EVALUATION OF THE EFFECT OF 2.5 IU vs 5 IU OXYTOCIN ON UTERINE TONE DURING ELECTIVE CAESAREAN SECTION AT WINDHOEK HOSPITAL COMPLEX: A DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL STUDY

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT

FOR THE DEGREE OF

MASTER OF MEDICINE IN ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT

OF

THE UNIVERSITY OF NAMIBIA

BY

DR FREDRIKA NEMBALE SHIGWEDHA

200404229

OCTOBER 2022

MAIN SUPERVISOR: DR KINGSLEY U TOBI (UNAM)

ABSTRACT

Introduction: Oxytocin is routinely administered during caesarean delivery to initiate and maintain uterine tone (UT) after delivery of the baby. It reduces blood loss thus preventing postpartum haemorrhage (PPH). However higher doses of oxytocin are associated with unwanted side effects namely; cardiovascular effects, headache as well as nausea and vomiting. However, the optimal dose of oxytocin at caesarean delivery remains ambiguous among various official bodies. This study compared the effect of two doses of oxytocin 2.5 IU vs 5 IU on uterine tone, haemodynamic changes, blood loss and side effects.

Methodology: A double-blinded, randomized controlled clinical study was conducted at Windhoek Teaching Hospitals Complex. Eighty (80) parturients undergoing elective caesarean section under spinal anaesthesia received an intravenous bolus of either 2.5 IU (n=40) or 5 IU (n=40) of oxytocin after delivery followed by an infusion of 5 IU/hr. Uterine tone, haemodynamic changes, side effects and blood loss were compared between the two groups. The two groups were statistically compared using a two-sided, independent samples *t*-test with a P-value set at 0.05 (5%) critical level of significance using the per-protocol analysis.

Results: The two groups were comparable in terms of demographic characteristics. Parturients in both study groups had adequate uterine tone at 3 minutes with a median (SD) score of 3.28(0.51) for the 2.5 IU group and 3.20(0.56) for the 5 IU group. A rapid increase in heart rate (HR) was seen in the 5 IU group with a mean increase of 17(17) and 12(16) beats/min at 1 min and 2 min with a p-value of 0.000 and 0.005 respectively. Higher incidence of nausea, headache and chest pain (40%, 25%, 15%) were noted in the

5 IU group compared to (15%, 2.5%, 0%) in the 2.5 group. Blood loss did not differ among the two groups.

Conclusion: 2.5 IU of oxytocin bolus was compared and non-inferior to 5 IU oxytocin bolus in initiating and maintaining adequate uterine tone and it was associated with fewer haemodynamic changes and other adverse effects.

Keywords: oxytocin, uterine tone, caesarean section, spinal anaesthesia,

Table of Contents

LIST OF ABBREVIATIONS

ASA – American Society of Anesthesiologists

ACOG – American College of Obstetricians and Gynecologists

BP – Blood pressure

BMI – Body Mass Index

CEMD – Confidential Enquiries into Maternal Deaths

CCA- Complete Case Analysis

C/S – Caesarean Section

CSF – Cerebrospinal fluid

COX-2 – Cyclo-oxygenase 2 enzymes

℃ – Degree Celsius

DBP – Diastolic blood pressure

FIGO – International Federation of Obstetricians and Gynecologists

EBL – Estimated blood loss

ECG – Electrocardiography

FBC –Full Blood Count

G – Gauge

GPCR – G-protein coupled receptors

GA –General Anaesthesia

Hb – Haemoglobin (g/dl)

I.U. – International unit

IM – Intra-muscular

IV – Intravenous

IP_3 – Inositol 1,4,5 triphosphate

ICM – International Confederation of Midwives

MAP – Mean Arterial Pressure

mmHg – millimetre Mercury

ml – millilitre

mg – milligram

mcg – microgram

MAR- Missing at Random

MCAR- Missing Completely at Random

MNAR- Missing Not at Random

MLCK – Myosin light chain kinase

NIBP – Non-invasive Blood Pressure

NCCEMD – National Committee for Confidential Enquiries into Maternal Deaths in South Africa

NICE – National Institute for Health Care Excellence

PPH – Postpartum Haemorrhage

PG – Prostaglandins

PGE_2 – Prostanglandins E_2

PGF_2 – Prostanglandins F_2

PP – Per-Protocol

RNA – Ribonucleic Acid

RR – Respiratory rate

SBP – Systolic blood pressure

SpO_2 –Peripheral oxygen saturation of blood

SD – Standard Deviation

SPSS – Statistical Product and Service Solutions

WHO – World Health Organization

UK – United Kingdom

LIST OF TABLES **Pages**

LIST OF FIGURES/GRAPHS **Pages**

LIST OF APPENDICES **Pages**

DEDICATION

I dedicate this thesis to my late father, Kristof Namupala Shigwedha

(31/08/1923- 08/06/2008)

Though you never got to see my progress in my medical profession, I know your spirit is watching over me. May your soul continue to rest in peace.

ACKNOWLEDGEMENTS

Firstly, I would like to express my gratitude to the Almighty Father who brought me this far. My sincere and exceptional gratitude goes to my family (my loving husband Salomon Namupolo, our lovely children Tristan and Thea), to my siblings and friends for their understanding, support and love throughout this program. I love you guys.

I wish to extend my deepest gratitude to my supervisor Dr Kingsley U.Tobi for his sustained guidance and critical review throughout the process of executing this research.
I am grateful to Tinashe Madziwanzira for her assistance with statistical analysis.

To all the Medical Officers and Registrars in the department of Anaesthesia at Windhoek Central hospital and Katutura Intermediate hospital, thank you all for making this study possible and for all your effort throughout the study period.

To all the research participants/respondents, this research would not have been realized without your consent, and your involvement will contribute to the development of medical knowledge.
May God bless you all.

DECLARATION

I, Fredrika Nembale Shigwedha, hereby declare that this study is my own work and it's a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any institution.

Fredrika Nembale Shigwedha		October 2022
Name of Student	Signature	Date

CHAPTER 1: INTRODUCTION

1.1 Background

According to the World Health Organization (WHO)[1], Postpartum Haemorrhage (PPH) is the leading cause of maternal morbidity and mortality in low-income countries accounting for 10-30%. It contributes to about 25% of maternal mortality globally[1, 2]. Postpartum haemorrhage can be defined as blood loss of more than 500 ml after normal vertex delivery and more than 1000 ml after Caesarean delivery occurring within 24 hours of delivery[2]. It was responsible for more than a quarter of the estimated 303 000 maternal deaths which occurred globally in 2015[3].

Uterine atony is the leading cause of PPH accounting for 80% of postpartum hysterectomy and blood transfusion[2, 4]. Other causes such as genital trauma, retained placenta tissue or bleeding disorder account for the remaining percentages[3]. Caesarean section is one of the commonly performed major operations in obstetrics. The rate of caesarean delivery has been on the increase in developing countries including Namibia. Minimizing the amount of blood loss during caesarean delivery has great benefits in decreasing postoperative morbidity and risks associated with blood transfusion[4]. Operative morbidity includes haemorrhage, anaemia, risk of blood transfusion, hysterectomy and in severe cases it can result in maternal death[5]. The routine use of oxytocin correlates with a significant reduction in the incidence of postpartum haemorrhage[4].

Oxytocin is the first-line agent used in the prevention and management of established PPH associated with uterine atony. It is routinely administered intravenously or intramuscularly

after delivery to initiate and maintain uterine tone after placental delivery and to reduce blood loss[1,6].

However, the use of oxytocin is not without adverse effects. Maternal morbidity and mortality have been reported following oxytocin use[7]. Its potential to produce adverse effects has featured in the report of Confidential Enquiries into Maternal Death (CEMD) in the United Kingdom (UK) and in the National Committee for Confidential Enquiries into Maternal Deaths in South Africa (NCCEMD)[8]. Awareness of these deaths resulted in its dose reduction in the UK to an IV bolus of 5 IU.[9] The WHO in 2018 recommended oxytocin 10 IU intramuscular (i.m) or intravenously (i.v.) as the uterotonic agent of choice for PPH prevention[3]. The bolus dose is noted to be associated with significantly more cardiovascular side effects than infusion route[7].

At our institutions, Windhoek Central Hospital and Katutura Intermediate Hospital (Windhoek Teaching Hospital Complex), the dose of oxytocin used for both elective and emergency caesarean sections range from 2.5 to 10 IU. The doses 5 and 10 IU of oxytocin are based on the recommendations of both the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE)[6].

The E_{D90} of oxytocin at elective caesarean section was calculated to be as low as 0.35 IU and after labour as 3 IU. A study by Butwick[10] and his colleagues demonstrated that doses as low as 0.35 IU to 3 IU bolus produced an adequate uterine tone with minimal side effects. Sartain[11] and his coworkers compared 2 vs 5 IU bolus of oxytocin during elective Caesarean delivery. The authors found that there were fewer haemodynamic changes and

nausea in the 2 IU group compared to the 5 IU group. This study demonstrated that doses less than 5 IU can be used to provide adequate uterine tone with minimal side effects.

1.2 Statement of Problem

At Windhoek Hospital Complex (WHC), the dose of oxytocin administered during elective Caesarean section is highly variable ranging from 2.5 IU to 10 IU. Rapid administration and increased dose of oxytocin can result in haemodynamic instability, cardiovascular collapse and even death[4]. Available literature has shown that doses larger than 3 IU of bolus oxytocin are associated with adverse effects such as hypotension, tachycardia, ST-segment changes on electrocardiography (ECG), chest pain, headache, nausea and vomiting.[2, 6] The magnitude of these adverse effects are dose-dependent and generally worse in patients with previous cardiovascular compromise.

There has been no study on the adequate doses of oxytocin carried out in the Namibian population. In addition, currently, there are no guidelines on the use of oxytocin during the caesarean section at our institution. In this study, 2.5 IU oxytocin was compared with 5 IU oxytocin in terms of uterine tone and the haemodynamic adverse effects. With the findings of this study, it is hoped that a guideline on the minimal effective doses of oxytocin with fewer side effects during caesarean sections will be established at our institutions.

1.3 Research Question

1. Is 2.5 IU of oxytocin effective in providing adequate uterine tone (UT) as compared to 5 IU of oxytocin following elective Caesarean section under spinal anaesthesia at Windhoek Hospital Complex (WHC)?
2. Does 2.5 IU of oxytocin produce less adverse effects as compared to 5 IU oxytocin following Caesarean delivery under spinal anaesthesia?

1.4 Objectives

Primary Objectives

- To determine whether 2.5 IU bolus of oxytocin will provide adequate uterine tone as compared to 5 IU of oxytocin following elective Caesarean section.

Secondary Objectives:

Equivalence objectives

- To determine the degree of uterine contraction with a bolus dose of 2.5 and 5 IU oxytocin within 20 minutes of administration.
- To determine the incidence of request for rescue doses of oxytocin with the respective doses.

Safety objectives

- To compare the incidence of adverse effects of oxytocin such as hypotension, tachycardia, chest pain or discomfort, nausea and vomiting in the two groups.
- To determine the blood loss with each bolus dose and the incidence of postpartum haemorrhage.

1.5 Hypothesis

Null hypothesis

There is no statistically significant difference between 2.5 vs 5 IU oxytocin on uterine tone, blood loss and adverse effects.

Alternative hypothesis

There is a statistically significant difference between 2.5 vs 5 IU oxytocin on uterine tone, adverse effects and blood loss.

1.6 Significance/Justification of the study

Different guidelines exist on the doses of oxytocin administered during Caesarean delivery, with dosages ranging from as low as 0.35 IU to 10 IU bolus. The recommended dose of oxytocin, timing, as well as the rate of administration from major obstetric societies/bodies vary widely ranging from as little as 1 IU to as high as 10 IU bolus of oxytocin[4,6].

Of recent, the 2019 International Guidelines on the use of uterotonic suggest a dose of 1 IU after delivery during elective cesarean delivery[10]. No studies have been done in the Namibian population to determine the minimum effective dose of oxytocin.

At our institution, most clinicians use different doses of oxytocin ranging from 2.5 to 10 IU. The 5 and 10 IU are based on the recommendations of the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE)[6].

This study was conducted to determine if a reduced dose of 2.5 IU will be effective in initiating and maintaining uterine tone during elective Caesarean delivery at our institutions. The dose of 2.5 vs 5 IU was decided based on the current practice and the

recent International Consensus guidelines on the use of uterotonics[6]. The results of this study would help to contribute to the formulation of guidelines regarding the effective dose of oxytocin at our institution and in Namibia as a whole. This might also help to reduce costs in a resource-limited setting like ours.

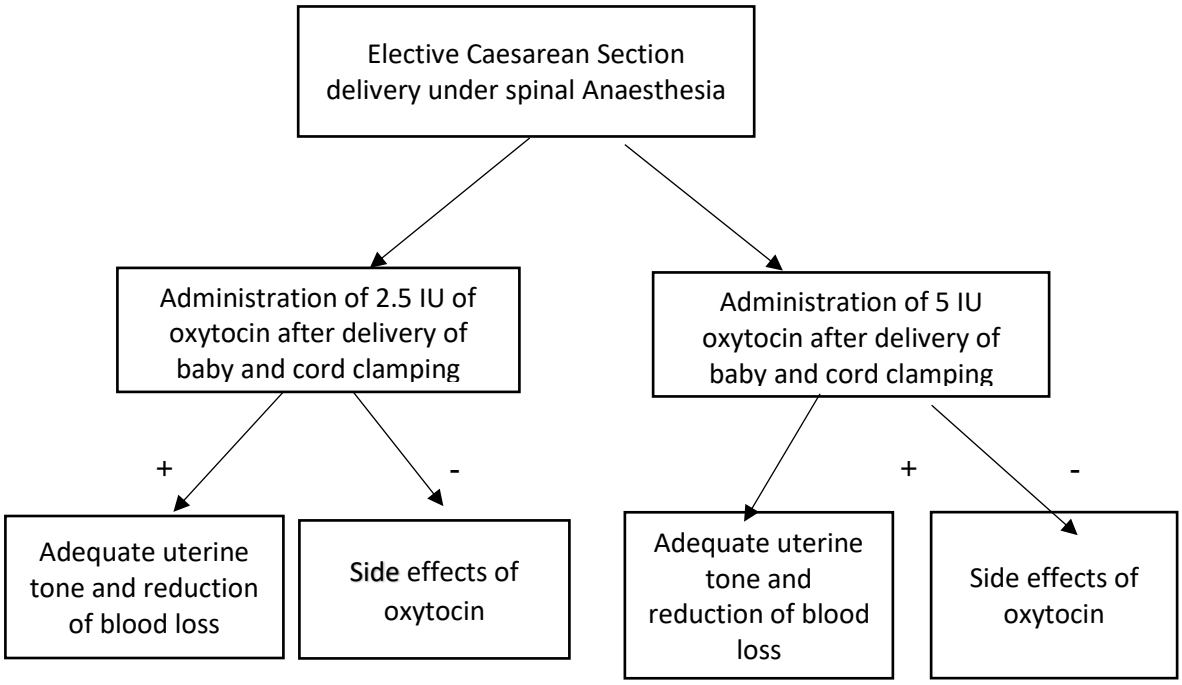
1.7 Limitation and Delimitation of the study

1. Assessment of the adequacy of uterine tone is subjective as it depends on the surgeon performing the caesarean section and their experience
2. Surgical techniques have a significant influence on the uterine tone and blood loss
3. Assessment of intraoperative blood loss is subjective, and this might lead to incorrect estimation of PPH
4. Different brands of oxytocin were used, depending on the availability and supply chain of oxytocin within the hospital complex.

Delimitation

1. Patients who received rescue doses more than once will be excluded from the study as the Per-Protocol (PP) principle was used. By adopting the per-protocol (PP) analysis only the effect of receiving the assigned treatment as specified in the protocol conditions is investigated.
2. The most experienced surgeon at the surgery was asked to assess the adequacy of uterine tone

1.8 Theoretical framework



CHAPTER 2: LITERATURE REVIEW

2.1 Pharmacology of Oxytocin

Endogenous oxytocin is a neuro-hypophysial hormone secreted by the posterior pituitary gland. It's a nonapeptide hormone, which is synthesized in the paraventricular and supraoptic nucleus of the hypothalamus[12]. It is transported in secretory granules to the posterior pituitary gland, where it is stored for subsequent release[2,13]. It is composed of nine amino acids containing a cyclic hexapeptide ring and an acyclic tripeptide tail[14]. Oxytocin is released in intermittent bursts determined by neurosensory stimuli such as sucking the nipple, stimulation of inferior genital tract and cervical dilatation[13].

The onset of action of oxytocin is immediate after intravenous injection and 3-5 minutes after intramuscular injection. It has a short plasma half-life of 3-12 minutes and is commonly administered as an IV bolus followed by an infusion to maintain adequate uterine tone[12]. It can also be administered as an intramuscular injection. It is known to be metabolised primarily in the liver but also by the enzymatic action of aminopeptidases in plasma or other organs such as kidneys[14]. The enzyme oxytocinase is largely responsible for the metabolism and regulation of oxytocin in pregnancy. Oxytocin requires refrigerated transport and storage at 2-8 ℃. It is relatively inexpensive and widely available[15].

2.2 Mechanism of Action

The peripheral action of oxytocin is mediated by oxytocin receptors that belong to the rhodopsin-type group of G- protein-coupled receptors (GPCR), and are expressed in the

myometrial cells[12]. Oxytocin exerts its effects by binding to the GCPR on the uterine myocytes resulting in the generation of 1, 2 diacylglycerols and inositol 1, 4, 5-triphosphate (IP3) via activation of phospholipase C. Inositol 1, 4, 5-triphosphate (IP3) triggers the release of calcium from the sarcoplasmic reticulum, exerting a contracting effect on the uterus via stimulation of Ca-dependent calmodulin and activation of myosin light chain kinase (MLCK) [13, 16, 17]. Oxytocin also increases intracellular calcium (Ca) and hence contraction through Ca entry via L-type Ca^{2+} channels and decreases calcium efflux. Calcium ions bind to calmodulin and activate myosin light chain kinase, which is central to the mechanism of uterine smooth muscles. The concentration of myometrial oxytocin receptors and myometrial junctions increases with advancing gestational age, increasing the sensitivity to oxytocin[17,18].

Oxytocin has numerous physiological effects. Recent studies have shown oxytocin to act as an inflammatory mediator, playing a central role in the inflammatory cascade, leading to labour onset. It also causes prostaglandins (PG) production, particularly PGE_2 and PGF_2 in other gestational tissue via upregulation of cyclo-oxygenase 2 enzymes (COX-2). This local release of prostaglandins particularly PGF_2 will produce a feedback mechanism to facilitate uterine contraction via similar mechanisms[17,18]. Oxytocin has various roles in other organs systems. It is well known for its cardiovascular regulation, sexual and maternal behaviour, memory and regulation of food and drinks intake[18].

2.3 Oxytocin Receptor desensitization

Oxytocin receptors undergo rapid molecular desensitisation due to homologous stimulation. This process involves phosphorylation, uncoupling, sequestration and

internalization of the receptors, ultimately leading to degradation by lysosomes and receptors recycling into cell membrane[19]. This phenomenon has been shown to occur both in vivo and in vitro and has significant clinical implications[15]. Desensitization occurs following continuous and prolonged exposure to oxytocin. Prolonged exposure to oxytocin results in down-regulation of oxytocin receptors and a decrease in oxytocin receptor messenger RNA as well as a reduction in the numbers of oxytocin receptors[16].

Desensitisation can occur in vitro or in vivo. Once the process of desensitisation has begun, there is a decrease in the response of myocytes to additional exogenous oxytocin, suggesting both structural and functional alterations of the oxytocin receptors. The clinical consequence of this is the higher incidence of uterine atony after prolonged augmented labours. The oxytocin receptor desensitization phenomenon is highly clinically relevant as it is evident in those women with failed induction, those who fail to progress during labour despite oxytocin augmentation and those with poor uterine responsiveness to oxytocin after delivery[15,16, 19].

2.4 Adverse Effects

Recent studies suggest that adverse effects of oxytocin are related to the dose administered, rate of administration, presence of comorbidities, volume status of the patient and whether repeated doses are given[6]. The mechanisms of these effects are not well known although some authors have attributed it to the preservative chlorobutamol[9, 16]. There is evidence that adverse effects may be reduced by alterations in the dose and the rate of administration, without compromising the effectiveness[6].

The adverse effects of oxytocin include cardiovascular instability (hypotension, tachycardia, myocardial ischaemia and arrhythmia), nausea and vomiting, headache as well as flushing [2,10,16]. Transient electrocardiogram (ECG) changes such as ST-segment and T- waves abnormalities with subjective symptoms such as chest discomfort and pain have been described following higher doses of oxytocin during caesarean delivery[16]. Hypotension is predominantly caused by transient relaxation of the vascular smooth muscles, probably via calcium-dependent stimulation of the nitric oxide pathway. Oxytocin also causes a release of atrial and brain natriuretic peptides[12, 18].

In most severe cases, it has been reported to cause cardiovascular collapse and even death. Oxytocin has about 0.5% to 1.0% of antidiuretic effects and it can cause water retention with subsequent pulmonary oedema and hyponatraemia due to its structural analogy with anti-diuretic hormone[8,16].

2.5 Optimal dosing for oxytocin

The optimal dose of oxytocin during caesarean delivery remains ambiguous among various official bodies with doses ranging from 5-10 IU bolus[6]. Carvalho et al[20]. in a report in 2004 conducted a dose-finding study of oxytocin. They recruited 40 parturients using an up-down sequential allocation design to estimate the ED_{90} of oxytocin. Their findings showed that doses as low as 0.35 IU (95%CI 0.2-0.5) bolus provided adequate uterine tone in 90% of women at three (3) minutes with minimal side effects. This dose is far less than the conventional dose of 5 to 10 IU. However, their sample size was small, with only 40 parturients and the study was single-blinded with the likelihood of bias.

Sarna et al[21] studied the response to different doses of oxytocin, 5, 10, 15 and 20 IU in 40 patients (10 patients in each group). The authors observed that there was no difference in uterine tone among the four groups and there was also no difference in estimated blood loss. However, they did not study doses lower than 5 IU and there were no records of adverse effects among the study groups. Their sample size was also small.

Butwick and colleagues[10] on the other hand, randomized seventy-five (75) patients undergoing elective caesarean section under spinal anaesthesia to receive a placebo or to one of the four bolus doses (0.5, 1, 3 or 5 IU). They demonstrated that adequate uterine tone can be achieved with doses as low as 0.5- 3 IU. Adverse effects were noted to be more in the 5 IU group than in the lower dosage groups. There was no difference in terms of blood loss among the study groups. Despite their findings, one obvious limitation was a small sample size. Furthermore, factors such as parity and number of previous Caesarean deliveries which are also determinants of uterine tone following Caesarean which were not accounted for in their study.

In a similar study, Sartain and co-workers [11] compared the efficacy of 2 vs 5 IU oxytocin during elective Caesarean delivery in 80 parturients. They demonstrated no difference in blood loss, uterine tone or request for additional uterotonic drugs between the two groups. However, they observed more haemodynamic changes in the 5 IU group compared to the 2 IU group.

In another study, Thomas et al[22] demonstrated the haemodynamic effects of 5 IU oxytocin given as a bolus or as an infusion over five minutes at elective Caesarean delivery in 30

parturients. The oxytocin bolus resulted in a greater increase in heart rate and a drop in blood pressure. However, there was no difference in terms of blood loss between the two groups. Despite this, the sample size was too small to show the statistical significance and the study was single-blinded.

From these studies, it is clear that the dose of oxytocin remains ambiguous among clinicians. There is wide variation in the use of uterotonics at caesarean section including choice of drug (1st line and 2nd line uterotonics), the timing of administration, dose, route, aspect of administration and maintenance regimen[6]. Various official bodies have different doses of oxytocin during caesarean delivery. The WHO guidelines of 2018, and the American College of Obstetricians and Gynaecologists (ACOG) practice bulletin of 2017, recommend prophylactic oxytocin dose of 10 IU bolus or intramuscular injection after caesarean delivery[3,6].

In a joint statement, the International Federation of Gynecology and Obstetrics (FIGO) and the International Confederation of Midwives (ICM) also recommend oxytocin 10 IU intravenous at all birth as the uterotonic agent of choice for the prevention and treatment of PPH[15]. The National Institute for Health Care Excellence (NICE) and the French College of Obstetricians and Gynaecologists in collaboration with the French Society of Anaesthesiology and Intensive Care of 2018 recommend 5-10 IU of oxytocin[6]. From all these guidelines, it is clear that a consensus guideline needs to be adopted to have a universal dose of oxytocin.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Study design

It was a randomized double-blinded clinical study

3.2 Study site

The study was conducted at Windhoek Central Hospital and Katutura Intermediate Hospital. Each hospital has a maternity theatre which is run on a 24 hours basis. Windhoek Central Hospital has three days in a week dedicated for elective caesarean section while Katutura Intermediate Hospital has two days. The study was conducted over five (5) months, from March 2021 to July 2021.

3.3 Study population

Inclusion Criteria:

Parturients who met the American Society of Anaesthesiology (ASA) class II, between the ages of 18 and 45 with singleton pregnancies, who completed thirty-seven (37) weeks of gestation were recruited. Parturients were recruited via the labour ward after giving verbal or written informed consent.

Exclusion Criteria:

Parturients at risk of PPH were excluded. This includes

- Abnormal placentation- Praevia, accrete, pecreta, abruptio
- Multiple gestations
- Grand multipara
- Uterine fibroids
- History of uterine atony or previous PPH
- Bleeding disorders and use of anticoagulants

- Significant cardiac, liver, renal and endocrine disease
- Previous C/S more than three times
- Allergy to oxytocin
- Patient refusal

3.4 Sample size estimation/calculation

The sample calculation of this study was based on a comparable study's change in heart rate variables which were retrieved via non-invasive monitoring. The primary outcome in a similar study by Sartain et al was the maximum change in HR after oxytocin administration as the changes in HR were considered more reliable than changes in mean arterial pressure (MAP) when using non-invasive monitoring.

Allen[23], states that a sample size calculation with the intent of comparing means μ_1 and μ_2 independent groups usually begins by assuming

- Normal distributions of variable
- Homogeneous variances
- Equal sample sizes
- And a 2-sided test

The sampling distribution of change in heart rate will be approximately normally distributed if the sample size $n \geq 30$ and since the samples are taken from the same population, it is justified to assume homogeneous variances and the sample sizes will be of equal size.

It is known from a published study by Thomas et al[20] that the HR difference between the groups was 7 beats min^{-1}, with a standard deviation of 11 beats min^{-1} and using

conventional values of the level of statistical significance α = 0.05 and probability of making type II error

β = 0.20 as according to Allen[23].

The sample size formula that would result in a sufficient number of 'subjects' to keep α and β at an acceptably low level without making the study unnecessarily large is given by the formulae below according to Sakpal[24].

$$n = \frac{2SD^2 * (Z_{\alpha/2} + Z_{\beta})^2}{D^2}$$

where

- n = sample size required in each group
- The significance level is set at $Z_{\alpha 2}$= Z(0.05)= 1.96
- Power (Z_{β}) of 80% = 0.84
- Standard deviation of (SD)= 11
- Difference (D) of 7.0

- The initial sample size per group $N = \frac{2SD^2 * (Z_{\alpha} + Z_{\beta})^2}{D^2}$= 40. The minimum sample size in each arm was calculated to be 40 patients, giving a total of 80 for the two groups.
- Adding a 10% attrition ratio will give a total of 88, with 44 patients in each arm.

In summary, a sample size of 80 subjects (40 subjects in each arm), is sufficient to detect a clinically important difference of 7 beats min^{-1} between groups in change in heart rate assuming a standard deviation of 11 beats min^{-1} using a two-tailed t-test of

difference between means with 80% power and a 5% level of significance. Considering a dropout rate of 10% the sample size required was 88 (44 per group).

3.5 Randomization and Blinding

Patients who met the inclusion criteria were approached in the maternity unit a day before surgery or on the day of surgery. They were randomized into two groups in a 1:1 ratio. Randomization was achieved by asking patients to blindly pick ballot papers with numbers written on them in an opaque envelope. This was carried out by the principal investigator or a trained anaesthesia resident for consecutive sets of twenty until the sample size was attained. Patients who picked **even** numbers received 2.5 IU of oxytocin (group A), while those who picked **odd** numbers received 5 IU of oxytocin as a bolus (group B). The dose of oxytocin was prepared by the principal investigator to a total volume of 2 millilitres (ml). The syringes were stored in the fridge. Both the anaesthetist and the obstetrician were blinded to the oxytocin dose.

3.6 Anaesthesia and procedure

Anaesthesia was standardized in all participants. Verbal or written informed consent was obtained from each participant before participation in the study. A detailed preoperative assessment of each patient was conducted the night before surgery or on the morning of surgery to ascertain fitness for surgery and anaesthesia. Patients were fasted according to the ASA fasting guideline, for six hours before the procedure for solid with exception of clear fluids that could be allowed for two hours before the procedure. The routine investigations which included full blood count (FBC), electrolytes, urea and creatinine

were ordered for each parturient. A group and screen for blood were done for all participants.

Parturients were categorized into ASA physical status and any ASA physical status greater than class 2 were excluded from the study. Participants were premedicated with metoclopramide 10mg and ranitidine 50 mg per *os* two hours before surgery. A urinary catheter was inserted and two (2X) 18 G intravenous cannulae were sited before coming to the theatre.

Anaesthetic machine, auxiliary equipment and suction machine were checked for availability and functionality before starting anaesthesia. General anaesthesia (GA) cart was also checked in case the need for GA arose. Emergency drugs (adrenaline, atropine, ephedrine, phenylephrine, naloxone) were also kept within reach.

Patients were positioned sitting on a theatre bed with their legs resting on a chair. ASA standard monitors with non-invasive blood pressure (NIBP), five lead ECG and pulse oximeter were applied. Baseline vital signs namely; heart rate, non-invasive blood pressure, respiratory rate, and oxygen saturation were recorded using a GE-Datex Ohmeda CARESCAPE monitor B650. Prophylactic antibiotic with cefuroxime 1.5 g was given intravenously before placing the spinal. Intravenous fluid with crystalloid either 0.9% saline or Ringer Lactate was commenced and the monitor was set to record vital signs every minute after citing the spinal.

Spinal anaesthesia was induced under strict aseptic technique with the patient in sitting position; hip and knee flexed knee level above the hip with legs resting on a chair and elbows placed on the ipsilateral thigh. Skin preparation was done with 0.5% chlorhexidine with alcohol. The L_3/ L_4 and L_4/L_5 interspaces were located and the skin and subcutaneous tissues were infiltrated with 2ml of 2% lignocaine using a 23 G (0.60x25mm) hypodermic needle. A 25G (0.53x88mm) Whitacre pencil-point spinal needle was inserted via a midline approach into the subarachnoid space evidenced by the appearance of free flow and clear cerebrospinal fluid (CSF) at the spinal needle hub. Hyperbaric bupivacaine 10 mg (2ml of 0.5%) with fentanyl 10μg was injected into the subarachnoid space. After injection of the local anaesthesia agents, the patient was gently returned to the supine position with a left uterine tilt of 15° with the head and shoulder supported with a soft pillow to prevent the excessive rostral spread of the local anaesthetic. Fluid co-loading with 500 ml of crystalloid either Ringer Lactate or 0.9% saline was given during placement of the spinal.

Sensory level was assessed using temperature sensation using an ice pack to achieve a sensory level of T4 to T6 before the commencement of surgery. In addition, the obstetrician was asked to test for pain with toothed forceps in the umbilical region before the surgical incision. After establishing the anaesthetic sensory level, a WHO checklist was conducted and surgery was allowed to commence. Spinal-induced hypotension was treated with phenylephrine boluses of 50-200 mcg or ephedrine 5mg -10 mg boluses.

Oxytocin 2.5 or 5 IU was administered immediately after delivery of the baby and cord clamping over 10-30 seconds. Group A (n=49) patients received 2.5 IU oxytocin and group B (n=46) patients received 5 IU oxytocin. At three minutes after the bolus of oxytocin, patients were placed on an oxytocin infusion with 20 IU oxytocin in 1 litre of crystalloids at 125ml/hr, (2.5IU/hr). The blood pressure and heart rate were noted before the oxytocin dose was given and every minute after oxytocin was given for 20 minutes with more attention to the first three minutes. Hypotension was treated with phenylephrine boluses of 50-200 mcg or ephedrine 5mg -10 mg boluses.

3.7 Measurement of Variables

3.7.1 Uterine tone

The uterine tone was assessed by the blinded obstetrician as either adequate, partial or inadequate. It was assessed by using a five (5) point Likert scale with 0= floppy (atonic), 1= partial contracted and not adequate, 2= adequate, 3= well contracted and 4= very well contracted (stony hard). The uterine tone was assessed immediately after delivery of the placenta every minute for twenty minutes. A rescue dose of 3 IU bolus oxytocin was available for those with less than 2 points on the Likert scale.

3.7.2 Haemodynamic changes and side effects

Hypotension was defined as a decrease in baseline mean arterial blood pressure of more than 10% within 5 minutes of oxytocin administration or any systolic blood pressure less than 100 mmHg. Each episode of hypotension was treated with phenylephrine 50-200mcg

or ephedrine 5-10 mg bolus. Blood pressure reading and heart rate were recorded every minute for 20 minutes after oxytocin administration.

Tachycardia was defined as an increase in maternal heart rate of more than 120 beats/min or more than a 10% increase of baseline value. Participants who experienced chest pain were given supplemental oxygen via facemask. Also, in cases where there was bradycardia (heart rate less than 60 beats per minute), 0.02mg/ kg of IV atropine was administered as well.

The subjects were asked how they were feeling immediately after the bolus of oxytocin specifically about nausea, vomiting, chest pain and headache. Those who experienced any of these symptoms were treated accordingly.

3.7.3 Blood loss

Intraoperative blood loss was estimated by noting surgical swabs soaked with blood and suction bottles volume during the procedure. A difference between pre-operative haemoglobin level and the postoperative haemoglobin level after 24 hours was also used to accurately calculate blood loss.

3.8 Data Collection and Analysis

Data were collected in a pretested questionnaire by the Medical Officers and Registrars in the department of Anaesthesia. Data that were extracted include the age, gravidity and parity, gestational age in weeks, indication for C/S, previous C/S, previous PPH and uterine atony, baseline vitals before oxytocin administration, vitals after oxytocin

administration, uterine tone, blood loss, oxytocin rescue doses, nausea, vomiting, headache and presence of chest pain.

Data collected were entered and verified in Microsoft Excel (2019) and data analysis was performed using SPSS version 23 (SPSS for windows 21.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the participants' socio-demographic, clinical characteristics as numbers, proportion, mean and standard deviation. Results were presented in form of tables and figures. The two groups were statistically compared using a two-sided, independent samples *t*-test with a P-value set at 0.05 (5%) critical level of significance using the per-protocol analysis principle. By adopting the per-protocol (PP) analysis only the effect of receiving the assigned treatment as specified in the protocol conditions is investigated[25]. Data were analysed by means of complete case analysis (CCA), which is an analysis restricted to individuals with complete information on all variables[26]. It has been noted that CCA is not biased by missing data when the data are Missing Completely at Random (MCAR), because the complete cases are representative of those with missing data[26,27]. Contrary to widespread belief that MCAR is required for CCA to be unbiased, CCA can give unbiased results in situations where data are Missing at Random (MAR) or even Missing Not at Random (MNAR)[28,29]

3.9 ETHICAL CONSIDERATION AND CLEARANCE

Ethical clearance was sought and obtained from the Research Ethics Committees of the University of Namibia and of the Ministry of Health and Social Services. Permission from the two hospitals, Windhoek Central hospital and Katutura Intermediate hospital was obtained before commencing with the study. Informed written or verbal consent was

obtained from the participants before surgery. Those who wished not to participate or to withdraw from the study at any given point were allowed to do so without any loss of benefits. This did not result in withdrawal of any treatment the patient may have required during the procedure. Patients autonomy was respected. The parturients participation was purely voluntary and there was no financial gain from the study.

3.10 DISSEMINATION OF RESULTS

Results will be disseminated to the following units:

1. Department of Anaesthesiology at the two hospitals
2. Department of Obstetrics and Gynecology at the two hospitals
3. University of Namibia School of Medicine
4. Ministry of Health and Social Services
5. To International peer-reviewed health journals for publication.

CHAPTER 4: RESULTS

4.1 Participants flow

A total of ninety-five (n=95) parturients were recruited for this study, with 49 (52%) in the 2.5 IU oxytocin group and 46 (48%) in the 5.0 IU oxytocin group. Fifteen (15) participants (15%) were excluded from the study, out of which nine were due to missing data. In each group, forty (40) parturients were thus analysed, which satisfied the initial sample size per group of 40 participants as calculated in the sample size estimation section, Figure 1.

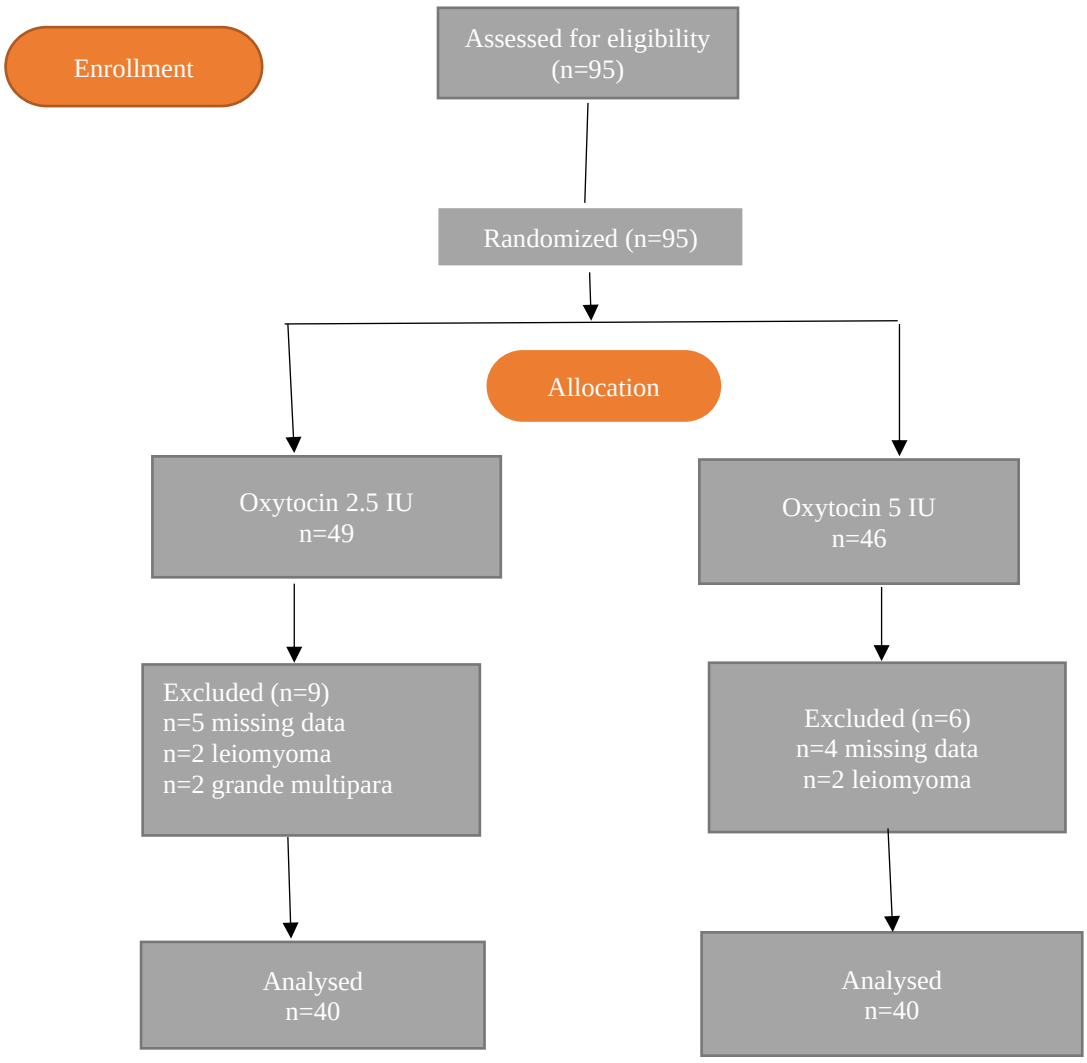


Figure 1. Consort flow chart of the study

4.2 Socio-demographic Characteristics

Table 1. shows the socio-demographic characteristic of the study participants. The mean age of parturients in the two study groups, 2.5IU and the 5 IU oxytocin were similar; 31.75±6.10 years and 30.57±5.32 years respectively (P = 0.361). The average weight of the participants was 79.09 in group A and 80.44 in group B. There was no statistically significant difference between the two groups with regards to height (P = 0.627), BMI (P = 0.787), gestational age (P = 0.918), gravidity (P=0.440) and parity (P = 0.605). The parity of enrolled participants ranged between 0-5, with the majority (82.5%) being between 1-2. The mean preoperative haemoglobin was comparative in the two study groups with mean haemoglobin of 12.00 ±2.10 in group A and 12.29 ±1.14 in group B respectively. The duration of surgery was also similar between the two groups with 79.09 ±16.79 minutes for group A and 80.44±15.80 for group B.

4.3 Indication for caesarean section

Table 2. shows the various indications for caesarean delivery among the parturients. The majority of the cases were done due to previous caesarean delivery, accounting for 78% in group A and 93% in group B, with a p-value of (P=0.135). Malpresentation included breech presentations, transverse lies and oblique lies which accounted for 15% in group A and 7% in group B. Other indications for caesarean delivery were postdates and patient own request which contributed 7% for group A and none in group B.

4.4 Baseline intraoperative vitals before administration of oxytocin

Table 3. shows the baseline parameters/vital signs for both groups before administration of oxytocin. The baseline parameters across the two groups did not differ with regards to HR, SBP, DBP and MAP. The mean baseline heart rate was comparative in the two study groups with mean HR of 83± 18.12 beats/min in group A and 82.83±1.60 beats/min in group B. The mean SPB in group A was 120.18± 11.96 mmHg vs 118.68± mmHg in group B, mean DBP in group A 62.63± 11.58 mmHg vs 64.73± 10.27 mmHg in group B and mean MAP of 86.25± 9.24 mmHg in group A vs 86.95± 8.33 mmHg in group B respectively.

4.5 Uterine tone

The uterine tone was assessed at 1, 3, 5, 7,10, 12, 15 and 20 minutes after administration of oxytocin using a Likert scale from 0-4. There was no statistically significant difference in the adequacy of uterine tone among the two study groups at various times. Parturients in both groups A and B had adequate uterine tone at 3 minutes with a median score of 3.28(0.51) for group A and 3.20 (0.56) for group B on the Likert scale. This is shown in figure 2. None of the participants in either group required additional doses of oxytocin.

4.6 Haemodynamic changes after administration of oxytocin

The mean changes in HR of parturients in both groups are depicted in Figure 3 after administration of oxytocin. A rapid increase in HR was seen in group B with a mean change of 17.52 ±17.90 and 12.91±16.57 beats/min at 1 min and 2 minutes respectively, with statistical significance of p-value at 1 min of (P=0.000*) and (P=0,005*) at 2 minutes

when compared to group A. In contrast to group A, the change in HR increased by 5.0±14.37 and 5.52±14.80 beats/min at 1 and 2 minutes respectively.

The systolic blood pressure (SBP) changes are shown in figure 4. There was a statistically significant decrease in SBP in group B at 1 minute compared to group A, with mean changes of 12. 52 ±13.27 mm Hg with (P=0.020*). The mean difference in group A was 5.62±12.81 mmHg at one minute. There was no statistically significant decrease in diastolic blood pressure in both groups at 1 minute and did not differ at follow up minutes with a p-value of (P=0.053) at 1 minute and (P=0.857) at 3 minutes respectively

The mean arterial blood pressure (MAP) changes are shown in figure 5. A decrease in MAP of up to 11.2±9.88 mm Hg occurred at 1 minute in group B compared to a decrease mean of 5.45 ±11.8 mm Hg in group A. This was statistically significant with a p-value of (P=0.023*).

4.7 Blood loss

Blood loss was recorded in both groups and is summarized in table 4 and figure 6. Blood loss intraoperatively was estimated by the amount of blood mixed with amniotic fluid in the suction bottle and patients drapes soaked with blood. The majority of participants experienced blood loss in the 500-750 ml category with 63% in group A and 73% in group B respectively as shown in figure 6. In group A, the percentage of blood loss <500 ml was 33% as compared to 25% in group B. The lowest percentage of blood was experienced in the 750-1000 ml category, with 5% of participants in group A as compared to 3% in group B. Blood loss was similar between the two groups with a p-value of (P=0.839) and no

participant experienced postpartum haemorrhage. Preoperative and postoperative haemoglobin levels were also measured and the difference was noted to assess blood loss as shown in table 4. There was no statistically significant difference between the two groups as evidenced by the p-value of (P=0.705).

4.8 Adverse effects

The study outcomes concerning the adverse effects of oxytocin are summarized in table 5. Occurrence of nausea, vomiting, headache and chest pain was recorded by binary outcome (Yes or No) after frequent direct questioning until the patient left the theatre. Participants in group B recorded a high level of chest pain, with 6(15%) parturients experiencing chest pain with none in group A with a p-value of (P=0.010*). Headache was recorded in 25% of parturients in group B compared to 2.5% in group A. This was statistically significant with a p-value of (P=0.003*). Nausea was recorded in 40% of parturients in group B in contrast to only 15% in group A, with a p-value at (P=0.012*) of significance. There were comparable results concerning vomiting among the two groups. In addition, the incidence of hypotension was similar between the two groups, with 65% of parturients in group A and 60% in group B respectively.

Table 1: Socio-demographics and baseline characteristics of the participants

	Baseline Characteristics	**A**	**B**	**P-value**
		mean(standard deviation)		
Demographics	Age (years)	31.75 (6.10)	30.57 (5.32)	0.361
	Weight (Kg)	79.09 (16.79)	80.44 (15.80)	0.712
	Height (m)	1.63 (0.06)	1.64 (0.07)	0.627
	BMI (Kg/m^2)	29.7 (5.51)	30.0 (5.20)	0.787
Obstetrics	Gestational age (weeks)	39.08 (1.25)	39.10 (0.87)	0.918
	Gravidity	2.7 (0.88)	2.55 (0.85)	0.440
	Parity	1.45 (0.81)	1.46 (0.72)	0.605
Haemoglobin	Preoperative haemoglobin (g/dl)	12.00 (2.10)	12.29 (1.14)	0.386
	Duration of surgery (mins)	60.38 (16.15)	57.33 (20.40)	0.461

Note: If the p-value is equal to or less than 0.05, then the result is considered to be statistically significant

Table 2: Indication for Caesarean delivery

Indication for CS delivery n (%)	**A**	**B**	**P-value**
Previous caesarean section	31 (78%)	37 (93%)	0.135
Mal presentation (breech, transverse)	6 (15%)	3 (7%)	
Others (postdates, patient request)	3 (7%)	0 (0%)	

Note: If the p-value is equal to or less than 0.05, then the result is considered to be statistically significant

Table 3: Baseline vitals 30 seconds before administration of oxytocin

Vitals	**A**	**B**	**P-value**
	mean(standard deviation)		
SBP	118.68 (10.37)	120.18 (11.90)	0.550
DBP	64.73 (10.27)	62.63 (11.58)	0.394
MAP	86.95 (8.53)	86.25 (9.24)	0.726
HR	82.83 (11.60)	83.03 (18.12)	0.953

Note: If the p-value is equal to or less than 0.05, then the result is considered to be statistically significant

Table 4: Comparison of Pre-operative (Pre-Op) and Post-Operative Haemoglobin (Hb) in gm/dl and the difference in the Hb levels between groups A and B.

Haemoglobin in gm/dl	**A**	**B**	**P-value**
	Mean (SD)	**Mean (SD)**	
Preoperative haemoglobin	12.00 (2.10)	12.29 (1.14)	0.386
Postoperative haemoglobin	10.16 (0.90)	10.34 (0.94)	0.316
Difference in haemoglobin	1.80 (1.92)	1.93 (0.64)	0.705

Note: If the p-value is equal to or less than 0.05, then the result is considered to be statistically significant

Table 5: Adverse Effects

Adverse Effect n (%)	**A**	**B**	**P-value**
Hypotension	26 (65%)	24 (60%)	**0.649**
Headache	1 (3%)	10 (25%)	**0.003***
Chest pain	0	6 (15%)	**0.010***
Nausea	6 (15%)	16 (40%)	**0.012***
Vomiting	1 (3%)	1 (3%)	**1.000**

Note: If the p-value is equal to or less than 0.05, then the result is considered to be statistically significant

Figure 2: Line graph showing uterine tone vs. time in minutes for both study groups

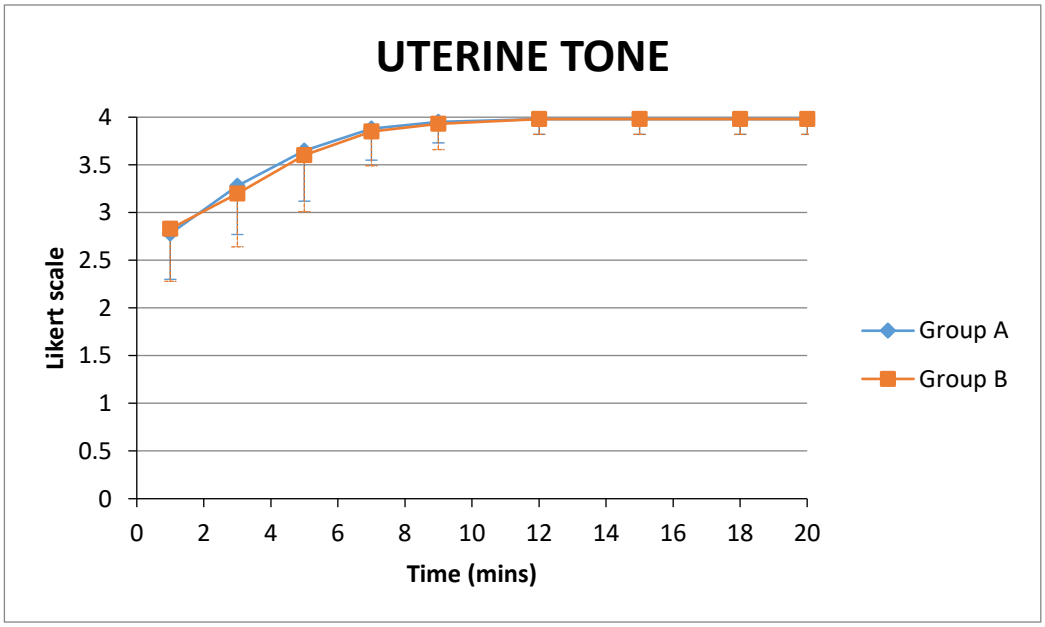


Figure 3: Line graph showing mean changes in HR for both study groups after administration of oxytocin

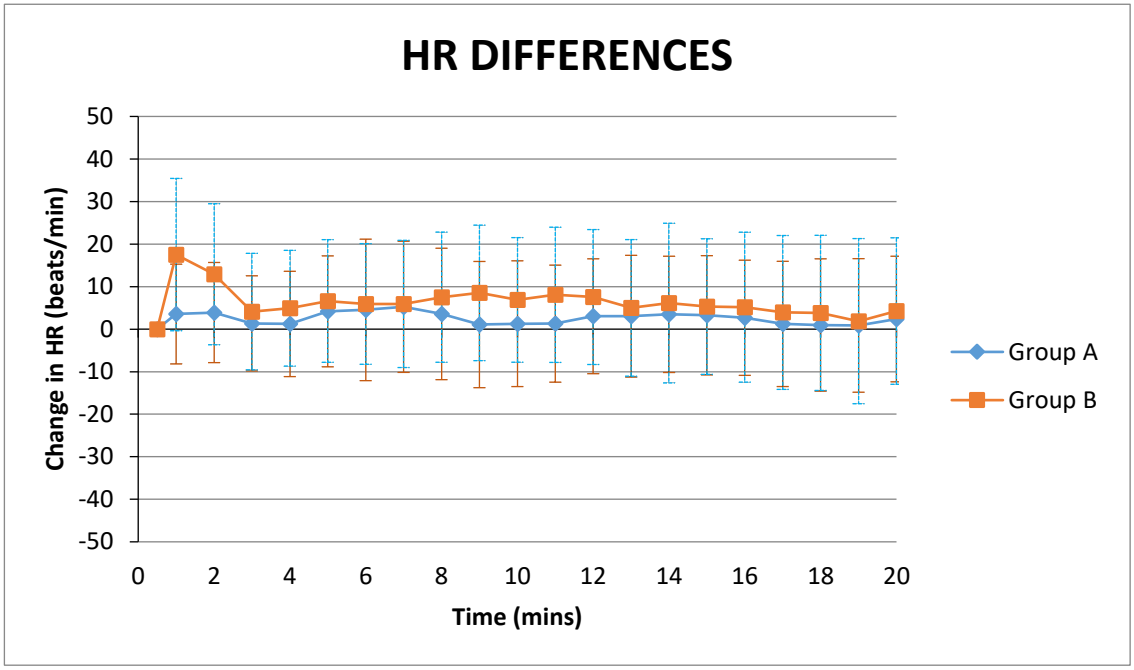


Fig 4: Line graph showing Changes in SBP after administration of oxytocin

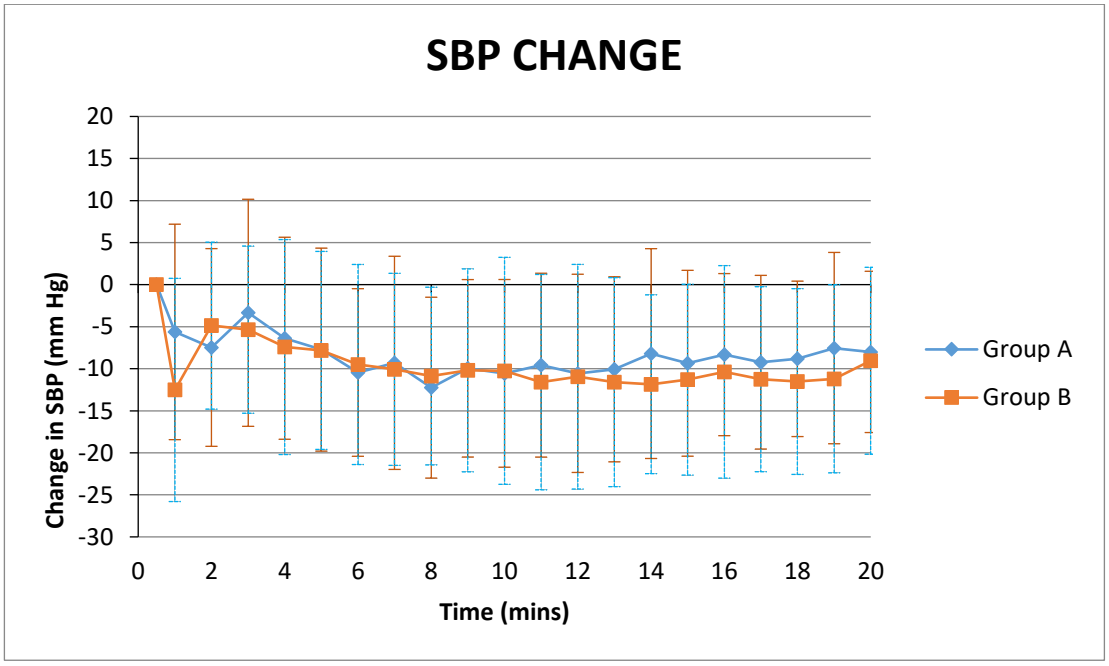


Fig 5. MAP changes with oxytocin administration between the two study groups

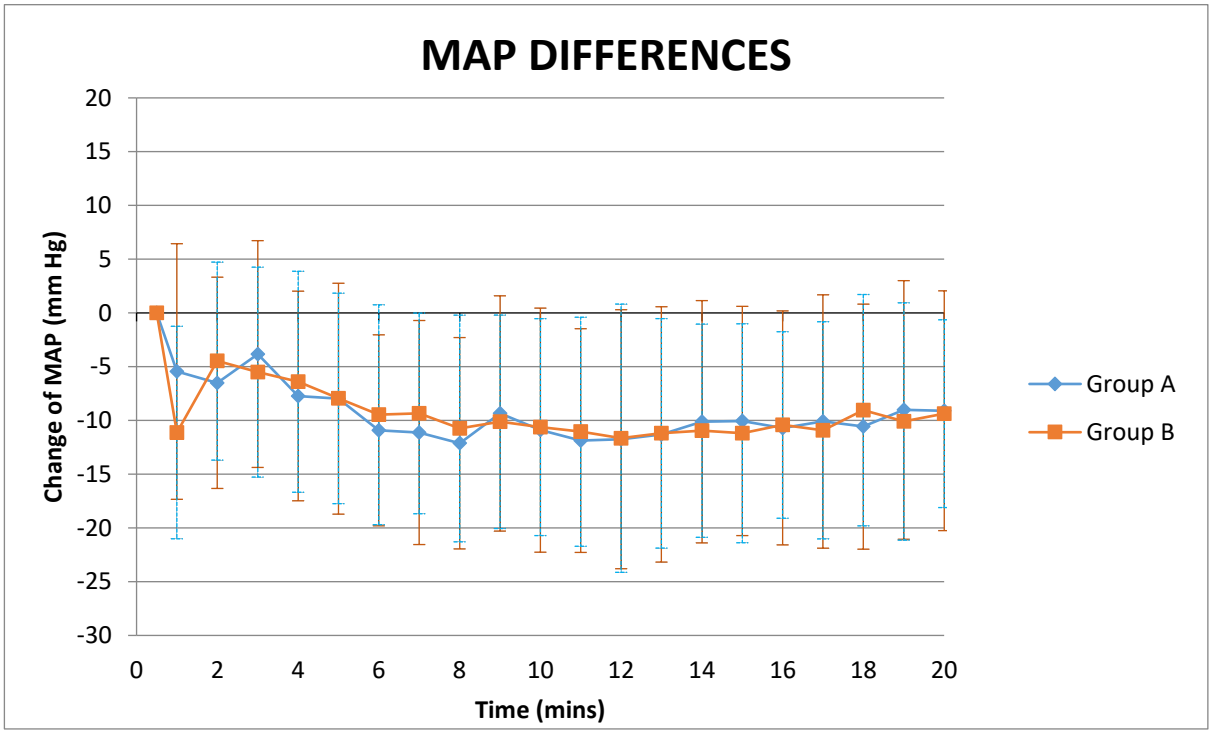
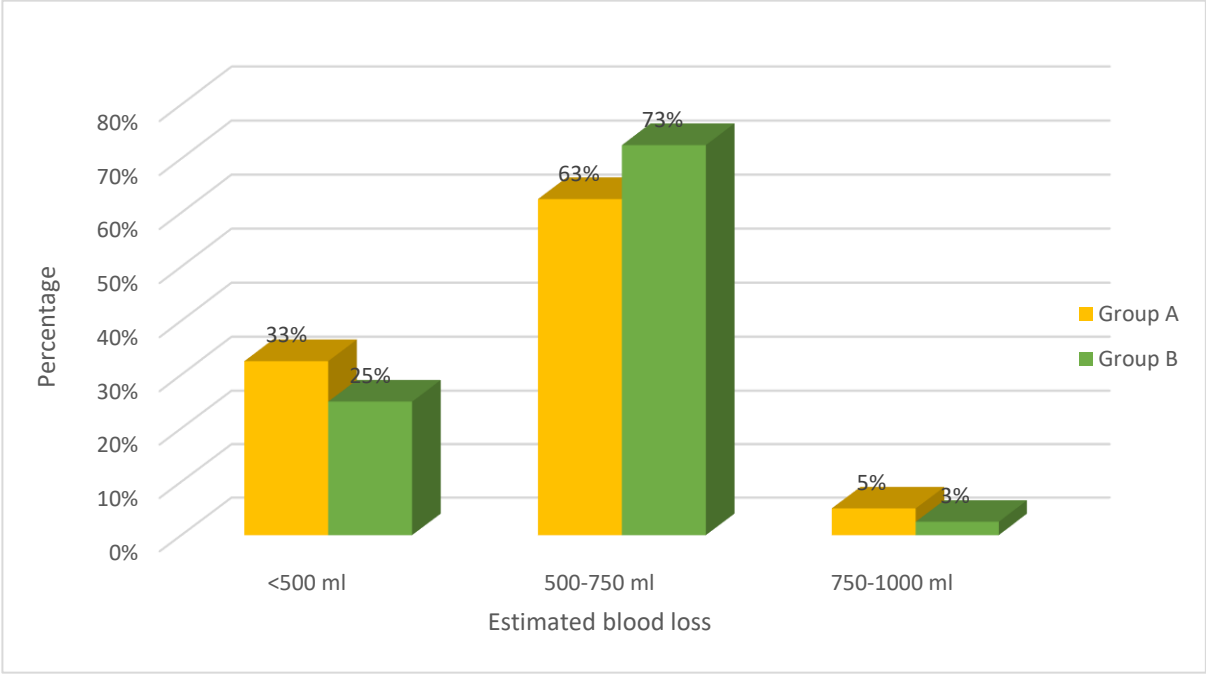


Fig 6. Distribution of participants blood loss among different categories intraoperative



CHAPTER 5: DISCUSSION

5.1 Uterine tone

This study was conducted to determine whether 2.5 IU of oxytocin would give adequate uterine tone as compared to 5 IU of oxytocin in parturients undergoing elective caesarean section under spinal anaesthesia. The results of this study demonstrated that 2.5 IU oxytocin administration was comparable to 5 IU oxytocin for initiating and maintaining adequate uterine contraction during caesarean delivery. There was no difference in uterine tone between the two groups at 1 and 3 minutes respectively and no additional doses of oxytocin were required in either group.

Butwick and his coworkers[10] also studied lower doses of oxytocin that could provide adequate uterine tone. They recruited 75 parturients undergoing elective caesarean section to receive oxytocin bolus (0, 0.5, 1, 3, 5) IU. The authors observed no significant difference in the adequacy of uterine tone among the study groups at 2 minutes (75%, 100%, 93%, 100%, 93%) for 0, 0.5, 1, 3, and 5 IU respectively. Although they used even smaller oxytocin doses compared to 2.5 IU used in this index study, the findings were however similar.

In their study, Sarna and colleagues[21] compared four different doses of oxytocin bolus (5, 10, 15, 20 IU) during elective caesarean delivery under neuraxial anaesthesia. They found no differences in the uterine tone among the four study groups. However, they used higher doses of oxytocin compared to the index study. Attempts have been made over the years to compare smaller doses of oxytocin with 10 IU. Somjit et al[30] recruited 155 women undergoing elective caesarean section into 5 IU and 10 IU oxytocin groups. They found

that 5 IU was not inferior to 10 IU in initiating and maintaining uterine contraction. The index study, therefore, took a step further by comparing the effects of 2.5 IU and 5 IU oxytocin doses on adequate uterine tone during caesarean delivery with similar observations.

5.2 Haemodynamic Changes

Maternal haemodynamic changes after caesarean section have many potential causes including removal of aortocaval compression, auto-transfusion from uterine contraction, blood loss, vasopressors use and maternal emotional excitement. Previous studies have shown that uterotonic drugs are the dominant factors[21].

This study found that 2.5 IU bolus of oxytocin was associated with fewer haemodynamic changes compared to 5 IU. Participants who received 5 IU had significantly higher increases in heart rate from the baseline value compared to the 2.5 IU patients. Interestingly, however, the mean changes in HR did not differ significantly after the initial two minutes between the two groups.

Sartain et al[11] studied the haemodynamic changes between 2 IU vs 5 IU oxytocin during elective caesarean section in 80 parturients. There was a greater increase in mean HR in participants who received 5 IU oxytocin 32±17 beats/min than those who received 2.0 IU with a mean increase of 24±13 beats/min. Derbel and his colleagues[31] also had similar findings when they compared 5 IU vs 10 IU oxytocin. There was a significant increase in heart rate and a high incidence of low blood pressure in the 10 IU group. From previous

studies and this present one, it can be inferred that higher doses of oxytocin produce a higher increase in the heart rate of parturients during caesarean section.

Langesaeter and his coworkers[32] studied the haemodynamic effects of repeated doses of oxytocin in 20 healthy parturients receiving 5 IU bolus first dose and second dose. Their findings were that both the first and second doses of oxytocin produced haemodynamics changes with changes in SBP in 31% (CI 27-35) and 23% (CI 20-27) with a p-value of 0.003 respectively. A study by Pinder and his colleagues[33] of the haemodynamic changes induced by a rapid bolus of 5 IU vs 10 IU oxytocin also had similar findings. They found a small but statistically significant reduction in MAP from baseline at 30 seconds after administration of 10 IU oxytocin. It was also observed in this index study that higher doses of 5 IU of oxytocin led to a significant decrease in both the systolic blood pressure and mean arterial pressure compared to 2.5 IU.

In another study, Thomas et al[22] made use of invasive blood pressure monitoring to demonstrate the haemodynamic effects of 5 IU oxytocin given either as a bolus or as an infusion over 5 minutes. Thirty parturients undergoing caesarean were recruited in their study. The authors observed marked cardiovascular changes in the 5 IU bolus group compared to the infusion group with an increase in HR by 17±10.70 beats/min in comparison to the infusion group with 10± 9.7 beats/min. The MAP also decreased by 27±7.6 mm Hg in the bolus group compared to 8±8.7 mm Hg in the infusion group. In our study, we observed similar changes but because we used non-invasive blood pressure measurement, the decrease in MAP might have been underestimated.

5.3 Adverse effects and blood loss

The adverse effects of oxytocin include cardiovascular instability (hypotension, tachycardia, myocardial ischaemia and arrhythmia), nausea and vomiting, headache as well as flushing.[2,6,16] Transient electrocardiogram (ECG) changes such as ST-segment and T- waves abnormalities with subjective symptoms such as chest discomfort and pain have been described following higher doses of oxytocin during caesarean delivery[16].

In this study, the incidence of these side effects, particularly nausea, headache and chest pain were higher in the 5 IU group. Nausea, headache and chest pain occurred in 40%, 25% and 15% of parturients in the 5 IU group respectively. The frequency of vomiting was similar in the two groups.

Kiran and his colleagues[34] found similar results in their study. The prevalence of nausea and vomiting was significantly higher after administration of 2 IU oxytocin vs 0.5 IU at 1 minute (13% vs 3%). Carvalho et al[20] also noted a higher incidence of side effects in the 1 IU oxytocin group (nausea, vomiting and flushing) with (38%, 13% and 63%) in comparison to the 0.5 IU group respectively. However, a study by Yaliwal et al[35] did not find any significant difference in the adverse effects between 3 IU oxytocin bolus with 7 IU infusion vs 10 IU infusion. Somjit and his co-workers[30] also found similar results to Yaliwal et al. These differences in the incidence of side effects may be attributed to the speed of oxytocin injection[20].

Patients undergoing caesarean section are at increased risk of obstetric haemorrhage and uterine atony is the most common cause[10]. In this study, there was no difference in blood loss between the two groups. Derbel et al[31] compared 5 IU vs 10 IU bolus during caesarean

section and they also found no significant difference between the two groups regarding blood loss. Kiran and colleagues[34] also found similar results to Derbel et al, although they used much lower doses of oxytocin (0.5, 1, and 2 IU) and their study was conducted in primigravidas. Visual blood loss estimation may be inaccurate and the changes in preoperative and postoperative Hb are difficult to interpret because of large fluid shifts that occur during delivery. The result of this study indicates that estimated blood loss and difference in preoperative and postoperative Hb are independent of the oxytocin dose.

CHAPTER 6: CONCLUSION AND RECOMMENDATION

As reported in previous studies, oxytocin remains the first agent of choice in preventing and managing postpartum haemorrhage. It is an effective uterotonic agent and can be used during normal vaginal delivery and caesarean delivery. The most effective/optimal dose remains ambiguous among different official bodies and remains a wide contested phenomenon.

Our results show that 2.5 IU oxytocin given as an intravenous bolus is comparable and non-inferior to 5 IU in initiating and maintaining adequate uterine tone in patients undergoing elective caesarean section. There was no statistical difference between the two groups in terms of adequate uterine contraction and there was no request for additional uterotonic agents in either group.

The 5 IU oxytocin bolus demonstrated a higher impact on the haemodynamics changes as well as adverse effects (nausea, headache and chest pain) compared to the 2.5 IU dose. We observed that these changes are dose-dependent. This study confirms that adequate uterine tone can be achieved with small doses of oxytocin while minimizing the haemodynamic changes and the side effects. Blood loss did not differ between the two groups.

LIMITATION OF THE STUDY

1. The study was undertaken in healthy parturients, ASA II with singleton pregnancies undergoing elective caesarean section under spinal anaesthesia. Hence these results cannot be assumed to be equivocal in those at risk of uterine atony and PPH and in those undergoing general anaesthesia.
2. Intrapartum patients may have a different response to oxytocin due to prolonged labour or the use of oxytocin to augment labour which can lead to receptor desensitization and render them unresponsive and may require additional uterotonics.
3. Adequacy of uterine tone is subjective, dependent on the surgeon performing the caesarean section
4. Estimation of blood loss intraoperatively is subjective and may be inaccurate
5. The use of non-invasive blood pressure monitoring underestimates and could miss detection of transient haemodynamic changes.

RECOMMENDATIONS

At Windhoek hospital complex (Windhoek Central hospital and Katutura Intermediate hospital) there is no formal protocol as to what dose of oxytocin to give during caesarean delivery. Most clinicians administer oxytocin doses ranging from 5 IU to 10 IU or as per request of the attending obstetrician after assessing the tone of the uterus for contractility. From this study, we recommend the following:

1. The use of 2.5 IU oxytocin as a bolus during elective caesarean section in patients who are not at risk of PPH.
2. It should be given as a slow bolus over 15-30seconds to reduce the haemodynamic effects associated with the rapid injection.
3. Further studies in patients at risk of uterine atony and PPH are required to assess whether current dosing would be adequate and in intrapartum patients undergoing emergency caesarean delivery.

REFERENCES

1. WHO recommendation: Uterotonics or the prevention of postpartum haemorrhage. Geneva. World Health Organization; 2018. http:/app.who.int (accessed 20/04/2020)
2. Upadya M, Nayak M. Oxytocics. *Update in Anaesthesia*; 2019; **34**: 78-80
3. Vogel JP, Williams M, Gallos I, Althabe F, Oladapo OT. WHO recommendations on uterotonics for postpartum haemorrhage prevention: what works, and which one? *BMJ Glob Health* 2019; **4:** e001466. doi:10.1136/bmjgh-2019-001466
4. Kovacheva VP, Soens MA, Tsen LC. A randomized, double-blinded trial of a "Rule of Threes" algorithm versus continuous infusion of oxytocin during elective cesarean delivery. *Anesthesiology* 2015; **123**: 92-100
5. Sheehan SR, Montgomery AA, Carey M, McAuliffe FM, Eogan M, Gleeson R et al. Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective caesarean section: double blind, placebo controlled, randomized trial. *BMJ* 2011; **343**: d4661 doi: 10. 1136/bmj.d4661
6. Heesen M, Carvalho B, Carvalho JCA, Durekot JJ, Dyer RA, Lucas DN et al. International consensus statement on the use of uterotonic agents during caesarean section. *Anaesthesia* 2019; **74:** 1305-1319.
7. Weale N, Laxton C. Prophylactic use of oxytocin at caesarean section: where are the guidelines? *Anaesthesia* 2013; **68**: 995-1009
8. Fanna Z, Fawcus S. Oxytocin-ensuring appropriate use and balancing efficacy with safety. *South African Medical Journal* 2015; **105**: 271-4.
9. Stephens LC, Bruessel T. Systematic review of oxytocin dosing at caesarean section. *Anaesth Intensive Care* 2012; **40**: 247-252.

10. Butwick AJ, Coleman L, Cohen SE, Riley ET, Carvalho B. Minimum effective bolus dose of oxytocin during elective caesarean delivery. *British Journal of Anaesthesia* 2010; **104**: 338-43.
11. Sartain JB, Barry JJ, Howat PW, McCormack DI, Bryant M. Intravenous oxytocin bolus of 2 units is superior to 5 units during elective Caesarean section. *British Journal of Anaesthesia* 2000; **101** (6): 822-6
12. Balki M, Wong GA. Refractory uterine atony: still a problem after all these years. *International Journal of Obstetric Anesthesia* 2021; **48**: 103207
13. Flood P, Rathmell JP, Shafer S. Stoelting's Pharmacology and Physiology in Anesthetic Practice. 5th edition. United States of America: Wolters Kluwer Health; 2015.737p.
14. Lee H-J, Macbeth AH, Pagani JH, Young 3rd WS. Oxytocin: The great facilitator of life. *Progress in Neurobiology* 2009; **88**: 127-151
15. International Federation of Gynecology and Obstetrics, International Confederation of Midwives. *Joint statement of recommendation for the use of uterotonics for the prevention of postpartum haemorrhage.* 2021. Available from: *www.figo.org/joint-statement-recommendation-uterotonics-prevention-pph*
16. Dyer RA, Butwick AJ, Carvalho B. Oxytocin for labour and caesarean delivery: implications for the anaesthesiologist. *Current Opinion in Anaesthesiology* 2011; **24**: 256-261.
17. Arrowsmith S. Oxytocin and vasopressin signalling and myometrial contraction. *Current Opinion in Physiology* 2020; **13**: 62-70
18. Dyer RA, Van Dyk D, Dresner A. The use of uterotonic drugs during cesarean section. *International Journal of Obstetric Anesthesia* 2010; **19**: 313-319

19. Drew T, Balki M. What does basic science tell us about the use of uterotonics? *Best Practice & Research Clinical Obstetrics and Gynaecology* 2019; **61**: 3-14
20. Carvalho JC, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective caesarean delivery: a dose finding study. *Obstetrics and Gynecology* 2004; **104:** 1005-10.
21. Sarna MC, Soni AK, Gomez M, Oriol NE. Intravenous oxytocin in patients undergoing elective Caesarean section. *Anaesth Analg* 1997; **84**: 753-6.
22. Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean section. *British Journal of Anaesthesia 2007*; **98**: 116-9
23. Allen Jr JC. Sample size calculation for two independent groups: a useful rule of thumb. *Proceedings of Singapore Healthcare 2011;* **20(**2):138-140
24. Sakpal TV. Sample size estimation in clinical trial. *Perspectives in Clinical Research 2010;* **1**(2): 67–69
25. Tripepi G, Chesnaye NC, Dekker FW, Zoccali C, Jager JK. Intention to treat and per protocol analysis in clinical trials. *Nephrology* 2020; **25**: 513-517. https://doi.org/10.1111/nep.13709
26. Hughes RA, Heron J, Sterne JAC, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. *International journal of Epidemiology* 2019; **48** (4): 1294-1304. https://doi.org/10.1093/ije/dyz032
27. Little RJ, D'Agostino R, Cohen ML et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; **367**: 1355-60
28. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med* 2010; **29**: 2920-31

29. Bartlett JW, Harel O, Carpenter JR. Asymptomatically unbiased estimation of exposure odds ratio in complete records logistic regression. *Am J Epidemiol* 2015; **182**: 730-36
30. Somjit M, Surojananon J, Kongwattanakul K, Kasemsiri C, Sirisom M, Prawannoa K et al. Comparison of low dose versus high dose of oxytocin for initiating uterine contraction during cesarean delivery: A randomized, controlled, non-inferiority trial. *International Journal of Women's Health* 2020; **12**: 667-673
31. Derbel M, Mekki D, Riahi A, Dimassi K, Mebazaa MS, Gara MF. Comparison of two oxytocin administration protocols in elective cesarean section: 5 iu versus 10 iu. *Tunis Med.* 2016; **94**(4): 253-258
32. Langesaeter E, Rosseland LA, Stubhaug A. Haemodynamic effects of repeated doses of oxytocin during caesarean delivery in healthy parturients. *Br J Anaesth* 2009; **103**(2): 260-2
33. Pinder AJ, Dresner M, Calow C, O'Riodan J, Johnsons R. Haemodynamic changes caused by oxytocin during caesarean section under spinal anaesthesia. *International Journal of Obstetrics Anaesthesia* 2002; **11**: 156-159
34. Kiran S, Anand A, Singh T, Gupta N. To estimate the minimum effective dose of oxytocin required to produce adequate uterine tone in women undergoing elective caesarean delivery. *Egyptian Journal of Anaesthesia* 2013; **29**: 161-165
35. Yaliwal RG, Biradar AM, Dharmarao PS, Kori SS, Mudanur SR, Patil NG et al. A randomized control trial of 3 IU IV oxytocin bolus with 7 IU oxytocin infusion versus 10 IU oxytocin infusion during cesarean section for prevention of postpartum hemorrhage. *International Journal of Women's Health* 2020; **12**: 1091-1097

APPENDIX I

RESEARCH QUESTIONNAIRE

EVALUATION OF THE EFFECT OF 2.5 IU VS 5 IU OXYTOCIN ON UTERINE TONE DURING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA AT WINDHOEK HOSPITAL COMPLEX

Patient group……A or B serial no……..

Date of collection……..

Name of collector……..

Demographic information

1. Age (years)……..
2. Weight (kg)……..Height (m)……. BMI (kg/m^2)……..
3. Gestational age (weeks)……
4. Premedication…….
5. **Past obstetric history**

- Gravidity…… Parity……..
- Previous PPH…….YES/ NO
- Previous uterine atony……..YES/NO
- Indication for C/S delivery…….
- Previous C/S delivery……YES/NO, If yes how many and what were the indications?.....

6. Preoperative haemoglobin…….
7. Postoperative haemoglobin (At 24 hours postoperative)…….
8. Dose of hyperbaric bupivacaine (mg)……..

9. Duration of surgery……

10. Baseline vitals 30 seconds before administration of oxytocin

- SBP……mmHg
- DBP……mmHg
- MAP……..mmHg
- HR……..beats/min

11. Vitals after Oxytocin administration

Time (min) / Vitals	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
SBP mmHg																				
DBP																				
MAP mmHg																				
HR b/min																				

12. Uterine tone

Time in minutes taken to achieve uterine tone	Uterine tone				
	0	1	2	3	4
1					
3					
5					
7					
9					
12					
15					

18					
20					

Numerical uterine tone

0= floppy (atonic)

1=partial contacted

2=adequate

3=well contracted

4= very well contracted (stony hard)

13. Secondary outcome Variables
    - Request for an additional dose of oxytocin:……YES/NO
    - If yes give 3 IU oxytocin bolus ……..
    - How many times? ……
14. Hypotension ……
    - Phenylephrine bolus (mcg)……infusion(mcg/min)……..
    - Ephedrine (mg)……

15. Estimated blood loss estimation by swabs and suction bottle

<500 ml	500-750 ml	750-1000 ml	>1000 ml

16. Side effects profile

	Yes	No
Headache		
Chest pain		
Nausea		
Vomiting		

APPENDIX II

PATIENT CONSENT FORM

Title:	*Dr*	**Initials:** *FN*
Surname:	*Shigwedha*	
Name/s:	*Fredrika Nembale*	
Academic or equivalent institution to which affiliated	**Past:** *University of Pretoria, University of Namibia*	**Present:** *University of Namibia, School of Medicine*
Present Academic Rank	*Anaesthesiology registrar year IV*	
Work and employment experiences	1. *Medical intern from Jan 2012-Dec 2013, Katutura Intermediate Hospital and Windhoek Central hospital* 2. *Medical Officer in Anaesthesia department. Jan 2014- Nov 2015, IHK and Windhoek Central Hospital* 3. *Medical officer in Anaesthesia department. Dec 2015- Dec 2017, Oshakati Intermediate Hospital* 4. *Anaesthesia Registrar Feb 2018 –up to date. Windhoek Central Hospital and Katutura Intermediate Hospital*	
Physical contact details	*Erf 4, Spitskop street, Eros* *Windhoek*	
Telephone number	**Work:** *061 2033100*	**Cell:** *0813507196*
Email address	*nembale@yahoo.com*	
Academic Qualification and year obtained/ Institution	1. *Bachelor of Medicine and Surgery (MBChB), 2012. University of Pretoria (UP)* 2. *Diploma in Anaesthetics (DA), 2016. Colleges of Medicines of South Africa (CMSA)*	
Area/s of Expertise/specialization	*Currently specializing in Anaesthesiology, critical care and Pain Management, year 3*	
Title of Research	*Evaluation of the effect of 2.5 vs 5 IU oxytocin on uterine tone during elective caesarean section at Windhoek Hospital complex*	
Principal Investigator	*Dr Fredrika N Shigwedha*	
Main Supervisor	*Dr Kingsley U Tobi*	

Information to the Participant

After delivery of a baby through an operation (caesarean section), the womb must contract to prevent and reduce blood loss. Oxytocin is a drug that is given to help the womb contract, but it is also associated with unwanted side effects. These side effects include chest pain or discomfort, heart beating fast, low blood pressure, nausea and vomiting. Patients who will experience any of the above-mentioned symptoms will be given treatment accordingly.

The purpose of the study is to obtain information that will be used to determine the lowest, safe and most efficacious intravenous slow bolus dose of oxytocin following caesarean section inpatients such as you. This will help the clinician to reduce the unwanted side effects of oxytocin experienced by mothers following caesarean delivery.

Informed Consent

I have been informed that Dr Fredrika Nembale Shigwedha is carrying out a study to find the minimum effective and safe dose of oxytocin following caesarean delivery at Windhoek Hospital Complex. By this form, written consent is being sought for my participation in the study.

Confidentiality and Ethical issues

The information provided by you will remain confidential. Nobody except, the principal investigator will have access to it. A serial number will be used instead of your name. The data obtained may be published in journals or elsewhere without disclosing your identity. You have the right to refuse or terminate participation at any point you wish. Your

participation will be purely voluntary and no financial benefit from the study. You will still be given oxytocin if you opt not to participate. Your termination will not result in withholding any medical treatment you may require during the procedure.

Participant's consent

I(name)…… have been informed by……..on the study, its risks and benefits. I understand that by signing this consent I accept to participate as a volunteer and I do not wave any of my legal rights, neither do I accept liability for anything. I have read and understood the study details.

Participant's signature/thumbprint……..

Date……..

Participants who cannot read or write

Witness Signature……

APPENDIX III

MOHSS APPROVAL LETTER

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198
Windhoek
Namibia

Ministerial Building
Harvey Street
Windhoek

Tel: 061 – 203 2537
Fax: 061 – 222558
E-mail: itashipu87@gmail.com

OFFICE OF THE EXECUTIVE DIRECTOR

Ref: 17/3/3/FNS
Enquiries: Mr. A. Shipanga

Date: 23 February 2021

Dr. Fredrika N. Shigwedha
PO Box 21183
Windhoek

Dear Dr. Shigwedha

Re: **The effect of 2.5 vs 5 IU oxytocin on uterine tone during elective caesarean delivery at Windhoek Teaching Hospitals.**

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;
3.2 No other data should be collected other than the data stated in the proposal;
3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
3.4 A quarterly report to be submitted to the Ministry's Research Unit;
3.5 Preliminary findings to be submitted upon completion of the study;
3.6 Final report to be submitted upon completion of the study;
3.7 Separate permission should be sought from the Ministry for the publication of the findings.

4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

BEN NANGOMBE
EXECUTIVE DIRECTOR

"Your Health Our Concern"

APPENDIX IV

WINDHOEK CENTRAL HOSPITAL APPROVAL LETTER

9-0/0001

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13215
Windhoek
Namibia

Harvey Street
Windhoek

Tel. No: (061) 203 3024
Fax No: (061) 222886

Enquiries: Mrs. S. Iipinge | **Ref. VNK 2021** | **Date: 26 May 2021**

OFFICE OF THE CHIEF MEDICAL SUPERINTENDENT
WINDHOEK CENTRAL HOSPITAL

Dr. Fredrika N. Shigwedha
P.O.BOX 21183
Windhoek
0813507196

Dear Dr. Shigwedha

SUBJECT: PERMISSION TO CONDUCT A RESEARCH STUDY ON THE EFFECT OF 2.5 vs 5IU OXYTOCIN ON UTERINE TONE DURING ELECTIVE CAESAREAN DELIVERY AT WINDHOEK CENTRAL HOSPITAL TEACHING INSTITUION.

1. Reference is made to your application to conduct the above-mentioned study.

2. This letter serves to inform you that permission has been granted for you to conduct a study at Windhoek Central Hospital, on the above mentioned subject as you have requested and does not include any remuneration.

3. Patient/Client's information should be kept confidential at all times.

4. Preliminary findings to be submitted to Customer care office, Windhoek Central Hospital upon completion of the study.

Thank you.

Yours sincerely.

Dr .D.I.UIRAB
CHIEF MEDICAL SUPERINTENDENT

MINISTRY OF HEALTH AND SOCIAL SERVICES
Private Bag 13215
27 -05- 2021
Windhoek
WINDHOEK CENTRAL HOSPITAL

"Your Health, Our Concern"

APPENDIX V

INTERMEDIATE KATUTURA HOSPITAL APPROVAL

Republic of Namibia

Ministry of Health and Social Services

Private Bag 13215
WINDHOEK
Namibia

Intermediate Hospital Katutura
Independence Avenue
WINDHOEK

Telephone (061) 203 4004/5
Telefax (061) 222706

Enquiries: Dr. F. M. Shiweda

Date 20 May 2021

OFFICE OF THE CHIEF MEDICAL OFFICER

Dr. Fredrika N. Shigwedha
P.O. Box 21183
Windhoek

Dr. A. N. Shigwedha

RE: **THE EFFECT OF 2.5 VS 5 IU OXYTOCIN ON UTERINE TONE DURING THE ELECTIVE CAESAREAN DELIVERY AT WINDHOEK TEACHING HOSPITALS.**

The above mentioned subject refers:

This office hereby grants you permission to do a research on the effects of 2.5 vs % IU Oxytocin Uterine Tone during elective Caesarean delivery at Katutura, Khomas Region, MoHSS.

Please provide this office with a copy of your findings.

Thank you

Yours in health,

MINISTRY OF HEALTH
AND SOCIAL SERVICES
P/BAG 13215
WINDHOEK NAMIBIA
20 -05- 2021
INTERMEDIATE HOSPITAL KATUTURA

.....
DR. N. T. AMAGULU
MEDICAL SUPERINTENDENT