Current knowledge and practice regarding Syntocinon® for caesarean sections in a department of anaesthesiology.

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree

of

Master of Medicine in the branch of Anaesthesiology

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DECLARATION

I, Marike de Jager, declare that this thesis is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Signature of candidate

Signed at: Chris Hani Baragwanath Academic Hospital, Johannesburg

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Date

ABSTRACT

Background: More than 166 000 women die annually from obstetric haemorrhage, with uterine atony being the most common causative factor (3). More than 50% of these deaths occur in Sub-Saharan Africa (4, 5). Synthetic oxytocin is integral in the prevention and management of postoperative post partum haemorrhage (PPH) and therefore it is essential for anaesthesiologists to have an adequate knowledge of this drug.

Aim: The aim of the study was to describe the current knowledge and practise of the anaesthetists in the department of Anaesthesiology at the University of Witwatersrand (Wits), regarding Syntocinon® during caesarean section under spinal anaesthesia.

Method: A validated questionnaire was distributed to anaesthetists working at Wits during departmental academic meetings in April 2015.

Results: The results of the study showed that 60% of the participating anaesthetists had inadequate knowledge of IV Syntocinon® and that practice varied widely and was based on individual participants' preference and was not consistent with international guidelines or protocols.

Conclusion: Urgent staff education and implementation of a standardised practice guideline and protocol regarding usage and dosing of IV Syntocinon® is needed to prevent poor maternal outcomes and poor service delivery.

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CHAPTER ONE

OVERVIEW OF THE STUDY

Introduction

This chapter will serve as an overview of the study and include the following: background, problem statement, aim and objectives, research assumptions, demarcation of study field, ethical considerations, research methodology, the significance of the study, validity and reliability of this study and study outline.

Background

According to the World Health Organisation (WHO) more than 210 million women fall pregnant every year, of whom more than 20 million will experience pregnancy related illness and approximately 500 000 will die as a result of the complications of pregnancy and childbirth (1, 2).

Internationally more than 166 000 women die from obstetric haemorrhage annually, with uterine atony being the most common causative factor (3). More than 50% of these deaths occur in Sub-Saharan Africa, the causes being widespread and include post-partum haemorrhage (PPH) (4, 5). Consequently uterotonic drugs such as synthetic oxytocin have become integral in the management and prevention of PPH (6-8).

Synthetic oxytocin e.g. Syntocinon® is an uterotonic drug that is a synthetic nonapeptide identical to oxytocin, a hormone released by the posterior lobe of the pituitary. Synthetic oxytocin is the first line treatment for the management of PPH and other drugs are available for second line management. (7, 8)

The Food and Drug Administration (FDA) has placed a black box warning on the correct usage and indication of Syntocinon® for usage during labour (9). Syntocinon® is associated with numerous adverse effects including severe hypotension, chest pain, myocardial ischemia, cardiac arrest as well as water intoxication due to its antidiuretic effects (8). Syntocinon® has a narrow therapeutic range in terms of maternal morbidity and a detailed knowledge of the pharmacology, dosage, route and rate of administration is essential (5).

Internationally, guidelines regarding prevention and management of PPH have been developed by the World Federation of Societies of Anaesthesiologists (WFSA), the Royal College of Obstetricians and Gynaecologists (RCOG), the National Institute of Clinical Excellence (NICE), American Congress of Obstetricians and Gynaecologists, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and the South African Society of Anaesthesiology (SASA).

No guidelines could be identified regarding the administration of Syntocinon® during spinal in uncomplicated caesarean section but a few guidelines were identified for Syntocinon® dosing during PPH.

International guidelines for the prevention and management of PPH vary in dose and method of Syntocinon® administration. Recent literature suggests that a lower dosage of Syntocinon® in the uncomplicated caesarean section is as effective as the dosage suggested by the various guidelines. (5, 8, 10-13)

Jansen (14) is of the opinion that medication is an essential part of a doctor's practice and therefore they are expected to have a comprehensive knowledge of medication. No doctor is allowed to prescribe or administer medication if they do not have an up-to-date knowledge of that medication.

Doctors' knowledge of medication in general is variable (15-19) .Two qualitative studies from India (17, 18) concluded that doctors, midwives, 'traditional' doctors and nurses had poor knowledge of the correct use of Syntocinon®. After an educational programme on the correct use of Syntocinon® Bolton et al (19) found that 23 % of doctors did not change their incorrect use of Syntocinon®.

1.3 Problem statement

Syntocinon® is a dangerous drug with a narrow therapeutic range in terms of maternal morbidity (3, 5, 11). Legally doctors should have comprehensive and up-to-date knowledge of medication that they prescribe and administer (14).

No specific protocol has been adopted by the Department of Anaesthesiology at the University of the Witwatersrand (Wits) for the administration of Syntocinon®. Current knowledge and practises regarding Syntocinon® amongst Wits anaesthetists was unknown.

1.4 Aim

The aim of the study was to describe the current knowledge and practise of the anaesthetists in the Department of Anaesthesiology at Wits regarding Syntocinon® during caesarean section under spinal anaesthesia.

1.5 Objectives

The primary objectives of this study were to:

- describe the anaethetists' knowledge of Syntocinon®
- describe anaethestists' practise regarding Syntocinon®.

The secondary objectives were to:

- describe the difference in knowledge between the medical officers, junior registrars, senior registrars and consultants
- compare the knowledge between the junior doctors and the senior doctors.

1.6 Research assumptions

The following definitions will be used in this study:

Oxytocin: refers to the synthetic oxytocin (Syntocinon®).

Knowledge: refers to the medical knowledge a doctor possesses regarding Syntocinon®.

Adequate Knowledge: attaining a score of 80 % or above in the knowledge section of the questionnaire.

Practise: is the dosage, frequency, rate and method (bolus or continuous infusion) of Syntocinon® administration currently being used by the doctors.

Anaesthetists: an anaesthetist refers to all medical officers, registrars and consultants currently working in the Department of Anaesthesiology at Wits. Interns and emergency medicine registrars working in the department at the time will be excluded.

Medical Officer: is a licensed doctor practising anaesthesia under specialist supervision who form part of the Department of Anaesthesiology at Wits. Junior medical officers will be regarded as junior registrars and career medical officers will be regarded as consultants.

Registrar: is a doctor that is in the process of obtaining a specialist anaesthesiology qualification, endorsed by the Health Professions Council of South Africa. A junior registrar is a registrar in anaesthesiology pre the part one exams. A senior registrar is a registrar in anaesthesiology post the part one exams.

Consultants: any anaesthetist who has completed the required South African College of Medicine examinations, and all other criteria to become a specialist in anaesthesiology. Career medical officers will also be included in this category.

Junior doctor: in this study refers to any medical officer and junior registrar (registrars pre part one exams)

Senior doctor: in this study refers to any senior registrar (registrars who have completed part one exams) and consultant.

1.7 Demarcation of study field

The study was conducted in the Department of Anaesthesiology at Wits, at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwaneth Academic Hospital (CHBAH), Helen Joseph Hospital (HJH), and Rahima Moosa Mother and Child Hospital (RMMCH).

1.8 Ethical considerations

Approval to conduct this study was obtained from the Postgraduate Committee and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

An information letter (Appendix 1) was provided to the participants explaining the purpose and process of the study. Consent was implied by accepting the invitation. Anonymity and confidentiality were ensured.

This study was conducted according to the South African Good Clinical Practice Guidelines (20) and the Declaration of Helsinki (21).

1.9 Research methodology

A descriptive, prospective, contextual study design was used.The study population consisted of the anaesthetists working in the Department of Anaesthesiology at Wits.
At the time that the study was conducted it was estimated that there were 228 anaesthetists working in the department. A biostatistician was consulted, and it was determined that if the power of the study was to be 80% (using EpiInfo™ version 6) a sample size of 116 respondents was needed.

A convenience sampling method was used. The questionnaire was presented at academic departmental meeting at each of the four individual hospitals, CHBAH, CMJAH, RMMCH and HJH. Doctors attending these meetings were approached for inclusion in the study. They were requested to only complete the questionnaire once. Inclusion criteria and exclusion criteria for study were defined.

1.9.1 Data collection

1. Development of questionnaire

No questionnaires assessing the appropriate administration of Syntocinon® were identified. A draft questionnaire based on a review of the literature was developed by the researcher with guidance from the co-supervisor, who is a specialist in the field of anaesthesiology and pharmacology.

The self-administered questionnaire consisted of three sections.

Section 1 requested demographic data

Section 2 consisted on knowledge questions

Section 3 addressed current practise regarding Syntocinon®.

2. Data analysis

A Microsoft ® Office Excel spreadsheet was used to capture the data. Data was analyzed using STATISTICA version 11. Descriptive and inferential statistics were used.

1.10 Significance of the study

Syntocinon® is used routinely in patients following delivery. This is a 'black box drug' and is associated with serious complication and therefore adequate knowledge when administering this drug is of utmost importance. Numerous studies (17-19) have shown that doctors have inadequate knowledge in regard to medication prescribed and administered.

It was therefore imperative that the current knowledge of doctors in the Department of Anaesthesiology was determined. Since knowledge was found to be lacking, educational initiatives were implemented and a formal protocol should be developed and introduced in the department adhering to international guidelines.

1.11 Validity and reliability

Measures were taken to ensure the validity and reliability of the study. Validity emerges from the internal and external consistency and relevance of the questionnaire, whilst reliability refers to the quality of the questionnaire.

The questionnaire (Appendix Two) underwent a validation procedure that accurately measured its objectives, regardless of the study population's status, timing of response and different investigators. The elements used in the validation of the questionnaire were: construct validity and content validity.

1.12 Study outline

This study is presented as follows.

Chapter One: Overview of the study.

Chapter Two: Literature review.

Chapter Three: Research methodology.

Chapter Four: Results and discussion.

Chapter Five: Summary, limitations, recommendations and conclusion.

1.13 Summary

An overview of the study was presented in Chapter one. In the following chapter a review of the literature relevant to this study is presented.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

The World Alliance for Patient Safety (22) states: “The main threats to patient safety worldwide are inadequate numbers of equitably distributed qualified health care providers and incomplete knowledge about safe practise.”

Globally PPH is the leading cause of maternal mortality and recent studies (3, 5, 11, 23) have shown that the rates of PPH due to uterine atony are increasing. Prevention and management of PPH is crucial to improve maternal safety.

Another of the aspects that contribute to safe practise is the knowledge and correct use of medication. Knowledge of physicians seems to be varied and often lacking in regards to administration, cost, pharmacokinetics and pharmacodynamics of medication. (24-27)

In this chapter the main discussion will be of oxytocin. The FDA has recently placed a black box warning on the correct indication for use and use during labour (28). Oxytocin is the first line treatment in prevention and management of PPH, therefore the literature review will begin with a brief overview of PPH.

The discussion on Oxytocin will include the history, mode of action, route of administration complications, dosage and guidelines for administration. Lastly there will be a discussion of doctors’ knowledge of medication in general and oxytocin specific.

2.2. Post-partum haemorrhage (PPH)

Globally PPH is the leading cause of maternal mortality and recent studies have shown that the rates of PPH due to uterine atony are increasing (11). Prevention and management of PPH is crucial to improve maternal safety (5-7).

2.2.1 Definition

PPH is defined as being an estimated blood loss of 500 ml or more during vaginal delivery and more than 1000 ml for a caesarean delivery. Primary PPH develops within 24 hours of delivery and is due to uterine atony; retained placenta; genital tract trauma; placenta accreta, increta or percreta; uterine inversion; or coagulopathy.

Secondary PPH is relatively infrequent, develops more than 24 hours after delivery, and is ascribed to subinvolution of the placental site, retained products of conception, infection, or inherited coagulation defects. (29)

2.2.2 Incidence

Caesarean section is one of the most commonly performed major operations in women throughout the world, with rates escalating to between 20-30% in developed countries yearly (30, 31).

According to WHO more than 500 000 women die as a result of the complications of pregnancy and childbirth with PPH due to uterine atony being the most causative factor (1, 2, 5). Internationally obstetric haemorrhage continues to be the most common avoidable cause of maternal death (6).

Between 1994 and 2006, rates of PPH have increased by 30% in the United States of America, almost entirely attributable to increases in postpartum uterine atony and accounts for 13 % of all maternal deaths (29).According to the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) the incidence of PPH in Australia is between 5 and 15% yearly (23).In India it was suggested that between 31% and 34% of maternal deaths were due to PPH (32).

In South Africa, during the period 2008-2010, there were 688 maternal deaths as a result of obstetric hemorrhage. This represented a significant increase (32,4%) in the Institutional Maternal Mortality Rate related to obstetric haemorrhage, from 18.82/ 100 000 live births in 2005-2007, to 24.91/ 100 000 live births in 2008-2010. (6, 33)

2.2.3 Risk Factors

According to the RCOG guideline causes and risk factors for PPH are related to:

- tone (abnormalities of uterine contraction)
- tissue (retained products of conception)
- trauma (of the genital tract)
- thrombin (abnormalities of coagulation). (34)

The most common cause for primary PPH is uterine atony, but other causes such as retained products, vaginal lacerations, ruptured uterus, broad ligament haematoma, extragenital bleeding and uterine inversion have also been implicated. Secondary PPH is often associated with endometritis. (34, 35)

2.2.4 Management of PPH

An uterotonic agent such as oxytocin is used to induce contraction of the uterus, it has also become the first line agent in the management and prevention of PPH.

Second line agents are available such as ergot alkaloids and prostaglandins but this study will focus on the use of oxytocin. (5, 30)

Guidelines will be discussed after oxytocin administration as there is overlap between the topics.

2.3. Oxytocin

2.3.1 History

Historically the posterior pituitary gland 'extract' has been used in the presence of PPH since 1901, and in 1928, Kamm et al (13) separated this 'extract' into oxytocin and a vasopressor. Oxytocin in its modern day form was first discovered by Sir Henry Dale and was also the first polypeptide hormone synthesised by Du Vigneaud, in 1953 (5, 36). In the late 1960s O'Driscoll advocated the use of oxytocin intrapartum as a component of active management of labour (36).

2.3.2 Mode of action:

The term oxytocic (or oxytocinergic) specifically applies to those drugs where the oxytocin receptor is the binding and activation site. Oxytocin is the most widely used uterotonic used for caesarean section and prophylactic routine use of oxytocin has been shown to reduce the incidence of PPH by 40%. (37, 38)

Oxytocin is a nonapeptide hormone produced by the paraventricular nuclei of the hypothalamus and is stored and released mainly by the posterior lobe of the pituitary, but also at other sites namely the corpus luteum, Leydig cells, adrenal medulla and retina (5).

Structurally oxytocin is very similar to anti-diuretic hormone (ADH), differing only in the substitution of two amino acids, explaining both its anti-diuretic actions and vasoactive properties in high doses. Both hormones are degraded and broken down by the same aminopeptidases.(13)

Oxytocin binds to a G-protein (oxytocin receptor) on the surface of the uterine myocyte, resulting in the generation of diacylglycerol (DAG) and inositol tri-phosphate (IP3) via the action of phospholipase C on phosphatidyl-inositol biphosphate (5, 39). DAG stimulates prostaglandin synthesis, and IP3 stimulates the release of calcium from the endoplasmic reticulum (5). Calcium released from the endoplasmic reticulum binds to, and activates, calmodulin, the calcium calmodulin complex then binds to myosin light chain kinase (MLCK), enabling phosphorylation of the short chain of myosin and causing formation of adenosine triphosphate (ATP) and muscle contraction (5, 7).

Oxytocin also activates the COX-2 via a further G-protein interaction thereby stimulating prostaglandin synthesis (5). There are oxytocin receptors in the uterus, and receptors are also located in the mammary, endothelial, and central nervous tissue (39, 40). The concentration of myometrial receptors and myometrial gap junctions increase as gestation advances, increasing sensitivity to oxytocin (5). The effect of oxytocin on endothelial receptors produces a calcium-dependant vasodilatory effect via stimulation of the nitric oxide pathway, thus producing hypotension and cardiovascular side effects (40). Most importantly it causes contraction of the uterus, which is why it is so useful in the management of PPH (8, 37, 38).

Oxytocin causes contraction of the myo-epithelial cells surrounding the mammary alveoli, thereby facilitating lactation in women experiencing difficulties with breast feeding (41). It also has a role in cardiovascular regulation, in sexual and maternal behaviour, and in memory and the regulation of food and fluid intake. Oxytocin has been shown to cause the release of atrial and brain natriuretic peptide, and in animal studies have shown to have negative inotropic effects. (5)

During pregnancy the uterine oxytocin receptors increase progressively and reach a peak at term. In late pregnancy prior to the onset of labour the amount of oxytocin receptors are on average 12 times higher than in early pregnancy and about 80 times higher than in the non-pregnant uterus. The plasma concentration of oxytocin is similar during pregnancy and during labour; however, there is a significant increase in the plasma concentration during the last part of the second stage of labour. (32)

The non-labouring uterus remains more sensitive to oxytocin at term and thus low dose oxytocin at this stage might have optimum efficacy, without the deleterious effects of high dosages (32). During the onset of labour, uterine sensitivity to oxytocin increases and oxytocin receptors express diffusely and heterogeneously. By increasing the dosage of oxytocin administered it could be assumed that more effective uterine contraction would take place but, the response will be inadequate. (32) This is due to the fact that with continuous exposure to oxytocin the human myometrial cells' oxytocin receptors lose their capacity to respond to the oxytocin by becoming desensitised and reduced. The oxytocin induced desensitization is dependent upon the duration of oxytocin exposure and occurs over a clinically relevant time frame of approximately 4.2 hours. Consideration should be given to the alternate pathway of uterotonic medications such as ergot derivatives, carboprost and misoprostol. (32, 38)

Oxytocin is released by the neurohypophysis in intermittent bursts determined by neurosensory stimuli, such as cervical dilatation, stimulation of the inferior genital tract, suckling by infant on the nipple and an increase in plasma osmolality (13).

2.3.3 Route of administration

Oxytocin may be administered intravenously (IV), intramuscularly (IM), or via the umbilical vein, buccal or nasal mucosa. The IV route has been in question due to the hemodynamic side effects; however the IM route has a much slower onset but lower side effect profile. (41, 42)

To diminish adverse effects when administering oxytocin as an IV bolus 'slow' dosing is advisable, but the most adequate speed of infusion has not yet been determined. (13)

Synthetic oxytocin such as Syntocinon® is the most widely used oxytocic, and it has a short half-life of approximately 3-5 minutes (8, 41, 42). It is often used as an IV bolus, but an infusion may be used to maintain uterine contraction especially in managing PPH (8, 41, 42). It can also be given as an IM injection, with the myotonic effects appearing on the uterus in 3-7 minutes and persisting for 30-60 minutes (42).

The timing of oxytocin administration remains debatable. Oxytocin intra-operatively can be administered before placental separation or after expulsion. Optimal timing is unclear and has not been evaluated in the literature. A randomized controlled trial comparing the different timing of administration did not find any difference between the groups in terms of blood loss and risk of placental retention (43). Most randomized trials administered oxytocin before placental separation (44).

Oxytocin clearance is via the kidneys and the liver and only a small fraction is excreted unchanged in the urine (13).

2.4 Guidelines and dosages

Internationally guidelines and protocols exist in the management of certain medical disorders, but often physicians do not follow guidelines. Physician adherence to guidelines is critical to the improvement of outcomes in patients, but following a guideline without adequate knowledge of the drug has also proven to be disastrous to patient outcomes. (23, 34, 45-47)

Currently no guideline exists on the administration of oxytocin for uterine atony in uncomplicated caesarean section internationally, although guidelines do exist in the management of PPH (6, 34, 37, 46, 47).

According to the ESMOE guidelines and the monograph of the management of PPH, the majority of PPH related deaths are preventable. The monograph also gives clear guidelines to doctors, midwives and paramedics as to how to prevent and manage women with massive PPH.(48)

SASA has no guidelines specific to use of oxytocin in uncomplicated caesarean section. (46)

The World Federation of Societies of Anaesthesiologists (WFSA) uses the guideline of a slow IV bolus of 5 U that can be repeated if needed, infusion can be commenced using 10 U/hr for 4 hours. (49)

The Royal College of Obstetricians and Gynaecologists (RCOG) and National Institute of Clinical Excellence (NICE) recommend the use of a bolus of 5 U oxytocin by slow IV injection with the option of repeated dosages, if further uterine atony continuous an oxytocin infusion of 40 U in 500 ml Hartmann's solution at a rate of 125 ml/hour is recommended. (8, 35)

The American Congress of Obstetricians and Gynaecologists recommends 20 U in 500 ml Ringer's lactate at 125 ml/hour. There should also be a low threshold when using second-line agents to avoid side-effects. (50)

The guideline for the management of PPH from the Society of Obstetricians and Gynaecologists of Canada is the administration of oxytocin either IM or IV in small doses (unspecified amount) and if bleeding still continues 20 U of oxytocin in 1 litre of Ringer's Lactate with no infusion rate specified. It also advises that oxytocin can be administered intra-myometrially 10 U in circulatory collapse (51).

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) guideline recommends the use of oxytocin by slow IV injection or infusion but no dosage or infusion rate is specified (23).

SASA has no prescribed guideline on the management of PPH, but according to the South African Saving Mothers Report of 2008-2010 the guideline for the management of PPH is a 2.5 U bolus IVI of oxytocin followed by an IV infusion of 10 U of Syntocinon® in 1 litre of Normal Saline, no dosing rate of infusion is given (6).

According to the South African Society of Obstetricians and Gynaecologists, the management guideline for PPH advises an IV infusion of 20 U of oxytocin with no rate of infusion specified (52).

According to the national ESMOE guidelines for district and regional hospitals, one should give 2,5 U oxytocin IV slowly over 1 minute and infuse 20 U of oxytoxin in 1 litre of clear fluid over eight hours.(53)

In comparison to anaesthetic guidelines, obstetric guidelines advise much higher dosages of oxytocin, not necessarily in keeping with recent anaesthetic literature. (52)

Recent studies have shown that lower dosages of oxytocin were as effective at contracting the uterus as higher dosages and in view of multiple side effects it is desirable to administer the lowest effective dose in a stable manner (5, 54).

A comparison of intravenous boluses of oxytocin, either 2 U or 5 U showed less marked heart rate and blood pressure changes after 2 U, with no difference in requests for additional uterotonic agents. This study also found that a slow infusion of 5 U of oxytocin compared to a fast bolus of 5 U produced less cardiovascular instability (5, 12). The efficiency of slow infusions in terms of uterine contraction is difficult to assess other than by subjective means clinically by the obstetricians (5).

A study done during 2010 at the Lucile Packard Children's Hospital in California found that the routine use of 5 U of oxytocin was no longer recommended since adequate uterine contraction could be achieved with lower doses of oxytocin (0.5- 3U), therefore also decreasing the risk of cardiovascular side effects with higher doses. (54)

In an observational study, oxytocin was used in incremental doses of 0.1-0.5 U during caesarean section in patients with advanced cardiac disease that included cardiomyopathy, congenital and valvular heart disease. There was acceptable hemodynamic stability, although even these small doses were associated with transient changes in blood pressure and cardiac output.(40)

The dose and rate of intravenous infusion of oxytocin after delivery during caesarean section remains controversial and there have only been four dose-finding studies (5, 54-57).

The first of these is a study by Carvalho et al (57) that reported the effective dose (ED90) for oxytocin was 0.35 U to order to achieve successful uterine contraction during elective Caesarean section. The up-down sequential method of establishing effective mean dose was used.

Butwick et al (54) conducted a double-blinded, randomised control study to examine the effects of four different doses (0,5 U; 1.0 U; 3 U and 5 U) and a placebo.

Seventy-three per cent of patients had adequate contraction with placebo or low oxytocin doses. The authors concluded that an oxytocin dose of 0.5-3 U was adequate to achieve uterine contraction.

The third study by Balki et al (56) carried out an emergency Caesarean section for labour arrest. The ED90 was reported to be 2.99 u, the highest dose needed to achieve adequate uterine contraction in non-elective cases.

There is little evidence for the optimal infusion rate following the initial bolus dose of oxytocin. Using an up-down sequential allocation with a biased coin design, George et al (55) estimated the ED90 of an oxytocin infusion for adequate uterine contraction at 3 min after cord clamping, in patients undergoing elective caesarean section. The estimated ED90 was 0.29 U/min (95% Cl= 0.15-0.43 U/min), i.e. approximately 15 U of oxytocin in 1 litre of IV fluid administered over one hour.

Oxytocin is much less active as an antidiuretic when the infusion rate is less than 45 milliunits/min and thus guidelines and protocols for the prophylaxis of PPH should be restricted to an infusion rate lower than this (5).

Hypovolaemic patients should be managed with great care, as adverse effects with oxytocin infusion are often greater than in well resuscitated patients. (5)

In a recent study by Langaester et al (40), with the administration of a second dose of oxytocin the cardiovascular response was diminished due to the desensitisation of the oxytocin receptors. Oxytocin receptors concentration decreased 60 times during oxytocin augmented labour and 300 times during oxytocin induced labour. Prior exposure of oxytocin to a rat's myometrium suggests that efficacy falls inversely to the concentration, and this was independent to time of exposure. Thus repeated doses of oxytocin become increasingly ineffective and second line uterotonic agents should be administered. (5)

Some studies have also been done by obstetricians with high doses of oxytocin IV infusions, as shown by Munn et al (13) that demonstrated that the continual infusion (2,667 milliunits/minute) of high doses of oxytocin (80 U in 500 ml of Ringer's Lactate) was superior to low doses (10 U in 500 Ml of Ringer's lactate at 333 milliunits/minute) in the prevention of PPH in caesarean section. In a more recent study in 2012, Roach et al (58) used dosages between 5 U and a 100 U of oxytocin with administration time varying from 5 seconds to 30 seconds IV bolus to 8 hour IV infusion in 500 ml Ringer's lactate. The higher infusion doses of 80 U in 500 ml appeared to be more effective at reducing PPH during caesarean section than lower dosages.

However, in both studies no mention is made of any side effects demonstrated by the patients on high dosages of oxytocin, and no mention was made of monitoring done for cardiovascular instability during infusions (13, 58).

2.5 Complications

In the Report on Confidential Enquiries into Maternal Deaths in South Africa of 2004-2007, two deaths were reported where oxytocin played a contributory part (5). Oxytocin also played a role in at least one maternal death in the UK based on the Confidential Enquiry into Maternal Deaths in 1997-1999, and the Food and Drug Administration (FDA) has placed a black box warning on the correct usage and indication for usage during labour (9). A black box warning (or boxed warning) is a type of warning issued by the FDA to a prescribed drug's label and is designated to call attention to serious and life threatening risks (28). Oxytocin is therefore a dangerous drug and adequate knowledge when administering this drug is of utmost importance. Oxytocin is the most recent addition to the Institute for Safe Medication Practises' list of only 12 high-alert medications that carry a heightened risk of causing harm when used erroneously (15).

Oxytocin is associated with numerous side effects especially when given IV as a rapid bolus (38). Side effects include (5, 9, 11, 59-62):

- cardiovascular (hypotension, chest pain, myocardial ischemia and cardiac arrest)
- headache
- flushing
- nausea and vomiting
- water intoxication with hyponatremia
- pulmonary oedema
- seizures and coma
- foetal adverse effects.

2.5.1 Cardiovascular

It was demonstrated that the rapid administration of a bolus of oxytocin IV could reduce mean arterial pressure by up to 30%, 10 to 40 seconds after the injection, lasting up to 210 seconds. (63)

The hypotension experienced with a rapid bolus dose of IV oxytocin may be due to numerous factors namely:

- Vasodilatation of the capacitance vessels decreasing venous return (59);
- Transient relaxation of the vascular smooth muscle cells via the calcium dependant stimulation of the nitric-oxide pathway (5) or;
- The effect of the preservative in some formulations of synthetic oxytocin, chlorbutanol, on atrial myocytes which stimulates the release of atrial natriuretic peptide and brain natriuretic peptide (64).

Patients with a normal volume status, heart valves and pulmonary vasculature usually respond to this hypotension with a compensatory increase in heart rate and stroke volume (65). Thus patients that are normovolaemic with no cardiac disorders tolerate the vasodilatation after a bolus or excessive dosage administration of oxytocin well. However, a large bolus of oxytocin may be fatal in patients with hypovolaemia or other pre-existing cardiac disorders (13).

A method of obtunding the adverse hemodynamic effects of oxytocin was investigated by Dyer et al (11).

A 2.5 U oxytocin bolus at elective caesarean delivery under spinal anaesthesia was given in combination with an 80 mcg dose of phenylephrine IV. The phenylephrine dose did not abolish the hemodynamic effects but managed to obtund them, and the author suggested that the administration of phenylephrine prior to oxytocin might be even more effective.

The vasodilatation of the capacitance vessels although temporary, is much more prominent in the presence of general anaesthesia (13).

Rapid bolus injection of oxytocin results in marked vasodilatation of arteries and capacitance vessels, thereby increasing cardiac output (up to two-fold) (59). Vasodilatation of capacitance vessels decreases venous return, leading to a fall in blood pressure, increase in heart rate and, in some patients, myocardial ischemia (59, 60). Patients presenting with hypovolaemia prior to surgery often respond more severely to a bolus of oxytocin with marked cardiovascular side effects which include cardiac arrest (5, 13, 32).

In a study by Bhattacharya et al (32) it was found that a significant number of cardiovascular events occurred with a bolus regimen of the oxytocin in comparison with an infusion, where uterotonic effects were similar in both groups. It was also shown that in the bolus group, chest pain and ST-T segment depression were more frequent than in the infusion group of patients (29).

Gutkowska et al (66) showed that oxytocin receptors were demonstrated in all the chambers of the heart and that these receptors mediate the action of oxytocin to release atrial natriuretic peptide (ANP) which slows the heart and reduces its force of contraction.

Tachycardia occurs commonly and can be compensatory (secondary to hypotension) or from stimulation of myocardial oxytocin receptors acting on atrioventricular conduction (β stimulation) and repolarisation. Myocardial ischaemia can result when there is an imbalance in the oxygen supply and demand with coronary vasoconstriction. (32, 67)

In a study by McLeod et al (59) it was found that with a slow IV injection of 5 U of oxytocin there was a temporary change in cardiac index and increased heart rate, but the blood pressure remained unchanged. An additional IV infusion of oxytocin did not adversely affect maternal hemodynamics.

A single double blinded study by Thomas et al (68) compared the effects of 5 U of oxytocin when given as an IV bolus or as an infusion over 5 min in 30 women undergoing elective caesarean section. The study measured heart rate (HR), mean arterial blood pressure (MAP) and estimated blood loss between the two groups.

In the bolus group HR increased by 17 beats/min compared to 10 beats/min in the infusion group. MAP decreased by 27 mmHg in the bolus group and a steady decline by 8 mmHg was noted in the infusion group. There was no difference in the estimated blood loss. (68)

Pulmonary artery pressures are markedly increased for at least 10 minutes following a bolus of 10 U of oxytocin during general anaesthesia, in patients with severe pre-eclampsia similar effects were seen at a much lower bolus dosage of 2,5 U (5).

According to the Report on Confidential Enquiries into Maternal Deaths in South Africa of 2004-2007 at least one patient suffered a fatal cardiac arrest after a 10 U bolus of oxytocin IV was administered during emergency caesarean section (5).

2.5.2 Headache and Flushing

A rapid fall in mean arterial pressure may cause a decrease in cerebral perfusion pressure, which often causes headaches and flushing in patients, especially when hypovolaemic. This could stimulate nausea and vomiting that could lead to aspiration and other complications in the pregnant patient. (5)

2.5.3 Water Intoxication and Hyponatremia

Due to structural similarity with vasopressin (an antidiuretic hormone), an overdose of oxytocin may also cause water retention, hyponatremia, pulmonary oedema, seizures and coma (5, 27, 61, 62).

Water Intoxication associated with oxytocin infusion was first reported by Liggins in 1962 (27, 62). It was found that the antidiuretic effect was dose dependant, and a study by Ahmad et al (27) showed that oxytocin caused a marked decrease in the free water clearance.

There is little evidence to determine an optimal rate of infusion following an initial bolus or slow iv administration of oxytocin, but oxytocin is much less active as an antidiuretic when the infusion rate is less than 45 milliunits/min (5).

2.5.4 Foetal Adverse Effects

One of the greatest dangers of an oxytocin infusion is umbilical vasoconstriction leading to foetal hypoxia and even uterine rupture. A decreased blood flow to the foetus could result in a lowered oxygenated arterial blood (SaO_2) in the foetus, seizures, and even retinal haemorrhages. (67)

A study in Asia showed that oxytocin was readily administered in third stage of labour to prevent PPH, but often guidelines for usage were not applied and maternal and foetal outcomes were often poor, with a high incidence of uterine rupture and/or foetal asphyxia (36).

2.6 Knowledge

Firstly knowledge in general of drugs will be discussed followed by doctor's knowledge of oxytocin.
Knowledge of physicians seem to be varied and often lacking in regards to drug administration, costs of drugs, pharmacokinetics and pharmacodynamics of drugs prescribed (19, 24-26).

A study done in Spain by Garcia et al (24) analyzed 1220 physicians' knowledge on generic drugs through a questionnaire, as well as attitudes and professional competence with regards to prescribing these drugs. It was found that physicians' knowledge was inadequate and that Spanish health authorities should offer better training and information about generic drugs to physicians (24).

In Pakistan a cross-sectional study on 131 general practitioners showed that knowledge regarding the major therapeutic use and adverse effects of drugs prescribed was deficient amongst all practitioners. Three commonly prescribed drugs were selected from a list of drugs approved by the Ministry of Health in Pakistan, and a multiple choice questionnaire distributed amongst general practitioners. A statistically significant ($p < 0.01$) lack of knowledge was identified amongst almost 61% of all respondents. (25)
Another study assessing primary health care physicians' knowledge, attitude and practise in the management of osteoporosis in the Al-Jouf province of Saudia Arabia, found that with a response rate of 85% (77/90 questionnaires were returned) most physicians lacked knowledge on the management of osteoporosis. Appropriate attitudes were identified amongst responders but practise regarding the disorder appeared inappropriate. (26)

Rowe et al (69) demonstrated that doctors' knowledge on drug costs was absolutely deficient in a study where 50 doctors working in the National Health Service in England completed a questionnaire on the cost of 15 commonly prescribed medications.

Internationally guidelines and protocols exist in the management of certain medical disorders, but often physicians do not follow guidelines. Physician adherence to guidelines is critical to the improvement of outcomes in patients, but following a guideline without adequate knowledge of the drug has also proven to be disastrous to patient outcomes.(23, 34, 45-47)

A multicentre study conducted in maternity hospitals in Ecuador, El Salvador, Mexico and Uruguay showed that the knowledge of the health providers in regard to giving corticosteroids in preterm labour to prevent risk of respiratory distress syndrome, intraventricular hemorrhage, and neonatal mortality was lacking. Very few health care providers (midwives and physicians) used the recommended regimens. Of the total of 353 healthcare providers, between 11% and 35% responded that their knowledge on the administration of corticosteroids was poor, and in only one country 90% of the responders were following the recommended regimen. (16)

A study in Karnataka, India in-depth interviews were conducted on 140 health care providers which included, physicians, nurses, traditional midwives and unlicensed village/traditional doctors, it was found that oxytocin administrative practises were varied and most responders had little knowledge of adverse effects. Several of the village doctors also insisted that there were no adverse effects, and had never encountered obstetric complications while attending deliveries. (17)

Through this study, physicians and a few village doctors expressed the belief that there was a rampant misuse of uterotonics by unqualified, poorly-knowledgeable health care providers in the community. Nurses also reported that family members insisted on the usage of uterotonic drugs during labour without being aware of potential adverse effects of excessive usage. This study concluded that communication needed to improve between community members and health care providers regarding uterotonic usage and training and other interventions were needed to address identified gaps in knowledge by health care providers as well as up to date information on appropriate uterotonic usage and adverse effects. (17)

Another study done in India's most populous state, Uttar Pradesh, showed that there was uterotonic agent misusage in labour augmentation in both institutional and community deliveries. This was partially due to uterotonics being widely available, the perception that uterotonics were curative agents, and the lack of knowledge of the health care provider administering the drug during delivery. This study also showed that financial incentive played a role in the misusage of oxytocin during delivery, often leading to higher dosages being administered with more adverse effects. (18)

"A private doctor may give one or two injections of Syntocinon® (synthetic oxytocin) for the money, but in government hospital a limited amount is given"- Village Doctor, Gorakhpur. (18)

The administration of any drug thus may be dangerous if given by a health care provider without the adequate knowledge regarding the adverse effects, dosage and administration of that particular drug. Up to date information is essential for safe practise by any health care provider, ranging from physicians, traditional doctors, midwives, nurses and any other practitioner prescribing and administering medication to a patient.

Even with the knowledge that a bolus of 10 U IV oxytocin caused a maternal death in the UK, Bolton et al (19) showed that 23% of physicians still did not change their clinical practise of administering a 10 U bolus.

Irrespective of the fact that guidelines and protocols exist, change in clinical practise is not guaranteed. The implementation of knowledge is therefore the responsibility of the health care provider themselves. (19, 45)

Doctors' in general seem to have variable knowledge of drugs they prescribe and administer to patients (15-19, 24, 26). Jansen et al (14) is of the opinion that doctors should have a comprehensive knowledge of medication they prescribe and administer to patients as these are essential to a doctors' daily practise. No doctor should be allowed to prescribe or administer medication if they do not have up-to-date knowledge of that medication.

2.7 Summary

In this chapter PPH and the management, and usage of oxytocin was discussed. Knowledge of drugs in general and oxytocin was reviewed. In Chapter Three the research methodology will be discussed.

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Introduction

In this chapter the problem statement, aim and objectives, ethical considerations, research methodology and validity and reliability will be discussed in detail.

3.2 Problem Statement

Syntocinon® is a dangerous drug with a narrow therapeutic range in terms of maternal morbidity (3, 5, 11). Legally doctors should have comprehensive and up-to-date knowledge of medication that they prescribe and administer (14).

No specific protocol has been adopted at the Department of Anaesthesiology of the University of the Witwatersrand (Wits) for the administration of Syntocinon®. Current knowledge and practises regarding Syntocinon® amongst Wits anaesthetists was unknown.

3.3. Aim

The aim of the study was to describe the current knowledge and practise of the anaesthetists in the Department of Anaesthesiology at Wits regarding Syntocinon® during caesarean section under spinal anaesthesia.

3.4 Objectives

The primary objectives of this study were to:

- describe the anaethetists' knowledge of Syntocinon®
- describe anaethestists' practise regarding Syntocinon®.

The secondary objectives were to:

- describe the difference in knowledge between the medical officers, junior registrars, senior registrars and consultants
- compare the knowledge between the junior doctors and the senior doctors.

3.5 Ethical considerations

Approval to conduct this study was obtained from the Postgraduate Committee (Appendix 1) and the Human Research Ethics Committee (Medical) (Appendix 2) of the University of the Witwatersrand.

An information letter (Appendix 1) was provided to the participants explaining the purpose and process of the study.

Consent was implied by completing the questionnaire (Appendix 2). To limit data contamination, the researcher was present during the completion of every questionnaire. The researcher aimed to ensure anonymity and confidentiality by requesting that all participants fold and place completed questionnaires in a sealed, closed collection box. By being present during the completion of the questionnaire the researcher ensured that no data contamination could take place between participants in a meeting. Data will be stored securely for six years following completion of the study.

This study was conducted according to the South African Good Clinical Practice Guidelines (20) and the Declaration of Helsinki (21).

3.6 Research Methodology

3.6.1 Research design

A descriptive, prospective, contextual study design was used.

A descriptive study describes data and characteristics about the population or phenomenon being studied. The data description is factual, accurate and systematic. The variables cannot be manipulated by the researcher. (70) This study describes the knowledge and practice of anaesthetists regarding Syntocinon®.

A prospective study is a study design where the variables are measured during the time the study is taking place. (70) By using a questionnaire in this study the variables were measured during the time the study took place.

This study described the level of knowledge and practise regarding Syntocinon ®amongst the anaesthetists working in the Department of Anaesthesiology at Wits, and will be deemed contextual as it took place in a specific location or area. (71)

3.6.2 Study population

The study population consisted of the anaesthetists working in the Department of Anaesthesiology at Wits.

3.6.3 Study sample

3.6.3.1 Sample size

At the time that the study was conducted it was estimated that there were 228 anaesthetists working in the department. A biostatistician was consulted, and it was determined that if the power of the study was chosen to be 80% (using EpiInfo™ version 6), a sample size of 116 respondents was needed.

3.6.3.2 Sample method

A convenience sampling method was used. The questionnaire was presented at academic departmental meeting at each of the four individual hospitals, CHBAH, CMJAH, RMMCH and HJH. Doctors attending these meetings were approached for inclusion in the study. They were requested to only complete the questionnaire once.

3.6.3.3 Inclusion and exclusion criteria

Inclusion criteria and exclusion criteria for study were defined.

An inclusion criterion for this study was all anaesthetists attending the academic departmental meetings and those willing to participate in the study. Incomplete questionnaires were included and questions not complete were taken as incorrect.

An exclusion criterion was defined as questionnaires where individuals could be identified.

3.6.4 Data collection

3.6.4.1 Development of questionnaire

No questionnaires assessing the appropriate administration of Syntocinon® were identified. A draft questionnaire based on a review of the literature was developed by the researcher with guidance from the co-supervisor, who is a specialist in the field of anaesthesiology and pharmacology and the supervisor who has a special interest in obstetric anaesthesiology. The questionnaire underwent validation as follows:

- It was evaluated by four specialist anaesthesiologists who have an interest in obstetric anaesthesia and who are affiliated with Wits.
- It was then evaluated by a professor of anaesthesiology who has a special interest in obstetric anaesthesiology, has undertaken research and published articles regarding Syntocinon® in obstetric usage in anaesthesia, and is also the head of the Obstetric Anaesthesia Special Interest Society (OASIS), a special interest group affiliated with the South African Society of Anaesthesiologists (SASA).

- It was then re-evaluated by specialist anaesthesiologists, and professor emeritus affiliated with Wits who has an interest in obstetric anaesthesiology and pharmacology, who has published a textbook regarding pharmacology application in anaesthesiology.

The self-administered questionnaire (Appendix 2) consisted of three sections.
Section 1 requested demographic data (questions 1 to 3)

- gender.
- years of experience in anaesthesiology
- professional designation e.g. registrar, consultant, medical officer

Section 2 consisted on knowledge questions (questions 4 to 9)

- side effects related to Syntocinon®
- drug receptors and pharmacokinetics of Syntocinon®.

Section 3 addressed current practise regarding Syntocinon®. (questions 10 to 12)

- dosage
- frequency
- rate
- method.

3.6.4.2 Data collection process

Data was collected at random academic departmental meetings until the sample size has been realised. Participants were requested to only complete one questionnaire and refrain from completing questionnaires at each meeting. The researcher was present during completion of questionnaires to assist with possible queries and prevent data contamination. Before distribution of questionnaires they were numbered in order to keep track of completed questionnaires and to calculate a response rate.

Information letter (Appendix 1) and questionnaires (Appendix 2) were distributed following a brief introduction to the study. Anaesthetists were requested to return questionnaires, whether completed or not, in a sealed marked “Return Questionnaire” box.

3.6.5 Data analysis

A Microsoft ® Office Excel spreadsheet was used to capture the data. Data was analyzed using STATISTICA version 11. Descriptive and inferential statistics were used.

3.7 Validity and reliability

Validity of a study shows whether the conclusions of the study are justified based on the design and interpretation (72). Validity of an instrument is defined as its accuracy to perform the intended measurement. (71)

Reliability is associated with the consistency of the measurement technique. (71)

The validity and reliability of this study was ensured by:

- an appropriate study design and data gathering techniques
- a representative sample size determined by a biostatician
- the study population and sample was close to the same size
- selection bias was minimized by approaching all doctors in the department
- the researcher being the only data collector and that the same information is given to all participants, and therefore by being present ensured that no data contamination occurs
- all questionnaires being collected, completed or uncompleted, in a sealed box marked “return questionnaires”
- data analysis techniques being decided upon in consultation with a biostatician.

3.8 Summary

In Chapter Three the problem statement, aim, objectives, ethical considerations, research methodology and the validity and reliability of this study were presented. In the following chapter, Chapter Four the results are presented and discussed.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Introduction

The results of the study according to the primary and secondary objectives, as well as the discussion are presented in this chapter.

The primary objectives of this study were to:

- describe the anaethetists' knowledge of Syntocinon®
- describe anaethestists' practise regarding Syntocinon®.

The secondary objectives were to:

- describe the difference in knowledge between the medical officers, junior registrars, senior registrars and consultants
- compare the knowledge between the junior doctors and the senior doctors.

4.1.1 Sample realisation

A total of 121 questionnaires were distributed between the four hospitals during the period 14 to 28 April 2015. Two questionnaires were excluded as they were returned blank and one was excluded as participant was identified from questionnaire and anonymity was not maintained. Therefore a total of 118 were included in the statistical analysis (n=118) with a response rate of 98%.

4.2 Results

The findings have been described and analysed using descriptive and inferential statistics. All percentages are rounded to whole numbers. Where a question had more than one correct answer each correct answer was allocated one point. Thus, the knowledge section of the questionnaire totalled to 15. Adequate knowledge was described as attaining an average of 80% or more.

4.2.1 Demographics

The gender, years of anaesthesiology experience and professional designation of the participants are shown in Table 4.1.

Table 4.1 Demographics of participants

Demographics	Number (n)	Percentage (%)
Gender		
• Male	56	47
• Female	62	53
Years of anaesthesiology experience		
• 0-4 years	47	40
• 4-8 years	46	38
• More than 8 years	25	22
Professional designation in anaesthesiology department		
• Medical Officer	28	24
• Junior Registrar	35	30
• Senior Registrar	21	18
• Consultant	34	29

4.2.2. Primary objective: to describe the anaesthetists' knowledge of Syntocinon®

None of the 118 participants answered all the knowledge questions correctly. Only 10 (8%) participants received a score ≥ 80%.The mean (SD) score attained for the knowledge questions was 59% (12.11). The number and percentage of correct, incorrect and unanswered questions are shown in Table 4.2.Only 6 (5%) participants correctly identified all six risk factors.

Table 4.2 Results of knowledge test

Question and description	Correct n (%)	Incorrect n (%)	Unanswered n (%)
4. What are the most 5 most common side effects of Syntocinon® administration IV?			
Hypotension	112 (95)	6 (5)	0
Nausea	91 (77)	27 (23)	0
Headache	67 (57)	51 (43)	0
CNS side effects	46 (39)	72 (61)	0
Bradycardia	41 (35)	77 (65)	0
5. Where are the receptors for Syntocinon found?	8 (7)	110 (92)	0
6. What are the risk factors for developing post-partum Haemorrhage (PPH)?			
Multiparity	82 (69)	36 (31)	0
Trauma of the genital tract	71 (60)	47 (40)	0
Retained products of conception	94 (80)	24 (20)	0
Coagulation abnormalities	93 (78)	25 (22)	0
Uterotonic drugs	42 (36)	76 (64)	0
Uterine atony	114 (97)	4 (3)	0
7. Who is the well published South African expert?	41 (35)	70 (59)	7 (6)
8. What is the first line agent in the management of hypotension?	19 (16)	99 (84)	0
9. What agent is an oxytocin antagonist?	32 (27)	76 (65)	10 (8)

4.2.3 Primary objective: to describe anaethestists' practise regarding Syntocinon®

The practise regarding the usage of drugs is often varied according to the knowledge and experience of the user, and when no protocol is in place at an institution regarding the dosage and indication when to use a drug in question, practice varies and may even be incorrect. The practice of anaesthetists regarding Syntocinon® IV administration is shown in Table 4.3.

Table 4.3 Practice of anaesthetists regarding Syntocinon® IV administration

Question and description	Number and percentage n (%)
10. What dose of Syntocinon® IV do you use in an uncomplicated caesarean section under spinal anaesthesia?	
Bolus 2U IV only	29 (25)
2U Bolus IV with 8 U in 1 litre Ringers Lactate at 125ml/hr	40 (34)
5 U Bolus IV only	8 (7)
10 U Bolus IV only	8 (7)
10 U in IV infusion of 1 litre Ringers lactate at a rate of 125ml/hr	14 (12)
2U IV Bolus with 20 U in 1 litre Ringers Lactate at a slow rate/ 125ml/hr IVI	19 (16)
11. Do you use Syntocinon® IV (bolus or infusion) during Caesarean section under spinal anaesthesia?	
Yes with every caesarean section	109 (93)
Yes but only when surgeon indicates it	6 (5)
No but use other uterotonic drugs instead	0
No never use it	3 (2)
12. How do you administer Syntocinon® IV?	
Bolus only	22 (19)
Infusion only	18 (15)
Bolus and infusion	78 (66)

4.2.4 Secondary objective: to describe the difference in knowledge between the medical officers, junior registrars, senior registrars and consultants

The scores obtained for the knowledge test, by professional designation, are shown in Figure 4.1.

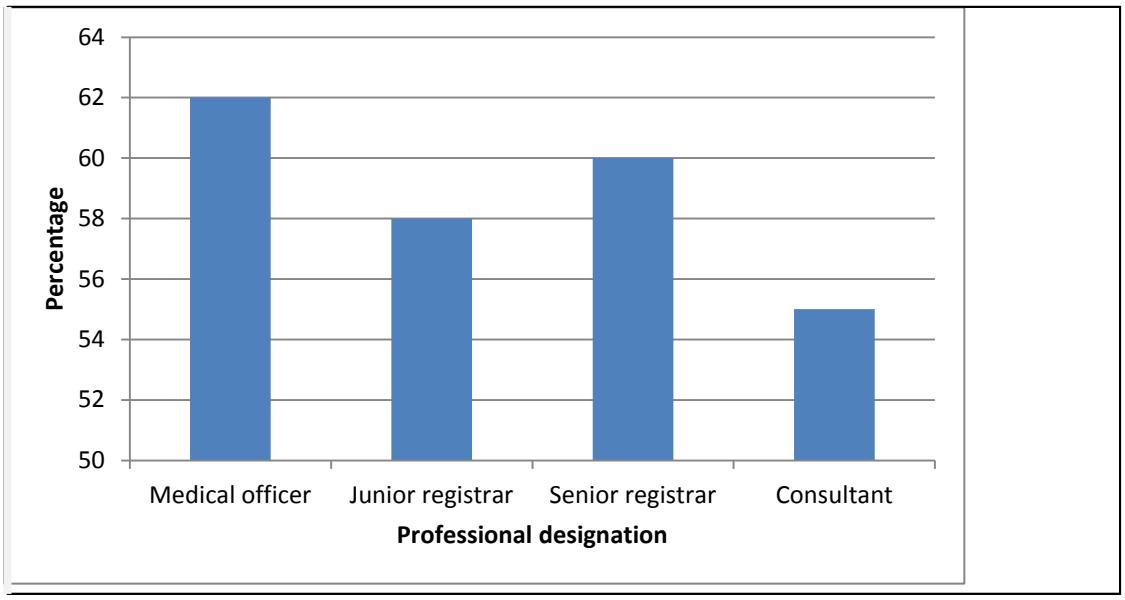

Figure 4.1. A graphic representation of comparison of knowledge of participants according to designation.

4.2.5 Secondary objectives: to compare the knowledge of junior and senior doctors in the anaesthesiology department.

Of the 118 participants, 63 (53%) were junior doctors and 55 (47%) were senior doctors. The junior doctors obtained a mean (SD) score of 60.1% (11.5) and the senior doctors 57.3% (12.7). The mean difference between the scores was -2.8% (95% CI -7.2:1.6) which was not statistically significant (p = 0.2).

4.3 Summary

The results of this study have been presented in this chapter and discussed as per the research objectives. Descriptive and inferential statistics were used in the analysis of these findings. In Chapter 5 the summary limitations, recommendations and conclusion are discussed.

CHAPTER FIVE

DISCUSSION

5.1 Introduction

In Chapter 5, the results and limitations of this study will be discussed in detail.

5.2 Sample Realization

At the time the survey was conducted it was estimated that there were 228 anaesthetists working in the department at Wits. With the assistance of a biostatistician it was determined that to achieve a power of 80% it would be necessary to obtain a sample size of 116 participants. As only 8% of participants obtained a score ≥ 80%, for the knowledge section of the questionnaires, the original calculated sample size may be insufficient.

A total of 121 questionnaires were distributed during the chosen collection period (April 2015), 120 were returned but only 118 were included in the statistical analysis as 2 questionnaires were found to have participant identifiers in the responses. Although the response rate for the survey was 98%, 118 participants represents only 52% of the department at Wits at the time the study was conducted.

Using Raosoft® survey sample calculator, if the population size is 228, the response distribution 50%, confidence level 95% and margin of error 5% the recommended sample size is 144 participants.

As the researcher was only able to distribute 121 questionnaires during the data collection period, an insufficient number of participants may have been enrolled as level of knowledge was found to be poorer than expected when the study was designed.

5.3 Data Contamination

As the researcher conducted the survey at 4 separate academic departmental meetings in order to obtain the necessary sample size, there is a possibility that data contamination could have occurred. It would have been preferable to complete the study on a specific day at a specific time, but due to the nature of the meetings during the period of data collection as well as poor attendance of academic meetings, this was unavoidable. However, the levels of knowledge were still poor and therefore the possibility that data contamination could have occurred has not affected the outcome and recommendations of the study.

5.4 Demographics

Unfortunately, when the questionnaire was designed an error was made in defining years of anaesthesiology experience. Categories of 0-4 years, 4-8 years and > 8 years were options available in the questionnaire, however these categories overlap, and should rather have been 0-4 years, 5-8 years and >8 years experience. This may have lead to participants misclassifying themselves. However, the researcher did not describe knowledge according to years of experience but if the questionnaire were to be used in any future studies the researcher recommends that this be addressed.

Although the definition of junior registrar and senior registrar was included in the research methodology it was not defined for participants on the questionnaire and participants were therefore allowed to self categorize. This may have lead to a misclassification of registrars and therefore the scores obtained for the knowledge test, by professional designation, may be misrepresentative and rather an overall percentage for registrars should have been described. If the questionnaire were to be used in any future studies the researcher recommends that the categories of Junior and Senior registrars be defined for participants on the questionnaire.

5.5 Knowledge Results

The results of this section are similar to other international studies conducted by Rowe et al (69) and Garcia et al (6), that showed in Spain and England knowledge of doctors were deficient when using drugs that are commonly prescribed, such as Syntocinon® IV for caesarean section.

Although only 8% (10) participants obtained adequate knowledge scores as defined as a score of > 80%, the three most common side effects were well identified, yet CNS side effects and bradycardia were poorly recognised. The question relating to the physiology of Syntocinon® was also poorly answered. The lack of knowledge in these areas needs to be addressed in future departmental education programmes.

Although participants scored well in identifying 5 of the 6 risk factors for PPH, the remaining risk factor (uterotonic drugs) was poorly identified with only 42% correctly identifying it as a risk factor for PPH. This may be due to the fact that the option presented may have been ambiguous for participants and that the option available should rather have been presented as inadequate usage of uterotonic drugs or absence of usage of uterotonic drugs. If the questionnaire is to be be used in future studies, the researcher recommends that this options (uterotonic drugs) be more clearly defined for participants.

At the time the study was designed an article regarding the usage of Syntocinon® was published in the South African Journal of Anaesthesia and Analgesia (SAJAA) volume 20, number 1 (2014), ‘New trends in the management of post partum hemorrhage’, the first author of this article was Professor Rob Dyer. Question 7 of the questionnaire, (who is the well published South African expert on Syntocinon®) was designed to indirectly assess if participants had read or knew about this recently published article. The fact that only 41% of participants correctly identified Professor Dyer as the South African expert, suggests that participants may not have up to date knowledge on this topic, or may not be accessing the SAJAA. The researcher recommends that studies regarding readership of the SAJAA and access to information in the SAJAA be performed.

The use of fluid as a first line agent in the management of hypotension was poorly answered with only 16% of participants answering correctly. This question was designed as an open ended question, and if the questionnaire were to be used in future studies perhaps offering options to participants may result in higher scores for this question.

The agent that is an oxytocin antagonist was poorly identified with only 27% of participants correctly identifying the drug. This needs to be addressed in future departmental education programmes.

The study showed that medical officers scored better than registrars, who in turn scored better than consultants in the knowledge section. This is in keeping with the fact that in the Wits anaesthesiology department, medical officers and junior registrars are most often assigned to the obstetric theatres. However, even in these groups the knowledge scores were poor and thus future education programmes should target all professional designations.

5.6 Practice of anaesthetists regarding Syntocinon® administration

Even with the knowledge that a bolus of 10 U IV oxytocin caused a maternal death in the UK, Bolton et al (19) showed that 23% of physicians still did not change their clinical practise of administering a 10 U bolus. As seen in our study at least 7% of participants administered a 10 U bolus IV of Syntocinon® with the knowledge that the latter drug has many side effects as seen from question 10 in the questionnaire (Appendix 2).

In a study by Bhattacharya et al (32) it was found that a significant number of cardiovascular events occurred with a bolus regimen of the oxytocin in comparison with an infusion. As shown in this study 19% of participants are still administering Syntocinon® IV as a bolus and this could contribute to significant maternal morbidity, and standardized protocols need to be urgently implemented to avoid adverse outcomes.

As shown in this study, the practice of anaesthetists at Wits also varied when it came to dosage and usage of Syntocinon® IV and even though international guidelines exist with recommended practice, no standardized practice has been adopted at Wits. This too, needs to be urgently addressed.

Of the 118 participants, 2% of participants reported that they never used Syntocinon® IV. The lack of usage of Syntocinon® IV could have a significant impact on maternal morbidity and mortality and significantly increases the risk of PPH.(5) This needs to be urgently addressed.

The World Federation of Societies of Anaesthesiologists (WFSA) guideline recommends a slow IV bolus of 5 U that can be repeated if needed, thereafter an infusion can be commenced using 10 U/hr for 4 hours. (49) SASA has no guidelines specific to use of oxytocin in uncomplicated caesarean section. (46)The Royal College of Obstetricians and Gynaecologists (RCOG) and National Institute of Clinical Excellence (NICE) recommends the use of a bolus of 5 U oxytocin by slow IV injection with the option of repeated dosages. If further uterine atony continuous an oxytocin infusion of 40 U in 500 ml Hartmann's solution at a rate of 125 ml/hour is recommended. (21,28) The American Society of Obstetricians and Gynaecologists also has a guideline which recommends 20 U in 500 ml Ringer's lactate at 125 ml/hour.(37) Only 66% of participants in this study stated that they use a bolus and infusion technique. This suggests that participants may not be aware of international guidelines and highlights the lack of standardized practice at Wits. Urgent protocols regarding Syntocinon® IV usage needs to be instituted and a standardised practice needs to be adopted in the Wits anaesthesia department.

5.7 Summary

In this chapter the results of the study were discussed. This study has highlighted that there is no current standardised practice at Wits and that knowledge of Syntocinon® in the Wits anaesthesia department is poor. A standardised protocol needs to be urgently implemented and adopted and ongoing departmental education needs to be instituted to prevent adverse maternal outcomes.

CHAPTER SIX

SUMMARY, LIMITATIONS, RECOMMENDATIONS AND THE CONCLUSION

6.1 Introduction

In this chapter a summary of the study, the limitations, recommendations for clinical practice and further research and a conclusion are presented.

6.2 Summary of the study

6.2.1 The aim of the study

The aim of the study was to describe the current knowledge and practise of the anaesthetists in the Department of Anaesthesiology at Wits regarding Syntocinon® during caesarean section under spinal anaesthesia.

6.2.2 Objectives of the study

The primary objectives of this study were to:

- describe the anaethetists' knowledge of Syntocinon®
- describe anaethestists' practise regarding Syntocinon®.

The secondary objectives were to:

- describe the difference in knowledge between the medical officers, junior registrars, senior registrars and consultants
- compare the knowledge between the junior doctors and the senior doctors.

6.3 Summary of the methodology used in the study

A descriptive, prospective, contextual study design was used. A convenience sampling method was used in this study. The study population consisted of 118 anaesthetists working in the Department of Anaesthesiology at Wits. The questionnaire was presented at random academic departmental meetings at each of the four individual hospitals. A self-administered questionnaire (Appendix 2) with a demographics section, knowledge section and a practice section was used to collect data.

The first three questions were demographic related questions. The next six questions (question 4 to 9) tested the participants' knowledge on side effects, pharmacology, and physiology of Syntocinon®. The practice section was divided into 3 questions (question 10 to 12) concerning the administration of Syntocinon®.
The anaesthetists were approached at work during the various departmental meetings and informed of the study purpose via an information letter (Appendix 1) and via the researcher. It was explained that the participant's identity would remain confidential and that there would be no consequence to participating or declining to participate in the study. A questionnaire (Appendix 2) was given to anaesthetists consenting to participate in the study.

The questionnaire was personally distributed to the anaesthetists by the researcher. The researcher was present during the completion of the questionnaire to prevent contamination of information. Once completed, the questionnaire was inserted back into a sealed collection box by the researcher. Blank questionnaires were excluded from the study and those that had questions that were unanswered were taken as incorrect answers. 121 questionnaires were initially handed out and two were returned blank, and one had a participant's name on it, these three were not included in the analysis of the questionnaires, thus 118 questionnaires were included in the study.

6.4 Results

The demographic section consisted of three questions and results showed that approximately half of the participants were female 62 (53%). Of the participants 47 (40%) had between 0-4 years of experience, 46 (38%) 4-8 years of experience and 25 (22%) had more than 8 years of experience.

Only 10 (8%) anaesthetists had adequate knowledge (more than 80% correct answers in the questionnaire).Thus the primary objective to describe anaesthetist's knowledge of Syntocinon® showed an inadequate knowledge in general between all designations of anaesthetists after completion of the questionnaire (Appendix 4).

The second primary objective was to describe the anaesthetists practice with regards to Syntocinon® and the outcome of the questionnaire showed that practice varied amongst anaesthetists and individual's practice was not standardised according to a protocol.

109(93%) participants used Syntocinon.

The knowledge section of the questionnaire showed an inadequate knowledge in general between all designations of anaesthetists. ® IV with every caesarean section and 6(5%) participants only administered Syntocinon® IV at the surgeons' request, whilst 3(2%) participants never gave Syntocinon® IV .Of the 115(98%) participants who did administer Syntocinon® IV the practice varied with regards to dosage and bolus of Syntocinon® IV only and combining a bolus of Syntocinon® IV with IV fluid.

The secondary objectives were to describe the difference in knowledge between the medical officers, junior registrars, senior registrars and consultants. The mean score amongst all participants was found to be 59% and medical officers scored the highest with scores of 62% followed by senior registrars who scored 60%, junior registrars scoring 59% and the consultants scoring 55%.

Of the 118 participants there were a total of 63 junior doctors and 55 senior doctors. The junior doctors obtained a mean score of 60% compared to the senior doctors who obtained a mean score of 57% thus comparing the knowledge between the two designations.

6.5 Limitations

This study was done contextually in the Department of Anaesthesiology at Wits. Therefore, the results may not reflect the knowledge and practices of any other anaesthetists in the anaesthetic community or in other departments.

Convenience sampling was used and thus only the knowledge and practice of those present at the academic departmental meetings was assessed and therefore this study may not reflect the knowledge and practice of the whole department via either over or under representation.

Sample size may not be representative of the whole department as only 52% of the department completed the questionnaire.

As the survey was conducted at 4 seperate academic departmental meetings, data contamination may have occurred.

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6.6 Recommendations for clinical practice

6.6.1 Educational Lecture and email

An educational presentation on Syntocinon® will be given at a combined academic departmental meeting and a follow up email sent to the entire Department of Anaesthesiology at Wits to ensure that all anaesthetists' knowledge and practice is improved.
The outcome of our study showed inadequate knowledge and varied practice in regards to the administration of Syntocinon® in the Department of Anaesthesiology at Wits.
Doctors should also be encouraged to read more recently published articles on IV Syntocinon® as the use of this drug has recently changed. Articles relevant to this topic could be distributed to the department via email.

6.6.2 Guideline and Protocol for Department

A protocol for dosing of Syntocinon® in an uncomplicated caesarean section under spinal anaesthesia should be developed and implemented so that standardised dosing occurs amongst all designations of anaesthetists at the Department of Anaesthesiology of Wits. These guidelines should be distributed amongst the staff and should be clearly displayed as a poster in obstetric theatres.

Guideline posters based on the Essential Steps to the Management of Obstetric emergencies' (ESMOE) recommendations for management of caesarean section emergencies such as PPH should be strategically placed in the labour ward where the doctors and nursing staff can view them frequently and easily.

6.7 Recommendations for further research

a) A follow up study is needed to evaluate the efficacy of the educational programmes put in place to improve the knowledge of the anaesthesiologists at Wits.

b)This study should also be repeated in other Departments of Anaesthesiology across the country as anaesthetists elsewhere may also have a poor knowledge and understanding of Syntocinon®.

c) Research regarding readership of SAJAA is recommended.

6.8 Conclusion

An inadequate level of knowledge and the varying practice with regards to the administration of Syntocinon® amongst anaesthetists in the Department of Anaesthesiology at Wits was found. Further education in regards to practice and general knowledge are necessary to improve patient outcomes and reduce mortality rates.

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Appendix One: Participant information letter

Dear Colleague.

Hello, my name is Marike De Jager. I am an anaesthesiology registrar in the Department of Anaesthesiology at Wits.

I would like to invite you to participate in a research study titled: “Current knowledge and practise regarding Syntocinon® for caesarean sections in a department of anaesthesiology”. This study will contribute towards the fulfilment of my MMed degree in the Faculty of Health Sciences at the University of Witwatersrand.

The aim of the study will be to determine current knowledge and practise regarding Syntocinon® of anaesthetists at Wits. Syntocinon® is a dangerous drug and adequate up-to-date information is necessary to ensure safe practise. This will be assessed using a self-administered questionnaire.

The study has been approved by the Human Research Ethics Committee (HREC) and the Postgraduate Committee of the University of the Witwatersrand.

Taking part in this study may also assist in determining how the department can improve teaching and may possibly lead to the development and implementation of a formal Syntocinon® protocol.

The questionnaire which includes both multiple choice questions as well as open-ended questions will take approximately 10 minutes to complete. The questionnaire completed or uncompleted should be placed into the unmarked envelope supplied and sealed. The information will be anonymous as your name will not appear on the questionnaire. It will also be confidential as only my supervisors and I will have access to the completed questionnaires.

Participation in this study is voluntary and if you decide not to participate no penalty will be incurred.

Before completion of this questionnaire, please ensure that you understand the above information. If you have any questions regarding this study please contact: Professor Cleaton-Jones (chairperson of the HREC) 011 717 1234 or myself, Marike de Jager 082 825 1218.

Thank you for taking the time to read this letter and being willing to participate in the study.

Yours sincerely, Marike de Jager

Appendix Two

Questionnaire:

Please complete/and or circle the most appropriate answer for the following questions:

1. Please specify Gender:

Male	Female

2. Years of Anaesthesiology Experience:

0 – 4 years	4 – 8 years	More than 8 years

3. Position in Anaesthesiology Department at WITS:

Medical Officer	Junior Registrar	Senior Registrar	Consultant

4. What are the most 5 most common side effects of Syntocinon® administration IV? Please tick appropriate boxes

Nausea	Headache	Hypotension	Myocardial Ischemia
Shivering	Water Intoxication	QT lengthening on ECG	Bleeding Tendencies
Bradycardia	CNS side effects	Cardiac Arrest	Visual Disturbance

5. Where are the receptors for Syntocinon® found:

_____

6. What are the risk factors for developing post-partum haemorrhage (PPH)?

Multiparity	Advanced maternal age	Retained products of conception	Primigravida	Twin Pregnancy
Trauma of the genital tract	Coagulation abnormalities	In-vitro Fertilisation (IVF)	Uterotonic Drugs	Uterine Atony

7. Who is the well published South African expert regarding Syntocinon®?

_____

_____

8. What is the first line agent in the management of hypotension after a bolus of Syntocinon® IV was administered?

_____

9. What agent is an oxytocin antagonist indicated for tocolysis in labour?

_____

_____

10. What dose of Syntocinon® IV do you use in an uncomplicated caesarean section under spinal anaesthesiology?

_____

11. Do you use Syntocinon® IV (bolus or infusion) during Caesarean section under spinal anaesthesia?

Yes with every Caesarean section	Yes but only when indicated by the surgeon	No but other uterotonic drugs are used instead	No never

12. How do you administer Syntocinon® IV?

Bolus	Infusion	Bolus and Infusion

Appendix Three: Approval from Ethics Committee