University of Cape Town

Part A: Study protocol

As approved by the Department Research Committee and the Human Research Ethics Committee University of Cape Town

Introduction

The incidence of intraoperative nausea and vomiting (IONV) during spinal anaesthesia (SA) for caesarean section (CS) is extremely variable and is dependent on the anaesthesia technique used, together with preventive and therapeutic measures employed by the anaesthetist.[1]

There is no data on the incidence of IONV during SA for CS within our population.

Recently it has been shown that postoperative nausea and vomiting (PONV) in Black South Africans (African) undergoing general anaesthesia is significantly lower than in multi-ethnic South African patients (non-African).[2] We hypothesize that the incidence of IONV amongst African patients will also be lower during spinal anaesthesia for caesarean section.

Objectives

1 To assess the incidence of IONV during SA for CS.

2 To compare the incidence of IONV between Black and multi - ethnic patients.

Methodology

A prospective observational study was conducted at Mowbray Maternity Hospital and New Somerset Hospital, after approval had been obtained from the Human Research Ethics Committee of the University of Cape Town. Healthy, term patients undergoing elective SA for CS during daylight hours (8h00-17h00), were studied, during the period August 2014 - February 2015

Inclusion criteria

- All elective caesarean sections
- Age > 18 years
- ASA I and II

Exclusion criteria

- Non-South African Black patients
- Patients who have had > 2 previous caesarean sections
- Previous major abdominal surgery
- 1500 ml estimated blood loss
- Anti-emetics administered prior to theatre
- Preoperative opioid use
- Known adverse reaction to metoclopramide

- Conversion to general anaesthesia
- Preeclampsia or other causes of severe hypertension
- The use of ergometrine

Antibiotics cefazolin (1-2 g) or, if allergic to penicillin, clindamycin (600mg), will be given over a minimum time period of 5 minutes, and at least 10 minutes prior to induction of SA. Should any nausea or vomiting occur as a result it shall be noted separately.

Standard practice for SA for CS at UCT will be employed (i.e. 2 mL hyperbaric bupivacaine plus 10 ug Fentanyl intrathecally, 15 mL/kg crystalloid coload via 18G cannula). Preoperatively, systolic blood pressure (SBP) will be measured twice in theatre with the patient in the left lateral position, and the mean value calculated. The target for treatment of hypotension will be 80% of this value. Blood pressure will be measured every minute for the entire procedure. The initial vasopressor will be phenylephrine 50 µg. A 30% decrease in SBP will be treated with 100 µg of phenylephrine. This will be repeated every minute until the target is achieved (within 20% of baseline value). If the heart rate decreases to less than 55 beats per minute in association with hypotension (SBP decreased by 30% from baseline), ephedrine 10 mg will be administered, followed by atropine 0.25-0.5 mg if bradycardia persists. Ephedrine may also be administered if there is a poor response to two consecutive doses of phenylephrine. Nausea and vomiting will be treated with intravenous phenylephrine to restore blood pressure, and metoclopramide 10 mg.

The patient will then be positioned supine, with 20 degrees left lateral tilt. Block height will be assessed with ethyl chloride cold spray. The highest level of the block will be recorded prior to incision, and again in recovery room. Oxytocin 3 IU will be given over 60 seconds after delivery, preceded by 50 ug phenylephrine.

The following data will be collected by the attending anaesthetist: patient age, booking weight, gestational age, gravity, parity, and number of previous caesarean sections. The lowest systolic blood pressure (SBP) during the procedure will be recorded as well as the highest level of the spinal block, total fluid volume administered, and the total dose of phenylephrine, ephedrine, atropine and metoclopramide. The total blood loss will be estimated by measurement in a graded suction bottle and inspection of swabs. Exteriorisation of the uterus will be recorded. Nausea and vomiting episodes, as well as when they occurred, will be documented. Duration of surgery and other adverse events will be recorded at the completion of the case.

Interviews are to be conducted after the operation, in the recovery room, prior to the patient being discharged to the ward and consent requested at this time for participation in the study. This will be done in order to exclude potential suggestion bias introduced by explaining the study objectives prior to surgery. The following direct questions will be asked: "What race do you classify yourself?", "Have you ever experienced motion sickness or post-operative nausea and vomiting?", and "Did you experience nausea during this operation?"

Statistical analysis

Sample size calculation for the primary outcome was based upon a clinical estimate of an incidence of nausea and/or vomiting of 25% overall, with an absolute accuracy of +/- 6%. This requires 184 patients. Sub-group analysis is planned a priori. With an expected proportion of African/Non-African patients of 66/33%, and an expected incidence of nausea and/or vomiting of 15% amongst Black Africans and 35% in Non-Africans, allowing for 90% power and $p<0.05$, 156 Black African- and 78 Non-African patients were required. In the time available for the conduction of the audit, 143 Black African- and 112 Non-African parturients were studied. Individual categorical variables will be summarised with frequency and percentage frequency distributions and illustrated using bar charts. Continuous variables will be summarised using means and standard deviations or medians and interquartile ranges. Associations between categorical variables will be summarised in two-way frequency tables and tested for statistical significance using a Chi-square test. Observed p-values are quoted. P-values smaller than 0.05 were considered to be statistically significant. The joint associations between the predictor variables and the presence/absence of nausea/vomiting were modelled using a logistic regression model. The exponentiated coefficients of this model are estimated on adjusted odds ratios. Multinomial logistic regression models were used to estimate the association between predictor variables and the three-level categorical outcomes. These models are equivalent to parallel binary logistic models where the relative odds of each of the categories compared to a chosen reference category is estimated. We chose "none" as the reference category.

Ethics

All patients will be asked to categorise themselves as African (Black South African), or Non-African (Multi-ethnic South African). To avoid bias in this study on nausea and vomiting, the patient will be asked after the

completion of the CS, whether the data recorded may be used for the audit, and a record will be made on the anaesthesia chart. Any patient who is unwilling to participate in the audit, or unable to communicate, and thus cannot be included in the audit, will still receive post-operative treatment based upon good clinical practice. All information shared by patients with the investigators will be kept confidential. Strict confidentiality will be maintained within the health care team environment at all times during the audit.

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Part B: Narrative literature review

Objectives

The aim of this literature review is to answer the following questions:

1) What is the incidence of intraoperative nausea and vomiting (IONV)?

2) What are the causes of IONV?

3) What antiemetics are effective?

4) Are there ethnic differences with regard to the incidence of IONV?

Literature search strategy

The literature search was performed using the PubMed database from the University of Cape Town Health Sciences Library. Articles not published in English were excluded. The keywords and phrases used in different combinations were; “intraoperative nausea and vomiting”, “regional anaesthesia”, “caesarean section”, “nausea and vomiting”, “prevention of nausea and vomiting”. Additional articles were found from published papers or using the “related links" PubMed function.

Introduction

Spinal anaesthesia (SA) is the method of choice for caesarean section (CS) due to its rapid onset, safety, and symmetrical sensory and motor blockade. However, despite major advances in neuraxial techniques, intraoperative nausea and vomiting (IONV) is still common and an unpleasant side effect.

Nausea and vomiting during SA is a very distressing experience, with patients reporting feelings of discomfort and fear.[1] Disruption of maternal bonding may occur, while at the same time causing anaesthetic and surgical complications. Surgical risks include protrusion of abdominal contents with associated visceral injuries, increased bleeding and an increased surgical time. Abrupt contraction of the upper gastrointestinal tract may lead to aspiration, especially in the pregnant patient who is at an increased risk.[2]

Physiology of nausea and vomiting

The chemoreceptor trigger zone (CTZ) and the vomiting centre regulate nausea and vomiting. The CTZ is located in the area postrema on the floor of the fourth ventricle. The vomiting centre is situated in the medulla and controls the vomiting response. This centre receives input from the gastrointestinal tract via vagal sensory fibres, the cortex of the brain, the vestibular nuclei in the labyrinth of the ear, pressure receptors in the cranium, and the chemoreceptor trigger zone. Histamine, dopaminergic, muscarinic, serotonergic and opioid receptors are involved. The mechanical action of vomiting is initiated via efferent activity to the phrenic, vagal and spinal nerves that supply the abdominal musculature.[3]

The high level of progesterone in the presence of oestrogen during pregnancy leads to smooth muscle relaxation that hinders gastric motility and lowers tone in the lower oesophageal sphincter. Small bowel transit times may also be longer during the 3rd trimester. These hormonal changes may also lead to an increase in IONV due to their effects on the neurovestibular system and the vomiting centre.[4]

The pressure effects from the gravid uterus add to the increased risk of nausea and vomiting. Pressure on the stomach leads to delayed gastric emptying and an increased risk of reflux.[4]

1 The incidence of IONV during spinal anaesthesia for caesarean section

There are few studies measuring the incidence of IONV. Therefore, the incidence of IONV is often taken from the placebo groups of studies examining the effect of antiemetic preventative measures. Some review articles

do quote the incidence of IONV during SA for CS, but most of these have also included postoperative nausea and vomiting (PONV).

Table 1: The incidence of intraoperative nausea and vomiting during spinal anaesthesia for caesarean section

	Nausea and/or vomiting	Nausea	Vomiting
Ishiyama (2001) [5]		70%	40%
Voigt (2013) [1]	22.5%		
Caba (1997) [6]		20% – 60%	

2 Causes of IONV

Many factors contribute to the incidence of nausea and vomiting during caesarean section. The contributory factors are anaesthetic and non- anaesthetic. The anaesthetic risks are hypotension, the use of opioids (both neuraxially and intravenously) and an increase in vagal activity. The non-anaesthetic factors include manipulation and exteriorisation of the uterus, vigorous motion and the use of uterotonic agents such as oxytocin.[7]

Anaesthetic causes

Hypotension

Many studies have shown the correlation between blood pressure control and IONV. A decrease in blood pressure of >30% below baseline has been found to increase the risk of IONV to 60%.[8] The incidence of IONV has been reported to increase in proportion to the percentage decrease from baseline blood pressure. Ngan Kee et al. found the incidence of IONV to be 4%, 14%, and 40% with the target as a percentage of baseline blood pressure of 100%, 90%, and 80% respectively.[9] Hypotension may be compounded by aortocaval compression during SA, particularly if lateral tilt is not adequately applied.[10] Hypotension can lead to hypoperfusion of the bowel resulting in the release of emetogenic substances such as serotonin from the intestine.[1]

To prevent and/or treat hypotension and the associated IONV, a colloid preload or crystalloid coload,[11] a wedged position to prevent aorto caval compression[12] and a vasopressor in the form of phenylephrine boluses or infusion [9,13,14] can be used. Crystalloid coload in combination with phenylephrine is most effective.[14]

Vagal hyperactivity

Sympathetic blockade during spinal anaesthesia results in an increased activity of the vagal nerve. This leads to gastrointestinal hyperactivity and an increased risk of IONV. Glycopyrrolate given prior to induction of SA, may reduce the incidence of nausea and vomiting, but is not effective in preventing hypotension.[15]

Non- Anaesthetic causes

Surgical stimuli

Surgical stimulation such as intra-uterine manipulation, peritoneal traction and the exteriorisation of the uterus can cause IONV. The mechanism is thought to be due to stimulation of visceral afferent fibres and subsequent unmyelinated C-fibre activation. The incidence can be as high as 50% in patients undergoing SA.[5]

Uterotonic agents

Oxytocin

The administration of oxytocin leads to cardiovascular side effects, particularly hypotension and tachycardia. This is caused by the transient relaxation of vascular smooth muscle cells secondary to stimulation of the nitric oxide pathway. It has been shown that a slower infusion rate over five minutes decreases the hypotensive response.[16]

Ergot alkaloids

Ergot alkaloids, when given as a 0.5 mg IV dose at delivery to prevent blood loss, are associated with an increase in mean arterial pressure, and a high incidence of nausea and vomiting (46%) and therefore are not considered as a first line agent for uterine atony during SA for CS.[17]

Prostaglandins

Prostaglandins such as F2-alpha also cause nausea and vomiting, with an incidence of 10% for a 250 µg intramyometrial injection, and may cause fever and diarrhoea.[18]

Antibiotics

First generation cephalosporins are the antibiotic of choice for majority of surgical procedures, including caesarean section, and reduce post-operative infection by up to 60%.[19,20]

Notable side effects include nausea, vomiting, diarrhoea, skin rash and allergic reactions.[21] In view of the risk of nausea and vomiting, cephalosporins are given by slow IV injection.

Motion

For women who have a predisposition towards motion sickness, the added risk factors associated with pregnancy could lead to an increased risk of nausea and vomiting, especially when subjected to sudden movement, changes in position and transfer onto the stretcher at the end of the operation. This emetic response is controlled by afferent fibres to receptors in the vestibular system and efferent fibres to the GIT. Histamine-, muscarinic- and cholinergic receptors are involved.[22]

3 Antiemetic prophylaxis and treatment of IONV

Some of these causes of IONV can be manipulated and controlled, but certain patients may be particularly susceptible. This requires early identification and possibly the use of pharmacological prophylaxis. These medications are not without their risks, which may include agitation, extra-pyramidal symptoms and dystonic reactions.[23]

A recent Cochrane review of the interventions for preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section reviewed the efficacy of pharmacological and non-pharmacological methods.[24]

The pharmacological interventions included 5-HT_3- receptor antagonists, dopaminergic receptor antagonists, corticosteroids, antihistamines, anticholinergic agents, sedatives (e.g. midazolam, propofol) and opioids.

Anti-emetics

According to the latest Cochrane review, the most effective anti-emetics for the reduction of intraoperative nausea *and* vomiting were the dopamine antagonists (both metoclopramide and droperidol) and corticosteroids, whereas the 5-HT_3- antagonists and anti-cholinergic agents, such as glycopyrollate, were only effective at reducing the intraoperative nausea.[24]

Serotonin (5-HT_3) antagonists

Serotonin antagonists such as ondansetron act on the chemo-emetic trigger zone (CTZ), and block the vagal-stimulated emetogenic effect of serotonin. A single dose of intravenous ondansetron (4 mg) after the clamping of the cord has been shown to be more effective than intravenous metoclopramide (10 mg) in preventing nausea.[25] However, there is no difference between ondansetron and metoclopramide in the prevention of vomiting.[26] Serotonin antagonists are considered relatively safe, with minimal headache, tachycardia and sedation. They are, however, relatively expensive.[24]

Corticosteroids

Dexamethasone has been shown to be as effective as any other antiemetic drugs in PONV prophylaxis. The underlying mechanism is thought to be via modulation of the neurotransmitter receptor density in the nucleus of the solitary tract, the raphe nucleus and the area postrema.[27] The onset of action is delayed; however, the antiemetic effect is prolonged. It is therefore useful in PONV prophylaxis but not for IONV. Dexamethasone has no severe side effects, is reasonably priced, and may reduce surgical inflammation.[24]

Anti-histamines

Anti-histamines act on the histamine receptors in the CTZ and inhibit the integrative function of vestibular nuclei.[7] They are often used for motion sickness. Anti-histamines do not have major adverse effects and are cheap. Their use may be limited by major sedation, headache and tachycardia. They are effective at decreasing PONV associated with CS under SA, however there are no studies looking at their effect on IONV.[24]

Dopamine antagonists

These agents work on the dopamine receptors in the CTZ. They also act by increasing the resting tone of the lower oesophageal sphincter and in higher doses antagonises the serotonin receptors.[23] Dopamine antagonists have a fast onset of action (1-3 min). The more common side effects include sedation and dizziness. Their major adverse effects are agitation and extra-pyramidal side effects. After initial concerns about precipitation of ventricular arrhythmias such as Torsades de Pointes, droperidol was withdrawn from certain markets, but has subsequently been reintroduced.[1]

The recent Cochrane analysis found a reduction in PONV with dopamaine antagonists of 0.38 RR.[24] The dramatic increase in the price of droperidol has however, restricted its use.

Combination anti-emetics

There is a significantly lower incidence of IONV with the use of combination prophylaxis compared with placebo. The serotonin antagonist/dopamine antagonist had a relative risk reduction of IONV of 59% versus the antihistamine/corticosteroid that reduced the risk by 30% and the serotonin antagonist alone that reduced the risk of IONV by 46%.[1]

Acupressure

Acupressure is a non-invasive method of preventing IONV. Traditionally acupressure point P6 is used.[29] Its mechanism of action is through peripheral nerve stimulation and possibly by enhancing gastric motility.[30]

In a review by Allen in 2008, the benefits of acupuncture were found to be inconsistent.[29] Acupuncture did decrease intra-operative nausea but there was no proven reduction in intraoperative or postoperative vomiting.[24]

4 Ethnic differences in the incidence of intraoperative nausea and vomiting

It has been the perception amongst South African anaesthesiologists that Black South African patients have a decreased incidence in postoperative nausea and vomiting (PONV) after general anaesthesia. A prospective observational study performed in KwaZulu-Natal (KZN) measured the incidence of PONV in patients undergoing general anaesthesia, and showed a significant difference in nausea and vomiting between black South African (African) patients (27%) as opposed to multi-ethnic (non- African) patients (45%).[31]

It is postulated that the isoenzyme variation in the hepatic P-450 cytochrome system is a potential factor in the precipitation of nausea and vomiting. Patients who have a CYP2E1 poor-metaboliser phenotype may be at a greater risk for the development of PONV. This allele has not been identified in the KZN black population and this may explain the lower incidence of PONV.[32] With regard to intraoperative nausea and vomiting during SA for CS, this mechanism does not apply. Other centrally mediated mechanisms may be involved.

It has been shown that nausea and vomiting of pregnancy is more common in Western and Asian populations, than in African, Eskimo and Native Americans.[33] A Canadian study examining the racial differences in the incidence of nausea and vomiting of pregnancy showed that Asian and Black women were less likely to report these symptoms than Caucasians. This difference in the reporting of symptoms was attributed to cultural or genetic factors.[34]

A study investigating racial differences in response to chemotherapy found the African American population have a lower incidence of nausea and vomiting than Caucasian patients.[35]

Conclusions

Nausea and vomiting remain unpleasant symptoms during SA for CS. We therefore regarded it as important to establish the incidence of these side effects in our population, using crystalloid coload and phenylephrine boluses for spinal hypotension, with metoclopramide as rescue anti-emetic. The intention is to introduce interventions to reduce the incidence of IONV, and improve patient experience of the birth and bonding process. Within our literature search criteria, we found no studies specifically examining ethnic differences in susceptibility to IONV during SA for CS. Therefore, it was considered important, in the light of the literature quoted above, to include this aspect as an additional study aim. The findings could necessitate pharmacological prophylaxis in high-risk patients.

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Part C: Publication ready manuscript

Title page

Incidence of intraoperative nausea and vomiting during spinal anaesthesia for caesarean section

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Abstract

The incidence of intraoperative nausea and vomiting during spinal anaesthesia for caesarean section.

Background

Nausea and vomiting (IONV) during spinal anaesthesia (SA) for caesarean section (CS) is unpleasant and may interfere with surgery. We studied the incidence of IONV during elective CS, as well as the influence of ethnicity on this outcome.

Methods

Two hundred and fifty eight healthy term patients undergoing SA for elective CS were recruited to this prospective observational study conducted at two Cape Town Level 2 hospitals. Standard practice was employed for SA for CS at UCT (University of Cape Town): 2 mL hyperbaric bupivacaine plus 10 µg fentanyl at the L3/4 interspace, and 15 mL/kg crystalloid co-load. Spinal hypotension was managed with phenylephrine boluses according to a standard protocol. Nausea and/or vomiting were treated by restoration of blood pressure, and metoclopramide. Intraoperative complaints of nausea, and vomiting, were noted. Patients were also interviewed postoperatively as to any experience of intraoperative- or previous history of nausea.

Results

Of the 258 patients enrolled in the audit, 112 (43.4%) were non-African and 146 (56.6%) were Black African patients. The overall incidence (95% CI) of nausea was 32% (0.27-0.38), with 20% occurring prior to- and 11% after the delivery. The overall incidence of vomiting was 7% (0.05-0.11), with 3.2% occurring prior to, and 3.8% after, delivery. The incidence of nausea and/or vomiting was 33% (0.28 – 0.40). Black Africans experienced significantly less nausea than non-African patients (36/145 [24.8%] vs 47/112 [42.0%] respectively, $p = 0.004$). There was no significant difference in the incidence of vomiting (10/145 [6.8%] vs. 8/112 [7.1%] respectively, $p = 0.865$). The odds of experiencing intraoperative nausea for patients with any blood pressure value <70% of baseline, were 2.46 (95% CI 1.40-4.33).

Conclusions

Though in keeping with international standards, the clinically significant incidence of nausea and/or vomiting of 33% requires adjustments to the management protocol for spinal hypotension. The inclusion of ethnicity as a risk factor for nausea during SA for CS should be considered.

Keywords: intraoperative, nausea and vomiting, caesarean section, spinal anaesthesia, ethnicity

Manuscript

Introduction

Intraoperative nausea and vomiting (IONV) causes distress to the patient and may interfere with the surgery. The incidence of IONV during spinal anaesthesia (SA) for caesarean section (CS) is dependent on the anaesthesia technique used, together with preventative and therapeutic measures employed by the anaesthetist (Balki, 2005). There is little research on the incidence of IONV during SA for CS within the South African population. In a recent study it was shown that postoperative nausea and vomiting (PONV) in Black South African (African) patients undergoing general anaesthesia (GA) is significantly lower than in the remainder of the multiethnic South African population (non-African) (Rodseth, 2010). Clinical experience suggests that the incidence of nausea and vomiting during SA for CS is low in African patients. The primary outcome of this study was thus an assessment of the incidence of nausea and vomiting, and the secondary outcome was a comparison of the incidence of these symptoms between African and non-African patients during SA for CS.

Methods

A prospective observational study was conducted at Mowbray Maternity Hospital and New Somerset Hospital, after approval had been obtained from the Human Research Ethics Committee of the University of Cape Town. Healthy, term patients undergoing elective SA for CS during daylight hours, were studied, during the period August 2014 - February 2015. Exclusion criteria were three previous caesarean sections, previous major abdominal surgery, anti-emetics administered prior to CS, preoperative or intraoperative systemic opioid administration, known adverse reaction to metoclopramide, conversion to general anaesthesia, preeclampsia or other causes of severe hypertension, and the use of ergometrine.

Cefazolin (1-2 g) or, if the patient was allergic to penicillin, clindamycin (600 mg), was given over a minimum time period of five minutes, and at least ten minutes prior to induction of SA. If nausea or vomiting occurred as a result of administration, it was noted separately. Preoperatively, systolic blood pressure (SBP) was measured twice with the patient in the left lateral position, and the mean value calculated. The target for treatment of hypotension was 80% of this value. The procedure included the standard practice for SA for CS at the University of Cape Town, i.e. 2 mL intrathecal hyperbaric bupivacaine plus 10 µg fentanyl, 15 mL/kg crystalloid co-load via 18G cannula. The patient was positioned supine, with 20 degrees left lateral tilt. Dermatomal block height was assessed by temperature sensitivity as assessed by ethyl chloride spray. Blood

pressure was measured every minute for the entire procedure. The initial vasopressor used was phenylephrine 50 µg. A 30% decrease in SBP was treated with 100 µg of phenylephrine. This was repeated every minute until the target SBP was achieved (within 20% of baseline value). If the heart rate decreased to less than 55 beats per minute in association with hypotension (SBP decreased by 30% from baseline), ephedrine 10 mg was administered, followed by atropine 0.25-0.5 mg if bradycardia persisted. Ephedrine was also administered if there was a poor response to two consecutive doses of phenylephrine. Nausea and vomiting were treated with intravenous phenylephrine to restore blood pressure, and metoclopramide 10 mg. Oxytocin 3 IU was given over 60 seconds, after clamping of the cord.

The following data was collected by the attending anaesthetist: patient age, booking weight, gestational age, gravity, parity, and number of previous caesarean sections. Also recorded was the lowest systolic blood pressure (SBP) during the procedure, the highest level of the spinal block, total fluid volume administered, and the total dose of phenylephrine, ephedrine, atropine and metoclopramide. The total blood loss was estimated by measurement in a graded suction bottle and inspection of swabs. Whether or not the uterus was exteriorised was also noted. Episodes of nausea and vomiting were noted, and whether these events occurred prior to, or after, delivery. Other adverse events, as well as duration of surgery, were recorded at completion of the case.

Interviews were conducted after the operation and consent requested at this time for participation in the study. This was done in order to exclude potential suggestion bias introduced by explaining the study objectives prior to surgery. The following direct questions were asked: “What race do you classify yourself?”, “Have you ever experienced motion sickness or post-operative nausea and vomiting?”, and “Did you experience nausea during this operation?”

Statistical analysis

Sample size calculation for the primary outcome was based upon a clinical estimate of an incidence of nausea and/or vomiting of 25% overall, with an absolute accuracy of +/- 6%. This required 184 patients. Sub-group analysis was planned a priori. With an expected proportion of African/Non-African patients of 66/33%, and an expected incidence of nausea and/or vomiting of 15% amongst Black Africans and 35% in Non-Africans, allowing for 90% power and $p<0.05$, 156 Black African- and 78 Non-African patients were required. In the time available for the conduction of the audit, 143 Black African- and 112 Non-African parturients were studied.

Individual categorical variables were summarised with frequency and percentage frequency distributions and illustrated using bar charts. Continuous variables were summarised using means and standard deviations or medians and interquartile ranges. Associations between categorical variables were summarised in two-way frequency tables and tested for statistical significance using a Chi-square test. Observed p-values are quoted. P-values smaller than 0.05 were considered to be statistically significant. The joint associations between the predictor variables and the presence/absence of nausea/vomiting were modelled using a logistic regression model. The exponentiated coefficients of this model are estimated on adjusted odds ratios. Multinomial logistic regression models were used to estimate the association between predictor variables and the three-level categorical outcomes. These models are equivalent to parallel binary logistic models where the relative odds of each of the categories compared to a chosen reference category is estimated. We chose "none" as the reference category.

Results

Two hundred and fifty eight patients were recruited (146 Black South Africans and 112 multi-ethnic [Non-African] parturients). One patient was excluded from the analysis because of erroneous recruitment (3 previous caesarean sections). Patient demographic data and baseline haemodynamic values were similar in the two groups (Table I). Patient age ranged between 18 and 44 years, and all were American Society of Anaesthesiologists Class I or II.

Primary outcome – Incidence of IONV during SA for CS:

The overall incidence of nausea was 32%, with 20% occurring prior to delivery of the baby and 11% after the delivery. The overall incidence of vomiting was 7%, with 3.1% prior to delivery and 3.8% after the delivery. The combined incidence of nausea and vomiting was 33%.

Secondary outcome – between – group comparison:

There was a significant difference (p=0.004) in the incidence of nausea between African- and non-African patients 36/145 (24.8%) vs. 47/112 (42.0%), p=0.004; Odds ratio [95% CI] = 0.47 (0.27-0.82). There was also a significant difference (p=0.012) in the incidence of nausea and vomiting (combined) between African and non-African patients 38/146 (26%) vs. 48/112 (42%), p=0.012. There was no significant difference between the groups with respect to the incidence of vomiting: African patients 10/145 (6.8%) and non-African patients 8/112 (7.1%), p = 0.865.

In addition, logistic regression showed a correlation between hypotension (SBP<=70% baseline) and IONV. There was no association between IONV and baseline heart rate, incidence of smoking, history of motion sickness, or exteriorisation of the uterus (Table 2).

Discussion

This study showed an overall incidence of nausea of 32% during SA for CS. There was also a significantly lower incidence of nausea in African patients than in the Non-African group. The incidence of vomiting was low (18/258 [7%]), and not significantly different between the groups.

There are few studies measuring the incidence of intraoperative nausea and vomiting (IONV). Therefore, the incidence of IONV is often taken from the placebo groups of studies examining the effect of antiemetic preventative measures. Some review articles do quote the incidence of intraoperative nausea and vomiting (IONV) during SA for CS, but most of these have also included postoperative nausea and vomiting (PONV). Previous studies have reported varying incidences of nausea, ranging from 6,7% to 60%,[1–3] and vomiting (12% to 58%).[3,4]

Many factors, anaesthetic and non-anaesthetic, contribute to the incidence of nausea and vomiting during caesarean section. The anaesthetic risks are hypotension, the use of neuraxial- and IV opioids, and an increase in vagal activity. The non-anaesthetic factors include manipulation and exteriorisation of the uterus, vigorous movement of the patient, and the use of uterotonic agents such as oxytocin.[4]

In a review of the incidence of nausea and vomiting during SA for CS, it was suggested that hypotension, baseline heart rate, spinal dermatomal level, a history of smoking, or history of motion sickness increases the risk of nausea and vomiting, either intra- or postoperatively.[4] However, using logistic regression, we showed that heart rate, smoking and a history of motion sickness did not significantly increase this risk. It remains controversial whether exteriorisation of the uterus increases the risk of IONV.[5] We found in the present audit that although there was an increased incidence of vomiting in patients in whom the uterus was exteriorised, this was prior to delivery, and hence prior to exteriorisation of the uterus.

The two causal factors which were associated with intraoperative nausea were ethnicity and hypotension. Interestingly, as anecdotally observed by South African anaesthetists, being non-African is a risk factor for

intra-operative nausea. This is despite an increased incidence of smokers within this group – which is known to be protective for PONV.

Many studies have shown a correlation between blood pressure control and IONV. A decrease in blood pressure of >30% below baseline has been found to increase the risk of IONV to 60%.[6] The incidence of IONV increases in proportion to the percentage decrease from baseline blood pressure. Ngan Kee found the incidence of IONV to be 4%, 14%, and 40% with targets, as a percentage of baseline systolic blood pressure, of 100%, 90%, and 80% respectively.[7] Hypotension may be compounded by aortocaval compression during SA for CS, particularly if lateral tilt is not adequately applied.[8] In the present study, the odds of experiencing nausea with a minimum-recorded SBP less than 70% of baseline were 2.46 times higher than those in whom SBP was always higher than 70% of the baseline value. There was no difference in the incidence of hypotension between our two groups.

Some of the causes of IONV can be manipulated and controlled, but certain patients may be particularly susceptible. This requires early identification and possibly the use of pharmacological prophylaxis. A recent Cochrane review of interventions for prevention of nausea and vomiting in women undergoing regional anaesthesia for CS showed that many agents were effective in preventing IONV, keeping with the multifactorial pathogenesis of the condition. The best agents were 5-HT_3 antagonists, dopamine antagonists and sedatives. They also found that there was little evidence that combinations of treatments were superior to single agents.[1] These medications are not without their risks, which may include agitation, extra-pyramidal symptoms and arrhythmias.[9] In our study, we used metoclopramide 10 mg as treatment of vomiting or reported nausea. Only 7.7% of our patients received this intervention. This percentage was in keeping with the incidence of intraoperative vomiting.

It has been shown that nausea and vomiting of pregnancy is more common in Western and Asian populations than in African, Eskimo and Native Americans.[10] A Canadian study examining the racial differences in the incidence of nausea and vomiting of pregnancy showed that Asian and Black women were less likely to report these symptoms than Caucasians. This difference in the reporting of symptoms was attributed to cultural or genetic factors.[11] A study investigating racial differences in response to chemotherapy found the African American population have a lower incidence of nausea and vomiting than Caucasian patients.[12] It has been the perception amongst South African anaesthesiologists that Black South African patients have a decreased incidence in postoperative nausea and vomiting (PONV) after general anaesthesia. A prospective observational

study performed in KwaZulu /Natal (KZN) measured the incidence of PONV in patients undergoing general anaesthesia, and showed a significant difference between Black South African (African) patients (27%) as opposed to multi-ethnic (non- African) patients (45%).[13] It is postulated that the isoenzyme variation in the hepatic P-450 cytochrome system is a potential factor in the precipitation of nausea and vomiting. Patients who have a CYP2E1 poor-metaboliser phenotype may be at a greater risk for the development of PONV. This allele has not been identified in the KZN black population and this may explain the lower incidence of PONV.[14] With regard to intraoperative nausea and vomiting during SA for CS, this mechanism does not apply. Other centrally mediated mechanisms may be involved.

There are certain limitations to this study. We did not use a Visual Analogue Score (VAS) and thus the binary response of "yes" or "no" did not allow for the identification of different levels of nausea. Patient responses may also have been affected by confirmation bias. In addition, nausea is under-reported, and the absence of formally trained interpreters meant that the African patients might not have fully understood the meaning of the word nausea.

Nausea and vomiting remain unpleasant symptoms during SA for CS. We therefore regarded it as important to establish the incidence of these side effects in our population, using a standardised SA technique. The intention was to introduce interventions to reduce the incidence of IONV, and improve patient experience of the birth and bonding process. This study found the incidence of nausea and/or vomiting during SA for CS to be 33% in the South African population. Black South Africans had a significantly lower incidence of intraoperative nausea. The only other factor contributing to an increased incidence of IONV was hypotension. However, in keeping with international standards, the clinically significant incidence of nausea and/or vomiting of 33% require adjustments to our management protocol for spinal hypotension. The inclusion of ethnicity as a risk factor for nausea during SA for CS should be considered.

Table I: Patient demographic data, and relevant data pertaining to spinal anaesthesia

	African	Non- African	p-value NS- not significant
Number	146	112	
Age (years)	29.8	30.4	NS
Parity	2.6	2.9	NS
Number of previous caesarean sections	1.2	1.2	NS
Weight (kg)	83.2	79.2	NS
Smoker (y/n)	8 (5.5%)	40 (35.7%)	<0.001
History of motion sickness (y/n)	17 (11.6%)	12 (10.7%)	NS
Hypotension (% patients with SBP<=70% baseline)	65 (44%)	48 (42.9%)	NS
Baseline heart rate	89	87	NS
Exteriorisation of uterus	26 (17.8%)	9 (8%)	0.02
Duration of operation (min)	45	43	NS
Highest dermatomal level of block (mode)	T3 (C5 - T7)	T3(T1 – T7)	NS

Statistical significance was defined as $p<0.05$

Acknowledgements

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Conflict of Interests

There were no conflicts of interest

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Supporting documents

1. **Consent**
2. **Questionnaire**
3. **Ethics Approval**
4. **SAJAA Guidelines**

Consent form to participate in an audit

Incidence of intraoperative nausea and vomiting during spinal anaesthesia for caesarean section

Principle Investigator: Dr J Van Nugteren

Student : Dr Bridget Magni

UCT Department of Anaesthetics

Email: lottimac@gmail.com

Cell: 0738726902

We are doing a study to see how many women suffer of nausea and vomiting during the operation

for a baby (caesarean section). We would like to use the information on your anaesthetic chart. This

Information will be kept confidential.

This will not affect your treatment in any way.

The only question we will ask you is “Did you suffer of nausea during the operation?”

The study is completely voluntary and will not affect your hospital treatment in any way.

I hereby consent to my information to be used in this audit

Sign: _____

Name: _____

Date: _____

Questionnaire

Age: _____ Booking Weight _____ Gestational Age_____

G____ P_____ Number of Previous C/S_____

Previous history motion sickness/ PONV: Yes ☐ No ☐

Black African ☐ Coloured ☐ Indian ☐ White ☐

Smoker Yes ☐ No ☐

Baseline Heart Rate_____

Baseline Systolic Blood Pressure _____

80% of Baseline SBP_____70% of Baseline SBP_____

Total fluid volume received_____

Lowest SBP recorded_____

Total Phenylephrine used_____

Total Ephedrine used_____

Total Atropine used_____

Total Maxalon used_____

Any uterotonic used other than Oxytocin_____

Uterus: sutured in abdomen ☐ sutured outside abdomen ☐

MOST IMPORTANT!! Record N&V from induction until last suture

Nausea yes ☐ **no** ☐

pre-delivery ☐ **post-delivery** ☐

Vomiting yes ☐ **no** ☐

pre-delivery ☐ **post-delivery** ☐

Other adverse events_____

Highest block height_____

Length of operation (Induction of SA to final suture) _____

Total Blood Loss_____

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 July 2014

HREC REF: 505/2014

Dr J Van Nugteren
Anaesthesia
D23, NGSH

Dear Dr Nugteren

PROJECT TITLE: INTRAOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING ELECTIVE CAESARIAN SECTION (MMed candidate- Dr B Magni)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th July 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the MMed student, Dr B Magni is also involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

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Cite references in numerical order in the text, in superscript format (Format> Font> Click superscript). Please do not use brackets or do not use the foot note function of MS Word.

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The following are sample references:

1. Jun BC, Song SW, Park CS, Lee DH, Cho KJ, Cho JH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-dimensional reconstruction by high-resolution CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.
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