

**A COMPARISON OF COMBINED RECTAL MISOPROSTOL AND OXYTOCIN  
WITH OXYTOCIN ALONE IN THE CONTROL OF BLOOD LOSS DURING  
ELECTIVE CAESAREAN SECTION: A RANDOMISED CONTROLLED TRIAL.**

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**DECLARATION PAGE**

It is hereby declared that this work is original unless otherwise acknowledged. The work has not been submitted in support of an application for a fellowship/degree/diploma of this or any other institution of learning. It has also not been submitted for publication/conference presentation

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# CERTIFICATION



## **ABBREVIATIONS**

CS .....	Caesarean Section
cm .....	centimetre
CSE .....	Combined Spinal Epidural
°C.....	degree centigrade
EDTA.....	Ethylene diamine tetra acetic acid
ICU.....	Intensive Care Unit
IU.....	International unit
IV .....	Intravenous
IM.....	Intramuscular
LAUTECH.....	Ladoke Akintola University Teaching Hospital
µg.....	microgram
ml .....	millilitre
% .....	percentage
PPH .....	Postpartum Haemorrhage
SAB.....	Subarachnoid block
UCH.....	University College Hospital
UITH.....	University of Ilorin Teaching Hospital
UNFPA.....	United Nation Population Fund
UNICEF.....	United Nations Children Fund
UK.....	United Kingdom
Vs .....	Versus
WHO.....	World Health Organization

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## **ABSTRACT**

### **BACKGROUND**

With the rise in Caesarean section rate in many obstetric centres worldwide, control of blood loss during this procedure is of great importance in order to prevent post partum haemorrhage (PPH). Oxytocin is commonly used drug for this purpose but due to problems such as cost and storage especially in developing countries, there is a need to seek other alternatives. Misoprostol may be considered on account of its good uterine contractility and relatively lower cost among others.

### **OBJECTIVES**

The main objective of this study was to compare the effectiveness of the drug regimen of rectally administered misoprostol and oxytocin with oxytocin alone in control of blood loss during Caesarean delivery up to 24 hours after delivery.

### **METHODOLOGY**

The study was a randomised controlled trial involving parturients that had elective Caesarean section at the University of Ilorin Teaching Hospital. They were grouped into two arms. One of the arms had 600µg of misoprostol inserted per rectum while the other arm received 20IU of oxytocin infusion for 4 hours after delivery. Both of the arms had 5IU of oxytocin administered within one minute of delivery of the baby. Intraoperative and postoperative blood loss up to 24hours after delivery, pre and postoperative haematocrit and side effects profiles of the two arms were recorded. Data analysis was done using Statistical Package for Social Sciences software (SPSS) version 21 and a p value set as 0.05 as the level of significance.

## RESULTS

The mean intra operative blood loss was less in the combined oxytocin and misoprostol group than in the oxytocin group ( $550.59 \pm 170.54$ ml versus  $585.07 \pm 163.44$  ml,  $p=0.208$ ). Participants in the misoprostol group had a lower mean change in haematocrit level  $3.58 \pm 1.80$  versus  $3.72 \pm 1.61$  in the oxytocin alone group respectively. The need for additional oxytocics was more in the oxytocin group than in the misoprostol group (29.3% versus 26.7%). Blood transfusion was needed more in the oxytocin group than in the misoprostol group (5.3% versus 1.3%). Shivering and fever were significantly more common in the misoprostol group ( $p =0.02$  and  $p =0.002$  respectively). This was however transient and self limiting.

**CONCLUSION:** Pre delivery rectal misoprostol in addition to bolus oxytocin was comparable to oxytocin bolus and oxytocin infusion currently used in my centre for the control of blood loss during and after CS.

**RECOMMENDATION:** Pre delivery rectal misoprostol and bolus oxytocin is an alternative to oxytocin bolus and oxytocin infusion for the prevention of primary PPH during and after Caesarean section.

## KEY WORDS

Postpartum haemorrhage, Caesarean section, oxytocin, misoprostol

*Word count: Introduction=759 words; Literature review= 3671 words; Aims and objectives= 125 words; Methodology =2423 words; Strengths and limitation =371 words; Results =941 words; Discussion, Conclusions and recommendations =1651 words; Total word count =9941*

## **CHAPTER ONE: INTRODUCTION**

Control of blood loss during Caesarean section remains a major concern for Obstetricians worldwide as postpartum haemorrhage still ranks high as a cause of maternal mortality especially in Sub Sahara Africa.

Postpartum haemorrhage (PPH) is defined as loss of greater than 500ml of blood following vaginal delivery or 1000ml following Caesarean section.<sup>1</sup> It can also be defined as any amount of blood loss that compromises the haemodynamic stability of a woman, a 10% change in the haematocrit between the antepartum and postpartum periods or the need for blood transfusion.<sup>1-4</sup> The world wide prevalence of PPH is 6% with Africa and Asia having the highest prevalence of about 10.5%.<sup>5</sup> PPH contributes 25-30% to maternal mortality.<sup>2,5,6</sup> Majority of these deaths occur within 24hours of delivery. PPH occurring within twenty four hours of delivery is termed primary PPH.<sup>3,7</sup> Available data released in 2015 showed an estimated 58,000 Nigerian women died in child birth and this accounted for 19% of maternal death worldwide.<sup>8</sup> Ogunjimi et al found that primary postpartum haemorrhage accounted for 23-25% of maternal deaths in Nigeria.<sup>9</sup> Thus, it is conceivable that any intervention to prevent primary postpartum haemorrhage will reduce a quarter of maternal death in Nigeria as well as in Sub Saharan Africa. The most common cause of primary PPH is uterine atony accounting for 70-80% of cases.<sup>10,11</sup> Other causes include coagulation defects, genital tract laceration, extension of uterine incision into uterine vessels during Caesarean section and retained placenta.<sup>10,11</sup>

Caesarean section (CS) is about the most common major obstetric procedure done worldwide.<sup>11</sup> The World Health Organization recommends an arbitrary Caesarean section rate of 5-15% as ideal.<sup>12,13</sup> Efetie et al, Okezie et al, Igberase et al, and Adekunle et al in different studies done in Nigeria found Caesarean section rate of 20.8-35.5% with an increasing trend.<sup>14-17</sup> The average

blood loss at Caesarean section is between 500-1000ml.<sup>18-20</sup> This is almost twice the amount of loss during vaginal delivery. It is important to note the high prevalence of anaemia in pregnant women in South East Asia (48.2%) and Africa (57%) compared to 25% in Europe.<sup>21</sup> The prevalence of anaemia in separate studies in Nigeria by Adesina et al and Lamina et al was 30% and 55% respectively.<sup>22,23</sup> The pre-existing anaemia in many pregnant women in this part of the world causes an increased morbidity and (or) mortality for a likely insignificant blood loss and reciprocally increase the risk of postpartum haemorrhage<sup>21,24</sup> As such it is important to explore various modalities in a bid to reduce blood loss during Caesarean delivery.

The administration of oxytocics during Caesarean section is an important intervention to aid uterine contraction thereby preventing PPH. Many obstetric centres utilize oxytocin as the first line uterotonic agent.<sup>5,25</sup> The World Health Organization also recommends that the use of oxytocin is preferable where its use is feasible.<sup>5</sup> It is adjudged the agent of choice for the control of blood loss at delivery. An updated guideline of the Royal College of Obstetricians and Gynaecologists on Caesarean section recommends a slow intravenous bolus dose of 5IU of oxytocin after delivery of the neonate to ensure adequate uterine contractility, reduce delay in the delivery of the placenta, reduce intraoperative blood loss and prevent PPH.<sup>25</sup> Interestingly, despite being adjudged the agent of choice, studies have shown that 10-42% of women who had oxytocin as the sole uterotonic agent required an additional uterotonic agent in the form of prostaglandins or ergot alkaloids during Caesarean delivery.<sup>26-30</sup> Desensitization of receptors has been described after continuous oxytocin infusion<sup>31</sup> resulting in reduced efficacy and so even with repeated doses of oxytocin, there is no effect. The half-life of oxytocin is 5-12 min and implies that frequent repeated doses of oxytocin would not be effective.<sup>32</sup> This desensitization does not however affect response to other

uterotonic e.g. prostaglandins.<sup>32,33</sup> High dose of oxytocin produces hypotension, nausea, vomiting, chest pain, pulmonary oedema, and convulsions.<sup>34</sup>

Several studies have investigated the use of misoprostol in reducing blood loss during CS due to its long shelf life, stability at room temperature and the ease of administration via several routes especially in low resource settings.<sup>10,28,29,35-37</sup> These studies have tried to determine the efficacy of misoprostol and to compare its effectiveness with that of oxytocin when used as a uterotonic drug. Some of these studies have showed that sublingual misoprostol was more effective in reducing blood loss during C/S than oxytocin.<sup>37</sup> However others found misoprostol to be as effective as oxytocin with no significant difference in blood loss.<sup>28,29</sup> Side effects of vomiting, diarrhoea, and shivering were common with the oral and sublingual routes of administration.<sup>28,29,36,38</sup> Rectally administered misoprostol has a slower absorption rate, lower systemic concentration levels, and fewer side effects.<sup>39</sup>

## **CHAPTER TWO: LITERATURE REVIEW**

### **2.1 GENERAL OVERVIEW**

An estimated total of 303 000 maternal deaths occurred worldwide in 2015.<sup>8</sup> Sub Saharan Africa accounted for 201,000 (66%) of these deaths.<sup>8</sup> Furthermore, an estimated 58,000 Nigerian women died in child birth accounting for 19% of maternal deaths worldwide.<sup>8</sup> Maternal death from postpartum haemorrhage still ranks high worldwide and continues to receive attention of the researchers in the medical community.

Postpartum haemorrhage (PPH) is defined as blood loss of greater than 500ml following vaginal delivery or 1000ml following Caesarean section.<sup>1</sup> It is also defined as any amount of blood loss that compromises the haemodynamic stability of a woman, a 10% change in haematocrit between the antepartum and the postpartum periods or the need for blood transfusion.<sup>1-4</sup> Caesarean section is an integral part of obstetric practice. It remains one of the most common major obstetric procedures that is done worldwide.<sup>11</sup> Although blood loss estimation during Caesarean section can be difficult, an average of 500-1000ml is generally quoted.<sup>18-20</sup> The visual estimation of blood loss used in most obstetric centres is flawed with underestimation, hence the gravimetric method of blood loss estimation has been used in some studies during Caesarean section and found to be significantly more accurate and reproducible.<sup>20,40</sup> In a population with a high prevalence of anaemia, an insignificant blood loss of <1000ml can lead to increased morbidity and or mortality.<sup>22,24</sup>

The prevalence of PPH in Asia and Africa is 10.5% and it is responsible for 25-30% of maternal deaths.<sup>2,5,6</sup> Uterine atony accounts for 70-80% of the cause of PPH.<sup>10,11</sup> A large cohort study found the incidence of uterine atony after a primary Caesarean section to be 6%.<sup>41</sup> It is thus conceivable to study ways to reducing the magnitude of this problem.

## **2.2 CAESAREAN SECTION**

Caesarean section is a surgical procedure in which incisions are made through a mother's abdomen and on the uterus to deliver one or more babies.<sup>42</sup>The 1<sup>st</sup> modern (lower segment) CS was performed by a German gynaecologist, Ferdinand Adolf Kehler in 1881.<sup>43</sup>Thereafter, CS has been performed in increasing number with better outcomes. The procedure of CS is often performed when vaginal delivery would put the baby (ies) and (or) the mother's life or health at risk. A recent study carried out in United States of America found a CS rate of 23-40%, a 60% rise from 1996-2001.<sup>44</sup>

CS can be an elective or emergency surgery depending on the urgency with which the procedure needs to be carried out<sup>45,46</sup> The indications for performing this procedure include an abnormal fetal lie, previous scars on the uterus (CS or myomectomy scars), multiple gestation, obstructive tumour (s) in the lower segment e.g. fibroids etc<sup>47</sup>

### **The performance of elective lower segment Caesarean section**

The preparation for an elective CS starts prior to surgery. An informed consent is obtained from the patient after discussion of the indication for surgery, alternative management, and possible complication(s). The pregnancy should be term. The American College of Obstetrics and Gynaecology advice against non-medically indicated elective deliveries before 39 weeks of gestation as this has been shown to improve neonatal outcome without significantly increasing the morbidity to the mother.<sup>48</sup>A retrospective study performed in Enugu, Southeast Nigeria between 2004 and 2008 also found increased morbidity among fetuses born between 37-38 weeks compared to those born after 39 weeks.<sup>49</sup> Elective CS is done after 38 weeks in my centre.

## **Pre-operative management**

A typical 12 hour period of abstinence from food and water is prescribed for patients in my centre. Although Crenshaw et al corroborated this in their study,<sup>50</sup> another study prescribed a minimum abstinence of 2 hours from clear fluids, 6 hours from light meals and 8 hours from regular meals without increased morbidity.<sup>51</sup> Pre-operative evaluation of packed cell volume is important and a value of 30% is adjudged adequate.<sup>52</sup> The increased blood volume that is associated with normal pregnancy typically accommodates the obligatory blood loss during CS.<sup>53</sup> Other pre-operative care practiced include establishment of intravenous (IV) line, infusion of IV fluids, placement of a Foley catheter (continuous bladder drainage and urine output monitoring), as well as attachment of monitors to the patient to monitor the blood pressure, pulse rate determination and oxygen saturation. Pre-operative antibiotic prophylaxis to reduce risk of infectious morbidity is also required. This reduce the incidence of post-partum endometritis by 2/3-3/4 and the incidence of wound infection by 3/4.<sup>54,55</sup>

## **Anaesthesia for Caesarean section**

The anaesthesia for Caesarean section is challenging due to the physiologic changes of pregnancy. Both general and regional anaesthesia are acceptable.<sup>56</sup> Over the years, there has been a shift from general anaesthesia for Caesarean delivery. The type of anaesthesia chosen is dependent on factors such as the urgency and the indication for the surgery, maternal preference as well as co-existing medical problems.<sup>57</sup> The main types of regional techniques used for Caesarean delivery are single shot spinal anaesthesia, epidural anaesthesia and Combined Spinal-Epidural anaesthesia. The odds that a woman will experience PPH is 8.15 times higher with general anaesthesia than with combined spinal epidural anaesthesia.<sup>58</sup> A proper anaesthetic review prior to surgery will

determine the form of anaesthesia that is appropriate for each patient. This is usually performed on the day prior to surgery.

### **Physiology of blood loss during Caesarean section**

Significant changes occur in the haematologic and haemostatic system during pregnancy. These changes help to adapt the body to tolerate the blood loss that occurs during delivery.<sup>53</sup> During the course of pregnancy, circulating blood volume slowly increases by 30-45% with an increase in cardiac output by 40-50%<sup>59,60</sup> The average supply of blood to the uterus at term is 500-800ml/min representing 10-15% of cardiac output.<sup>61</sup> About 400-500mls courses through the placenta bed per minute while the remaining blood supplies the musculature<sup>61</sup> A cut in the major blood vessel during the procedure in order to access the fetus leads to significant blood loss. Constant powerful and effective uterine smooth muscle contractions and retractions are vital to arrest bleeding. The permanently shortened uterine smooth muscle leads to a reduction in the surface area to which the placenta is attached.<sup>62</sup> The incompressible placenta subsequently gets detached from its endometrial lining and is thus delivered.<sup>62</sup> Administration of IV oxytocics and cord traction for placenta removal during Caesarean delivery is associated with less blood loss when compared with manual removal.<sup>63</sup> A systematic review of randomised controlled trials by Anorlu et al found that cord traction for the removal of placenta during Caesarean delivery was associated with less blood loss and decrease in haematocrit level post-operatively; reduced risk of postpartum endometritis, as well as reduced hospital stay when compared with manual removal of placenta<sup>64</sup> An average of 1000ml of blood is lost during the procedure.<sup>18-20</sup>

## **Estimation of blood loss during elective Caesarean section**

It is often difficult to accurately perform an estimation of blood that is lost during CS. Factors contributing to this include amniotic fluid mixing with the blood during the procedure as well as dispersion of the blood on drapes, gowns etc.

Visual estimation remains the most widely used method in Obstetric centres worldwide.<sup>65</sup> This might not be un-related to its being straight forward without the need for major equipment and appliances. This method is however associated with a 30-50% risk of underestimation of blood loss especially with volumes greater than 600ml.<sup>40,65</sup> Other methods of blood estimation include gravimetric method, clinical method, direct collection into measuring containers and acid haematin methods.

The gravimetric method assumes that the density of blood and water are equal at 1gm=1ml.<sup>66</sup> It involves the weighing of materials such as soaked sponges on a measuring scale and subtracting the known dry weights of these materials to determine the blood loss. It is considered the gold standard for comparative purposes.<sup>20</sup> It is also significantly more accurate than visually estimated blood loss.<sup>40,67</sup>

Direct collection of blood into measuring containers can also be used. Accurate measurement of blood can however be flawed with the mixture of amniotic fluid and irrigation fluid in some circumstances.<sup>20</sup>

The acid haematin method utilizes the fact that when blood is mixed with standardized solution, it converts the haemoglobin into acid haematin or cyanmethaemoglobin. The amount of blood can then be determined with spectrophotometry or colorimeter.<sup>68,69</sup> This method may not be suitable for every day obstetric practice.

Although an average of 1000ml is generally quoted as the blood loss during CS<sup>18-20</sup> several studies have found a significantly lower value of blood loss.<sup>29,30,36</sup>

### **2.3 POST PARTUM HAEMORRHAGE**

The definition of postpartum haemorrhage can be difficult and waiting for a patient to meet the postpartum haemorrhage criteria, particularly in resource-poor settings like ours may delay appropriate intervention. With the highest prevalence of 10.5% in Asia and Africa, PPH account for 25-30% of maternal deaths world-wide.<sup>2,5,6</sup> Local study found that PPH accounted for 23-25% of maternal deaths.<sup>9</sup> It is also noteworthy that for a woman who survives from PPH, severe morbidities such as coagulopathy, cardiac and pituitary ischaemia can ensue.<sup>5,9</sup> In a study of 1884 elective Caesarean delivery cases, Magann et al found a PPH rate of 4.84% and 1.9% for blood loss of >1000ml and >1500ml respectively.<sup>70</sup>

Many women who suffer from PPH have no identifiable risk factors.<sup>71</sup> Indeed no woman is immune to this grave complication of pregnancy and delivery. Although studies have found blood loss to be lower than 1000ml during CS,<sup>29,30,36</sup> and pregnant women can tolerate blood loss up to 1500ml,<sup>61</sup> the high prevalence of anaemia in many pregnant Nigerian women can make an almost insignificant blood loss lead to increased morbidity and or mortality.<sup>21,22,24</sup>

The most common cause of primary PPH is uterine atony accounting for as high as 70-80%.<sup>10,11</sup> This entails failure of the uterus to contract resulting in as much as 400-500ml of blood coursing through the placenta bed per minute.<sup>61</sup> Other causes of PPH include retained placenta, genital tract laceration, coagulation defects and uterine inversion.<sup>10,11</sup>

Complications of PPH include anaemia, fatigue, difficulty in care of the new born and failure/poor wound healing to mention a few.

Postpartum haemorrhage occurs most commonly during the third stage of labour. The third stage is defined as the period following complete delivery of the placenta and its membranes.<sup>73</sup> Failure of adequate uterine contraction and retraction leads to defective placenta separation hence excessive blood loss.

#### **2.4 Management of third stage of labour**

Active management of the third stage of labour is advocated. This is defined as a series of interventions that are instituted during the third stage of labour and include use of a uterotonic drug immediately following delivery of the fetus, controlled cord traction and early cord clamping and cutting.<sup>62,73</sup> It is highly effective at preventing postpartum haemorrhage during facility based deliveries.<sup>62</sup>

Systematic review of randomized control trials have shown that active management of third stage of labour was more effective than physiological management in preventing blood loss and severe postpartum haemorrhage (>500ml).<sup>74</sup>

#### **2.5 Uterotonic Agents**

Drugs that are used to stimulate uterine smooth muscle contraction are called uterotonic drugs. These drugs have been used in hastening placenta separation hence reducing the risk of postpartum haemorrhage. These agents include oxytocin, misoprostol, ergometrine, cabetocine as well as syntometrine.

##### **Oxytocin**

Oxytocin is a naturally occurring hormone that is produced in the hypothalamus, transported and stored in the posterior pituitary gland.<sup>75</sup> This cyclic nona peptide was discovered by Dale in 1906,<sup>76</sup>

while its amino acid sequence was elucidated about 50 years later by Vigneaud, leading to its chemical synthesis.<sup>77</sup>

Oxytocin is dispensed in 1ml ampoule containing 10IU of oxytocin and can be administered via intravenous or intramuscular routes.<sup>78,79</sup> Oxytocin is rapidly absorbed with an onset of action of 1 and 3-5 min when administered via the intravenous and the intramuscular routes respectively.<sup>79</sup> It has a plasma half-life of 5-12 min,<sup>32</sup> and duration of action of 40 min when given intravenously and 2-3 hours when given intramuscularly.<sup>79</sup> It has a negligible plasma protein binding capacity.<sup>79</sup> This drug undergoes proteolytic inactivation in the alimentary canal when administered via the oral route.<sup>78</sup> Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy and is responsible for the degradation of oxytocin producing metabolites that are mainly excreted in the urine.<sup>79</sup> Less than 1% of oxytocin is however excreted unchanged.<sup>78,79</sup> Oxytocin requires storage at 2-8°C.<sup>79</sup>

The action of oxytocin is exerted via G-protein coupled receptors.<sup>79</sup> These receptors gradually increase towards the end of pregnancy and in the immediate postpartum period and when activated trigger release of Calcium from intracellular stores leading to uterine smooth muscle contraction hence closure of the blood vessels thereby preventing postpartum haemorrhage.<sup>62,79</sup>

Notable side effects of oxytocin are severe decrease in maternal systolic and diastolic blood pressure, increase in heart rate, systemic venous return and cardiac output as well as arrhythmia.<sup>79</sup> Oxytocin has a weak anti-diuretic property and can induce water intoxication.<sup>34,79</sup>

### **Misoprostol**

This drug is a synthetic prostaglandin E1 analogue that was developed by Searle in 1973.<sup>80</sup> It was originally produced to prevent and treat peptic ulcer disease,<sup>80</sup> but its uterotonic and cervical

ripening property has made it an important drug in obstetric and gynaecologic practice. It is a medication used to induce abortion, induce labour, as well as prevent and treat postpartum haemorrhage.

Misoprostol which is dispensed in tablet form, can be administered via several routes.<sup>81</sup>This includes the oral, sublingual, vaginal, as well as the rectal routes. These various routes of administration affect the pharmacokinetic property of the drug, an understanding of which is essential for its various clinical applications with the relative side effect.

Orally administered misoprostol is rapidly absorbed with an onset of action of 8minutes.<sup>81</sup>It however undergoes extensive first pass metabolism with a total duration of action of 2hours. The sublingually administered drug also has a rapid onset of action of 11minutes with a total duration of action of 3hours.<sup>81</sup>When misoprostol is given per vaginum and per rectum, it is gradually absorbed and has an onset of action of 20minutes and 100minutes respectively with a total duration of action of 4hours both.<sup>81,82</sup> The peak serum concentration is higher in individuals whose drugs were administered via the sublingual route than those whose drugs were administered via the rectal routes. The plasma half life of misoprostol is 20-40minutes.<sup>81</sup> Mechanism of action of misoprostol is by binding to myometrial muscles leading to uterine contraction and closure of uterine blood vessels and prevention of PPH.<sup>62</sup>

Misoprostol given orally or sublingually has the relative ease of administration with rapid onset of action.<sup>81</sup>The vaginal and rectal routes have a sustained pattern of release hence a longer duration of action that is necessary to keep the uterus contracted to prevent PPH.<sup>63,81</sup>Patients undergoing general anaesthesia as well unconscious patient can utilise rectally administered

misoprostol.<sup>38</sup>Sublingual misoprostol has been found to cause unpleasant taste and sense of numbness over the mouth and throat.<sup>81</sup>

Misoprostol is cheap, widely available, stable at room temperature and has tolerable side effects.<sup>81</sup>It is noteworthy that uterine contractility is better with sustained level of drug rather than high serum concentration.<sup>81</sup>Common side effects include nausea, vomiting, diarrhoea, shivering and pyrexia.<sup>81,82</sup>

### **Ergometrine**

Ergometrine is an ergot alkaloid. It is given following delivery of the fetus to cause sustained myometrial contraction. It also acts on the vascular smooth muscle and thus is not suitable for patients with hypertension, heart disease and peripheral vascular disease. It is given as 0.25mg or 0.5mg either intramuscularly or intravenously with rapid clinical effect within 2 to 5 minutes of administration and can persist for 3hours.<sup>83</sup>Ergometrine is metabolized in the liver. It has a plasma half-life of 30minutes.<sup>83</sup> Nausea, vomiting and dizziness are commonly reported side-effects.<sup>83</sup>

### **Syntometrine**

This drug consists of a combination of 5IU of oxytocin and 0.5mg of ergometrine in a single preparation. It utilizes effects of the rapid onset of uterine contraction due to its oxytocin property and sustained contractility from the ergometrine component.<sup>84</sup>

### **Carbetocin**

Carbetocin is a long acting synthetic oxytocin analogue. It can be administered via the intramuscular or the intravenous route with recommended dose of 100µg. Carbetocin has a rapid onset of action of 2minutes irrespective of the route of administration. Intramuscular carbetocin has a longer uterine contractile effect of 2 hours when compared with the intravenous route of 1

hour.<sup>85</sup>Side effects of carbetocin include headache, hypotension, tremor, flushing, abdominal pain and nausea.<sup>85</sup>

Although rare, it can also be associated with dizziness, chest pain, dyspnoea, metallic taste, vomiting, back pain and chills.<sup>85</sup>

## **2.6 COMPARISON OF THE VARIOUS UTEROTONIC AGENTS**

The right choice and the proper use of one or two uterotonic agents can control PPH and reduce maternal mortality by up to 40%.<sup>5</sup>

For many years, the uterotonic agent that was most widely used was oxytocin. It is adjudged the agent of choice for the prevention of postpartum haemorrhage. Its proper use can be hindered in many developing countries like Nigeria with the requirement for storage at 2-8°C that might not be readily available and the need for extra consumables like intravenous fluids, gloves and syringes; increasing the cost. Its use can also be marred by lack of expertise and equipment to deliver the proper and adequate infusion dose while avoiding fluid overload, a known complication of oxytocin infusion.<sup>10,81</sup>

Ergometrine is an effective uterotonic agent that causes sustained uterine contraction necessary to prevent PPH. Draw back to its use include ampoule of the drug being unstable at room temperature thus requiring special temperature and light storage conditions to remain effective. It is also not suitable for women who are hypertensive due to its effect on vascular smooth muscle.

Carbetocin, although a very effective drug, is expensive and might not readily affordable in many developing countries. The side effects of this drug also limit its routine use in obstetric practice.

Misoprostol, an oral preparation of prostaglandin (PGE<sub>1</sub>) analogue, is a prime candidate due to its uterotonic properties. Its ease of use via several routes (oral, sublingual, buccal, vaginal, and rectal) makes misoprostol a good choice of drug. Misoprostol is also relatively low in cost. It is stable at high temperature that is found in most tropical countries like Nigeria. Known side effects like nausea, shivering, and vomiting are self-limiting usually without any sequelae. After rectal administration, plasma levels are maintained for a longer period than when administered via the sublingual route.<sup>81,82</sup> The rectally administered drug is also associated with less and more tolerable side effects because of its lower peak plasma concentration.<sup>39,83</sup>

Several studies have been done and reports published on the use of misoprostol for the prevention of PPH during CS, some of these studies have found misoprostol to be a potential alternative to oxytocin.<sup>29,37,86</sup> Owonikoko et al<sup>29</sup> compared the use of sublingual misoprostol to oxytocin infusion, the study reported blood loss to be less in the oxytocin group, it was not statistically significant. Another study by Ugwu et al<sup>36</sup> have compared the use of sublingual misoprostol and oxytocin with oxytocin alone, they reported a significant difference in the blood loss in the combined misoprostol with oxytocin group to the oxytocin group. This study aims to fill this knowledge gap by evaluating combined use of misoprostol via the rectal route with oxytocin and the use of oxytocin alone in the control of blood loss during CS.

## **2.7 EFFICACY AND SAFETY OF UTEROTONIC AGENTS**

Intraoperative blood loss, immediate postoperative blood loss (up to 4hrs), need for additional oxytocics, change in the pre and postoperative haemoglobin concentration at 24hrs, as well as occurrence of side effects are some of the factors that have been utilized in previous studies to determine the efficacy and effectiveness of misoprostol and oxytocin during CS.

Although the WHO recommends the use of oxytocin during CS,<sup>72</sup> systematic reviews of randomised controlled trials found no significant differences in intraoperative and postoperative haemorrhage when misoprostol was compared with oxytocin.<sup>10,30</sup> In fact Vimala et al and Fazel et al found blood loss to be lower in the misoprostol group when compared with the oxytocin group.<sup>37,87</sup> This was however not the finding of Owonikoko et al at LAUTECH where the mean blood loss was higher in the misoprostol group (667ml) as compared to the oxytocin group (650ml), although, this was not statistically significant.<sup>29</sup> In another study that was conducted by Ugwu et al, at the University College Hospital, Ibadan, South west Nigeria, recorded a blood loss was 451ml and 551ml in the misoprostol and oxytocin group respectively.<sup>36</sup> This finding was similar to that obtained by Sood et al in India.<sup>28</sup> Estimated blood loss in the postoperative period was lower in both Nigerian studies quoted above.<sup>29,36</sup> Adinakin et al found no difference in the postoperative blood loss.<sup>87</sup> Blood loss estimation was carried out with the aid of the gravimetric method and suction jar, hence the comparable results.<sup>28,29,36,87</sup>

Owonikoko et al<sup>29</sup> reported twenty four patients in the misoprostol versus 21 patients in the oxytocin group required the use of additional uterotonic agents.<sup>29</sup> Vimala et al, Ugwu et al and Sood et al however found the need for additional oxytocic in the oxytocin group.<sup>28,36,37</sup> Systematic review of randomized controlled trials also found that the need for additional uterotonic agents was less in studies of combined misoprostol and oxytocin versus oxytocin alone.<sup>10,30</sup>

Prostaglandins and their analogues exert their uterine contractility effect via a separate receptor from that of oxytocin. Prostaglandins and their analogues therefore have synergistic effect with oxytocin on myometrial contraction. Hence potentiate the uterine action of prostaglandins and analogues.<sup>79</sup>

Despite reported finding of lower blood loss in the misoprostol group in some studies, there was no significant difference in the mean pre and postoperative haemoglobin concentration.<sup>28,29,36,37</sup> Elsedek while comparing the use of rectal misoprostol and oxytocin with oxytocin alone reported a significant difference between the pre and postoperative haemoglobin concentration in misoprostol and oxytocin group (4.62 versus 8.15 respectively).<sup>38</sup>

Misoprostol was found to be associated with more side effects in these studies; the effects were usually transient, without serious sequelae and were preferable and acceptable when compared to the consequences of PPH especially in a low resource setting like Nigeria.<sup>29</sup> Overall, the rates of side effects, mainly shivering and pyrexia, were higher among women that received misoprostol alone or combined with oxytocin than among women that received oxytocin alone.<sup>30</sup> The increased risk of side effects was more apparent in trials that used sublingual when compared to other routes of administration.<sup>30</sup> Another reported side effect is unpleasant taste when misoprostol was administered via the sublingual route.<sup>37</sup> Other side effects include nausea, vomiting and hyperpyrexia.<sup>81</sup> The rectal routes of misoprostol use is an appropriate alternative for oxytocin in patients undergoing Caesarean section with less side effects and longer duration of action.<sup>38,86</sup>

### **CHAPTER THREE: JUSTIFICATION**

Maternal mortality due to postpartum haemorrhage remains a major obstetric problem in Sub Saharan Africa. Hence it is important to review factors like PPH that can contribute to adverse maternal and infant health with a view to reducing its occurrence.

Caesarean section rates are increasing in the sub region with some of the indications for surgery like prolonged obstructed labour actually predisposing to PPH. In a developing country like Nigeria, where poverty, illiteracy and chronic anaemia are endemic; stringent efforts to avoid excess blood loss during this procedure are needed.

Oxytocin is currently the drug used for the control of blood loss during Caesarean section. Despite this, some patients require extra oxytocics to prevent PPH with the resultant increase in cost. The use of repeated oxytocin has also been shown to have diminishing efficacy and increasing side effects.

Misoprostol has been shown to be effective in reducing blood loss at delivery. Its heat stability, ease of administration via several routes and a relative low cost when compared to other oxytocics (e.g. carboprost) makes it an alternative in a developing and tropical country like ours. The safety and efficacy through the rectal route in parturient during Caesarean section has not been fully elucidated. This study aims to compare the efficacy of oxytocin as it is currently being practised in my centre with oxytocin and rectal misoprostol for the control of blood loss during Caesarean section.

## **CHAPTER FOUR: AIMS AND OBJECTIVES**

### **GENERAL OBJECTIVE**

To compare the efficacy of rectal misoprostol and oxytocin with oxytocin alone for the control of blood loss during Caesarean section among parturient who undergo elective Caesarean section in UITH, Ilorin.

### **SPECIFIC OBJECTIVES**

- 1) To estimate blood loss among patients using rectal misoprostol and oxytocin with oxytocin alone during Caesarean section.
- 2) To determine and compare the pre and post-operative haematocrit levels of patients using rectal misoprostol and oxytocin with oxytocin alone for Caesarean section.
- 3) To compare the efficacy of oxytocin alone with oxytocin and rectal misoprostol for the control of blood loss during Caesarean delivery.
- 4) To determine and compare the safety of use of oxytocin alone with oxytocin and rectal misoprostol during Caesarean section.

## **RESEARCH HYPOTHESES**

### **NULL HYPOTHESIS**

1. There is no difference between the efficacy of rectal misoprostol and oxytocin with oxytocin alone in the control of blood loss during Caesarean delivery.
2. There is no difference between pre and postoperative haematocrit levels of patients using rectal misoprostol with oxytocin and oxytocin alone during Caesarean delivery.
3. The safety profiles of misoprostol with oxytocin and oxytocin alone are similar.

### **ALTERNATE HYPOTHESIS**

1. Rectal misoprostol with oxytocin is more efficacious than oxytocin alone in the control of blood loss during Caesarean delivery.
2. There is a difference between the pre and postoperative haematocrit levels of patients using rectal misoprostol with oxytocin and oxytocin alone for Caesarean delivery.
3. Rectal misoprostol and oxytocin is safer than oxytocin alone.

## **CHAPTER FIVE: METHODOLOGY**

### **5.1 STUDY AREA**

The study was conducted at the University of Ilorin Teaching Hospital, a tertiary institution located in Ilorin East local government area of Kwara state. Ilorin is the capital of Kwara state which is located in the North-Central geopolitical zone of Nigeria.

The University of Ilorin Teaching Hospital serves as a referral centre for patients not only within Kwara state but also for neighbouring states like Niger, Kogi, Ekiti, and Osun states. In addition to tertiary health care, it provides primary and secondary health care services.

The obstetric unit is housed in a 2 storey building and consist of an antenatal and postnatal ward, a 25 bed postnatal surgical ward, an 18 bed emergency ward and a 25 bed gynaecology ward. Also housed are the antenatal clinics, labour ward, ultrasound room, family planning unit, an operating theatre with two functional suites, and a neonatal intensive care unit adjoining the labour ward. There are 4 firms that are run by Consultants who supervise the Residents doctors and interns.

### **5.2 STUDY POPULATION**

The study population comprised of parturients that underwent an elective Caesarean section at term which is 37 completed weeks and beyond at the University of Ilorin Teaching Hospital.

### **5.3 STUDY DESIGN**

The study was a double blind randomized controlled trial comparing pre delivery rectally administered misoprostol in addition to slow bolus oxytocin with slow bolus oxytocin and oxytocin infusion in the control of blood loss during elective Caesarean section. Ethical approval was obtained from the Ethical Research Committee of UITH as per protocol of clinical trial. Eight research assistants were recruited by the researcher. Four of these research assistants were registrars, picked from the four subunits of the department while the other four were picked from

the department of anaesthesia. These research assistants were trained by the researcher for a period of 2 weeks prior to commencement of the study. The training was essentially on patient selection, randomization process, administration of research medications, blood loss estimation and other outcome assessment, vital sign assessment, blood sample collection and appropriate filling of the information data sheet. The researcher was involved in patient recruitment, vital sign monitoring, blood sample collection, blood loss estimation, side effects assessment as well as filling of the information data form. The research assistants helped out in instances when the researcher was not available. The primary surgeon was a minimum of a senior registrar. The protocol of the study was enlarged and pasted on the wall of the two operating theatre suites to enhance uniformity in the participant recruitment.

#### **5.4 PATIENT RECRUITMENT AND SELECTION**

Patient selection was based on systematic random sampling in which all eligible parturients that were admitted into the antenatal ward for elective Caesarean section, who gave consent to participate in the study and who had no contraindications to participate were randomly assigned into 2 groups, A or B by blind randomization using computer generated random numbers (Random numbers generator version 3.4.0). A or B was written on the right hand corner of the participants folder using a black marker for ease of identification of participants and follow up by the researcher. Group A were odd numbers and group B were even numbers.

Patients were counselled about the study and the information sheet given to them at admission into the antenatal ward on the day preceding surgery. Detailed explanation was given in most cases by the researcher or the research assistant when the researcher was unavoidably absent. Patients were encouraged to ask questions and answers were provided promptly in clear terms to the patients understanding. In cases of language barrier, an interpreter was used to ease the means of

communication. A written informed consent was obtained from the patient. The patient was reviewed by the anaesthetist a day prior to surgery. All recruited patients had their blood samples collected for haematocrit check and blood grouping and crossmatch for at least a unit of blood as per departmental protocol. This was done by applying tourniquet on the upper arm to enhance prominence of the veins of the forearm. The proposed puncture site was then cleaned with ethanol and allowed to dry before the blood sample was withdrawn. With the thumb of one hand holding down the skin below the puncture site, venepuncture was done with a size 21G needle attached to a 5ml syringe with the bevel of the needle directed upwards in the line of the vein. 5 ml of the blood sample was then withdrawn into the syringe and the needle was gently withdrawn after a dry cotton wool was placed on the puncture site and pressure applied to stop the flow of blood. Two ml of the withdrawn 5 ml was placed in a specimen bottle containing Ethylene diamine tetra-acetic acid (EDTA) anticoagulant for estimation of haematocrit while the remaining sample was placed in a plain bottle and sent for blood grouping and crossmatching. Patient was then fasted for a period of between 6-8 hours as routinely practised in my centre.

On the day of surgery, patient was wheeled to theatre and the requirements of participation in the study were reiterated to them. The patient's axillary temperature was taken using an electronic thermometer 1 hour prior to commencement of surgery and was documented. At the operating theatre, patients were placed in the supine position. An intravenous access using a size 16G cannula was instituted. A litre of crystalloid was administered using the secured IV access. Another IV access was instituted if the patient required resuscitation or blood transfusion. The anaesthetist then administered regional anaesthesia in the form of subarachnoid block (SAB), epidural anaesthesia or combined spinal epidural using L2-L3, L3-L4, or L4-L5 inter-space while in sitting position on the operating table. The patient was then returned to the dorsal position and an

indwelling two way urethral catheter was passed per urethra ensuring asepsis. At this time, the drugs were administered per rectum as per study protocol and participant group. Patients were then returned to the supine position. Routine cleaning and draping of the patients were performed. Incision was made on the anterior abdominal wall using either the Pfannenstiel or the mid line infra-umbilical route to gain access into the abdominal cavity. Following access into the abdominal cavity, a lower segment transverse incision was made on the uterus with extra caution to prevent cutting through the amniotic sac. A nip on the amniotic sac was made and the amniotic fluid suctioned using a suction nozzle connected to a suction machine with a two way switch and 2 calibrated suction jars. If the amniotic sac was ruptured while the lower segment transverse incision was made the suctioning catheter was used to suck fluid from the operating field while trying to avoid spillage on the floor. The incision thereafter was widened and the fetus delivered. The placenta was delivered via cord traction. The uterine incision was closed. Anterior abdominal wall was closed in layers.

#### **5.4 DRUG ADMINISTRATION**

The drugs administered were packed by an independent pharmacist in the pharmacy department of the hospital into sealed opaque envelopes labelled A or B with a red marker. Each envelope contained either 3 tablets of 200µg each of misoprostol (Marie Stopes International, London) dispensed in a water proof drug disposing bags and 2ml of sterile water withdrawn into a 5 ml syringe capped with a 21G needle or 3 tablets of vitamin C (Emzor pharmaceuticals, Nigeria) dispensed into a water proof drug disposing bag and 2 ml of 20IU of oxytocin (Rotex Medica, Germany) into a 5ml syringe capped with a 21G needle. The envelopes containing the drugs were received from the pharmacist once the patient was in the operating room and the drug was administered per rectum following urethral catheterisation after regional anaesthesia had been

instituted. The remaining content of the opaque envelope was then handed over to the anaesthetist already trained on the study protocol. The study group received 600µg misoprostol tablet passed per rectum followed by 5IU of oxytocin intravenously (slow bolus) within 1 minute of delivery of the fetus and a 2 ml placebo fluid added to 500ml of 0.9% saline that was given for 4 hours after delivery. The control group received 3 tablets of placebo (vitamin C) passed per rectum followed by 5 IU of oxytocin given intravenously (slow bolus) within a minute of delivery of the fetus and 20 IU (2ml) of oxytocin added to 500ml of 0.9% saline administered for 4 hours following delivery. The researcher and research assistants and the patients were blinded to the content of each opaque envelope. The need for additional oxytocic was dictated by the surgeon if there was evidence of poor uterine contraction and excessive blood loss.

## **5.5 BLOOD LOSS ESTIMATION**

Blood loss during surgery was estimated with the use of a calibrated measuring jar as well as the gravimetric approach. Blood that was lost at surgery was suctioned with the aid of a suctioning tube into the calibrated suctioning jar. Blood that was not sucked into the jar was collected using a dry pre weighed abdominal packs and gauze used to mop excess blood from the operating field. These gauze and abdominal packs were placed in a water proof disposable pack to avoid drying up when exposed to room air. Stringent efforts were made to avoid blood spillage on the floor of the operating theatre. Blood that spilled off the operating table were mopped up using pre weighed sanitary pads. All of these (abdominal packs, gauze, and sanitary pad) grouped into category and were weighed using a weighing scale (KERRO BL2001). The weighing scale has ability to detect differences up to 0.1g. Blood from the vagina immediately after surgery was cleaned with gauze and calculated with the intra operative blood loss. A one gram weight difference is equivalent to

1ml of blood.<sup>66</sup>The intra-operative blood loss was the sum total of the calculated gravimetric weighed packs and blood in the calibrated jar.

Post operatively, participants were transferred onto a receiving bed which had a pre-weighed adult diaper that was used to line the sheet and collect any blood spilled were from the sanitary pad. All sanitary pads and adult diaper used up to 24 hours post operatively were put in a water proof pack and also weighed to determine the blood loss in the post operative period. Each gram difference was equivalent to 1ml of blood.<sup>66</sup>

## **5.6 ASSESSMENT OF SIDE EFFECTS**

Axillary temperature was taken with the aid of an electronic thermometer before the rectal drugs were administered and recorded. A second axillary temperature was taken 1 hour after the rectal drug was administered then 4 hours later and recorded in °C. Temperature of 38<sup>0</sup>C was defined as fever for this study. Participants were asked questions regarding symptoms of nausea and observed for vomiting and same recorded in the information data sheet. Occurrence shivering was of also observed and recorded. Participants were followed up to 24 hours post Caesarean section and observed for any of the above symptoms.

Blood sample for haematocrit check was taken at 24 hours post surgery. This was done using the forearm of the participant. A tourniquet was tied to the forearm to aid the prominence of the proposed vein to be used. The site used was cleaned with ethanol and allowed to air dry. A 21 G needle attached to a 5ml syringe with the bevel faced up was used to access the vein and 2ml of blood was placed in EDTA bottle. The value was recorded in the data sheet. Participants that had blood transfusion had their blood sample for haematocrit checked after 24hours of the last transfusion. Patients who develop PPH were managed according to institutional guidelines.

## 5.7 EXCLUSION CRITERIA

1. Pregnant women with twin gestation
2. Pregnancy co-existing with uterine fibroids
3. Coagulation disorders
4. Febrile illness before surgery
5. Preoperative anaemia (packed cell volume less than 30% twenty four hours prior to surgery).
6. Previous ruptured uterus
7. Patients who have contraindication to misoprostol use eg asthmatics.

## 5.8 SAMPLE SIZE DETERMINATION

The sample was determined by the formula.<sup>88</sup>

$$n = \frac{(u + v)^2(\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

n = minimum sample size of each arm of the study group.

u = one sided percentage point of the normal distribution corresponding to 100% -the power. With power set at 90%, u =1.28

v = percentage point of the normal distribution corresponding to the (two sided) significance level. Significance level set as 5% (0.05); v =1.96

Using a previous study by Ugwu et al,<sup>36</sup> comparing the efficacy of sublingual misoprostol in addition to intravenous oxytocin with intravenous oxytocin alone in reducing blood loss during and after Caesarean section, the mean intraoperative and post-operative blood loss (ml) in the two

groups were  $474 \pm 218.2$  and  $593.4 \pm 214.7$  respectively in the misoprostol with intravenous oxytocin and oxytocin groups respectively.

$(\mu_1 - \mu_0)$ : difference between the means

$(\sigma_1, \sigma_0)$ : Standard deviations

$$n = \frac{(1.28 + 1.96)^2 (218.2^2 + 214.7^2)}{(593.4 - 474)^2}$$

n = 68 subjects

Making an attrition rate of 10% i.e.  $6.8 \sim 7$

Total sample size was 150 with 75 subjects in each arm of the study.

## 5.9 DATA ANALYSIS

Data was analysed using the Statistic Package for Social Sciences software (SPSS) version 21. The data were presented in frequency tables and bar chart. Continuous variables were presented as means with standard deviation and analysed using Student's T test, while ordinal variables were presented as median and analysed with Man Whitney U test. Categorical variables were presented as frequencies and proportions and analysed using Chi-square test or Fishers exact test where appropriate and Odds ratio with 95% confidence intervals was used to compare the proportions. Probability (p) values less than 0.05 was accepted as statistically significant.

## 5.10 OUTCOME MEASURES

The primary outcome measures were intra operative blood loss, 24 hours post-operative blood loss, and the change in haematocrit. Secondary outcome measures included need for use of

additional uterotonic agents, need for blood transfusion, pyrexia (temperature  $\geq 38.0^{\circ}\text{C}$ ), nausea, vomiting, shivering, need for intensive care unit admission for the mother and need for hysterectomy and other surgical management of PPH.

### **5.11 ETHICAL CONSIDERATION**

Ethical approval was obtained from the Ethical committee of the University of Ilorin Teaching Hospital. A written informed consent was obtained from the study participants prior to commencement of study.

### **5.12 FUNDING**

This study was funded by the researcher and the research grant from the hospital. The packaging of the drugs and other consumables that was used in the administration of the medication was provided by the researcher.

### **5.13 CONFLICT OF INTEREST**

The researcher declares no conflict of interest.

### **5.14 STRENGTH OF STUDY**

The study was a double blind randomised control trial in which the researcher and the participant were blinded to the intervention given to the participant. This reduced bias of under or overestimation of blood loss in either group. Patients were also randomised into the 2 groups using computer generated random numbers hence the researcher had no influence on the grouping of the participants. The drugs used were packed by an independent Pharmacist who was not involved in the process of blood loss estimation. The statistician was also blinded to the groups during the data analysis hence reducing the bias.

Blood loss was estimated using the gravimetric rather than the visual estimation approach. The gravimetric method of blood loss is adjudged accurate and reproducible. Side effects like shivering and vomiting can be physically expressed and seen by the researcher which can be documented. Pyrexia can also be determined with thermometer and documented. This removes bias of assigning a particular side effect to any group.

All of the participants received regional anaesthesia hence patients have comparable results for blood loss. The drugs used were administered per vagina during urethral catheterisation after anaesthesia had been instituted. This was convenient for the patients.

#### **5.15 LIMITATION OF THE STUDY**

The study population were parturients scheduled to undergo elective CS. Patients who had emergency CS and those patients that were at increased risk PPH were excluded from the study. Findings from this study can however be used to form a template to study these other subsets of patients.

Although the Caesarean sections were performed by different Surgeons; a minimum of Senior Registrar, the expertise of Surgeons differs and might affect volume of blood loss. The protocol of the study was pasted boldly on the wall of operating theatre to ensure uniformity of procedure.

The estimation of blood loss may be affected by amniotic fluid admixture with the blood although care was taken during the procedure to suction the amniotic fluid and a two way calibrated jar was used to ensure that the content of the second jar was blood from the operating field. The anaesthesia for all the patients was regional block; findings from this study may not apply directly to patients who undergo general anaesthesia.

## CHAPTER 6: RESULTS

A total number of 150 consenting pregnant women who had elective Caesarean section were recruited. 75 of the study group had misoprostol and oxytocin while the 75 in the other group received oxytocin alone.

Table 1 describes the baseline demographic and clinical characteristics of the 2 groups. The mean age was  $31.65 \pm 4.63$  years and  $31.72 \pm 4.62$  years for the misoprostol and oxytocin groups respectively. Most of the women in both groups were employed (92.7%) and had tertiary level of education (65.3%). The modal parity was 2-4. The mean gestational age at delivery was  $38.40 \pm 1.28$  weeks and  $38.40 \pm 1.12$  weeks for the misoprostol and oxytocin groups respectively. (p-value = 1.000).

Figure 1 showed the different indications for Caesarean section. Participants who had had 2 previous CS scars were the modal indication for CS (33% each in both groups). Other indications include patients who had previous scars with borderline pelvis and breech presenting fetus in primi gravida. Other indications were as noted in the bar chart.

Table 2 showed that all participants had regional anaesthesia. SAB was commonest regional technique used for the oxytocin and misoprostol groups (84% and 88%) respectively. Other regional anaesthetic techniques were epidural and CSE. Pfannestiel incision and midline sub umbilical incision were the incision employed in both groups. Pfannestiel skin incision was the most commonly employed in both groups (80% and 78.7%) for the misoprostol and oxytocin group respectively. The mean duration of surgery was  $66.07 \pm 17.24$  minutes in the misoprostol group and  $66.19 \pm 16.29$  minutes in the oxytocin group, these values were comparable ( $t = 0.44$  and  $p = 0.965$ ). The surgeons were Senior Registrars (80%) and Consultants (20%). All of the participants had a lower segment transverse incision and placentas were delivered via cord traction.

Table 3 showed the mean blood loss during and after Caesarean delivery. It also depicts the total blood loss in the study population. The mean intra operative blood loss in the misoprostol group was  $550.59 \pm 170.54$ ml (276-1233ml) while in the oxytocin group it was  $585.07 \pm 163.44$ ml (315-1400ml). The blood loss was higher in the oxytocin group than the misoprostol group, but the difference was not statistically significant ( $t = -1.264$  and  $p = 0.203$ ). The mean post partum blood loss up to 24 hours post delivery was also less in the misoprostol group ( $98.77 \pm 26.40$  ml) compared with oxytocin group ( $99.47 \pm 25.45$ ml) though it was not statistically significant ( $t = 0.164$  and  $p = 0.870$ ). The total blood loss was  $667.16 \pm 214.18$  ml in the misoprostol group and  $683.65 \pm 165.45$  ml in the oxytocin group. There was however no statistically significant difference. ( $t = 0.528$  and  $p = 0.598$ ). In general blood loss was lower in the misoprostol group than the oxytocin group. However, the difference was not significant statistically.

Table 4 showed the comparison of intervention in both groups to determine the efficacy. The number of parturients that required additional oxytocics in misoprostol group was less than that in the oxytocin group (20 versus 22), though it was not statistically significant ( $X^2 = 0.132$  and  $p$  value = 0.716). Four of the participants in the oxytocin group required blood transfusion intra operatively while only 1 participant in the misoprostol group required intra operative blood transfusion. None of the patients required additional oxytocics in the post partum period. One parturient in misoprostol group had blood transfusion in the post operative period.

The distribution of blood loss as a measure of how effective oxytocics given were able to reduce blood loss was depicted in table 5. Although the misoprostol group had more participants whose blood loss was  $< 500$ ml (12 versus 6) respectively, participants in the oxytocin group only had a patient that had blood loss  $> 1000$ ml while the misoprostol group had 4 participants.

Participants who had previous scars on their uterus had more blood loss than those who did not though the difference was not statistically significant. For participant in the misoprostol group who had midline incision had more blood loss than those that had pfannestiel, although it was not statistically significant. For patients in the oxytocin group, participants that had pfannestiel incision had more blood loss. It was also not statistically significant. Increasing parity was also associated with increasing blood loss in both the groups although none was statistically significant. The mean of the incision delivery interval was  $10 \pm 5$  minutes with a median 9minutes (inter-quartile range 6-13minutes). The range was 3-25minutes.

Table 6 showed the pre and post-op haematocrit and the change between the pre and post-op haematocrit in both groups. The mean pre operative haematocrit was comparable in both groups ( $32.79 \pm 4.68\%$  and  $33.25 \pm 2.53\%$ ) in the misoprostol and oxytocin group respectively. The pre operative and post operative haematocrit were not statistically different in both groups ( $p=0.449$ ,  $0.850$ ) respectively. The mean reduction in haematocrit in the misoprostol group was  $3.58 \pm 1.08\%$  while that of oxytocin group was  $3.72 \pm 1.61\%$ . The reduction in haematocrit was more in the oxytocin group compared to misoprostol group but the difference was not statistically significant ( $t=-0.497$  and  $p=0.62$ )

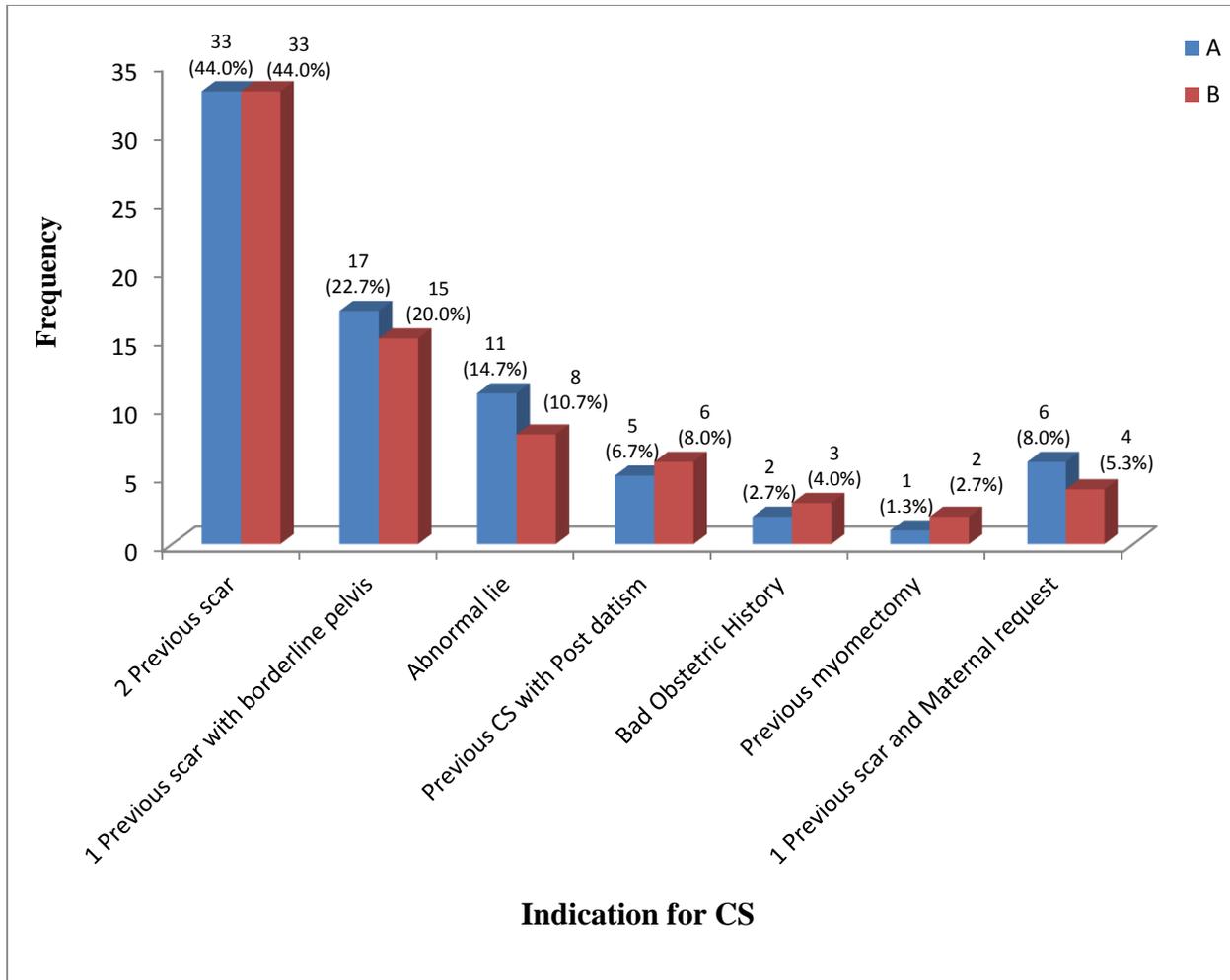
Table 7 compared some common side effects such as nausea, vomiting, shivering and pyrexia in two groups. In the misoprostol group, 11 women experienced nausea while only 4 women experienced it in the oxytocin group. ( $X^2=3.63$ ,  $p$  value =  $0.057$ ). Five women experienced vomiting in the misoprostol group while 3 participants in the oxytocin group had same complained ( $X^2=0.528$  and  $p$  of  $0.0467$ ). There was no significant difference in the occurrence of nausea and vomiting in both groups. More parturients in the misoprostol group had pyrexia and shivering as

side effects than the oxytocin group and both side effects were statistically significant ( $p$  value 0.020 and 0.002) for pyrexia and shivering respectively.

**Table 1: Socio demographic distribution of the study population**

Variable	A n (%)	B n (%)	Total n (%)	$\chi^2/ t$	<i>p</i> value
<b>Age-group (years)</b>					
< 25	8 (10.7)	4 (5.3)	12 (8)	7.128	0.129
26 – 30	24 (32)	24 (32)	48 (32)		
31 – 35	26 (32)	35 (46.7)	61 (40.7)		
36 – 40	16 (21.3)	8 (10.7)	24 (16)		
> 40	1 (1.3)	4 (5.3)	5 (3.3)		
<b>Mean <math>\pm</math> SD</b>	31.65 $\pm$ 4.63	31.72 $\pm$ 4.62		-0.088 <sup>t</sup>	0.930
Range	22 – 42	22 – 45			
<b>Tribe</b>					
Yoruba	65 (86.7)	63 (84)	128 (85.3)	0.529 <sup>Y</sup>	0.749
Igbo	8 (10.7)	7 (9.3)	15 (10)		
Hausa	2 (2.7)	5 (6.7)	7 (4.7)		
<b>Occupation</b>					
Unemployed	6 (8)	5 (6.7)	11 (7.3)	5.253	0.386
Artisan	7 (9.3)	9 (12)	16 (10.7)		
Trading	30 (40)	19 (25.3)	49 (32.7)		
Civil servant	20 (26.7)	27 (36)	47 (31.3)		
Professional	4 (5.3)	8 (10.7)	12 (8)		
Others	8 (10.7)	7 (9.3)	15 (10)		
<b>Education</b>					
Primary	7 (9.3)	6 (8)	13 (8.7)	1.983 <sup>Y</sup>	0.739
Secondary	13 (17.3)	20 (26.7)	33 (22)		
Tertiary	51 (68)	47 (62.7)	98 (65.3)		
Quranic	0 (0)	1 (1.3)	1 (0.7)		
None	4 (5.3)	1 (1.3)	5 (3.3)		
<b>Parity</b>					
0	11 (14.7)	10 (13.3)	21 (14.0)	5.239 <sup>Y</sup>	0.155
1	24 (32.0)	12 (16.0)	36 (24.0)		
2 – 4	38 (50.7)	52 (69.3)	90 (60.0)		
$\geq$ 5	2 (2.7)	1 (1.3)	3 (2.0)		
<b>EGA (weeks)</b>					
37 – 39	61 (81.3)	64 (85.3)	125 (83.3)	0.432	0.511
40 – 42	14 (18.7)	11 (14.7)	25 (16.7)		
<b>Mean <math>\pm</math> SD</b>	38.40 $\pm$ 1.28	38.40 $\pm$ 1.12		0.000 <sup>t</sup>	1.000

$\chi^2$ : Chi square; Y: Yates corrected Chi square; t: Independent Samples T test; *p* value < 0.05 (statistically significant) A: Misoprostol; B: Oxytocin



**Figure 1: Indications for Caesarean section in the study population.**  
**A: Misoprostol; B: Oxytocin**

**Table 2: Intra partum parameters/events in the study population**

<b>Variable</b>	<b>A n (%)</b>	<b>B n (%)</b>	<b>Total n (%)</b>	<b><math>\chi^2</math>/ t</b>	<b>p value</b>
<b>Skin incision</b>					
Pfannensteil	60 (80.0)	59 (78.7)	119 (79.3)	0.041	0.840
Sub umbilical midline	15 (20.0)	16 (21.3)	31 (20.7)		
<b>Type of Anaesthesia</b>					
SAB	66 (88)	63 (84)	129 (86)	5.070	0.079
Epidural	6 (8)	12 (16)	18 (12)		
Combined	3 (4)	0 (0)	3 (2)		
<b>Cadre of Surgeon</b>					
Senior Registrars	59 (78.7)	61 (81.3)	120 (80.0)	0.167	0.683
Consultants	16 (21.3)	14 (18.7)	30 (20.0)		
<b>Duration of Surgery (minutes)</b>					
Mean $\pm$ SD	66.07 $\pm$ 17.24	66.19 $\pm$ 16.29		-0.044 <sup>t</sup>	0.965

$\chi^2$ : Chi square; t: Independent Samples T test; p value < 0.05 (statistically significant)

A: Misoprostol; B: Oxytocin

**Table 3: Comparison of blood loss between Misoprostol and oxytocin groups**

Variable	A n (%)	B n (%)	t/U	p value
<b>Intrapartum blood loss(ml)</b>				
Mean ± SD	550.59 ± 170.54	585.07 ± 163.44	-1.264 <sup>t</sup>	0.208
Range (Min – Max)	276 – 1233	315 – 1400		
Median (IQR)	541 (420 – 617)	582 (477 – 678)	2320.500	0.064
<b>Postpartum blood loss (ml)</b>				
Mean ± SD	98.77 ± 26.40	99.47 ± 25.45	-0.164 <sup>t</sup>	0.870
Range (Min – Max)	46 – 206	61 – 258		
Median (IQR)	96 (84 – 106)	99 (86 – 107)	2653.000	0.550
<b>Total blood loss (ml)</b>				
Mean ± SD	667.16 ± 214.18	683.65 ± 165.45	- 0.528 <sup>t</sup>	0.598
Range (Min – Max)	423 – 1752	411 – 1515		
Median (IQR)	636 (533 – 722)	678 (570 – 776)	2422.000	0.142

**U: Mann Whitney U test; t: Independent Samples T test p value < 0.05 (statistically significant); A: Misoprostol; B: Oxytocin**

**Table 4: Blood transfusion and additional oxytocic use as a measure of efficacy in the study groups**

	<b>A</b>	<b>B</b>	<b>Total</b>	$\chi^2/ t$	<i>p</i> value
<b>Variable</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>		
<b>Blood transfusion</b>					
Yes	1 (1.3)	4 (5.3)	5 (3.3)	1.862	0.172
No	74 (98.7)	71 (94.7)	145 (96.7)		
<b>Need additional Oxytocics in intra-partum period</b>					
Yes	20 (26.7)	22 (29.3)	42 (28)	0.132	0.716
No	55 (73.3)	53 (70.7)	108 (72)		
<b>Need additional Oxytocics in Postpartum period</b>					
Yes	0 (0.0)	0 (0.0)	0 (0.0)	NA	
No	75 (100.0)	75 (100.0)	75 (100.0)		
<b>Need blood transfusion post-partum</b>					
Yes	1 (1.3)	0 (0.0)	1 (0.7)	1.007	1.000 <sup>F</sup>
No	74 (98.7)	75 (100.0)	149 (99.3)		

$\chi^2$ : Chi square; F: Fisher's exact *p* value; t: Independent Samples T test; SD: Standard Deviation; *p* value < 0.05 (statistically significant); A: Misoprostol B: Oxytocin

**Table 5: Distribution of blood loss in both groups as a measure of effectiveness of oxytocics used**

	<b>A</b>	<b>B</b>	<b>Total</b>	$\chi^2/ t$	<i>p</i> value
<b>Total blood loss (ml)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>		
< 500	12 (16.0)	6 (8.0)	18 (12.0)	2.693 <sup>Y</sup>	0.260
500 – 999	59 (78.7)	68 (90.7)	127 (84.7)		
≥ 1000	4 (5.3)	1 (1.3)	5 (3.3)		

$\chi^2$ : Chi square; <sup>Y</sup>: Yates corrected; *p* value = <0.05 (statistically significant);

A= Misoprostol; B= Oxytocin

**Table 6: Pre and Post-operative hematocrit levels in Misoprostol and oxytocin and oxytocin alone groups**

	<b>A (misoprostol)</b>	<b>B(oxytocin)</b>	<b>T</b>	<i>p</i> value
<b>Variable</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>		
Pre-op haematocrit (%)	32.79 ± 4.68	33.25 ± 2.53	-0.76	0.449
Post op haematocrit (%)	29.58 ± 2.81	29.49 ± 2.84	0.190	0.850
Change in haematocrit (%)	3.58 ± 1.80	3.72 ± 1.61	-0.497	0.620

**t: Independent Samples T test; SD: Standard Deviation; *p* value < 0.05 (statistically significant)**

**Table 7: Comparison of side effects between Oxytocin and Misoprostol groups**

Side Effects	A n (%)	B n (%)	$\chi^2/ U$	<i>p</i> value
<b>Nausea</b>				
Yes	11 (14.7)	4 (5.3)	3.63	0.057
No	64 (85.3)	71 (94.7)		
<b>Vomiting</b>				
Yes	5 (6.7)	3 (4)	0.528	0.467
No	70 (93.3)	72 (96)		
<b>Pyrexia (temp &gt;38<sup>0</sup>C)</b>				
Yes	13 (17.3)	4 (5.3)	5.374	0.020*
No	62 (82.7)	71 (94.7)		
<b>Shivering</b>				
Yes	29 (38.7)	12 (16.2)	9.413	0.002*
No	46 (61.3)	62 (83.8)		

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$\chi^2$ : Chi square; U: Mann Whitney U test; \*: *p* value < 0.05 (statistically significant);

A: Misoprostol; B: Oxytocin

## **CHAPTER 7 DISCUSSION, CONCLUSIONS AND RECOMMENDATION**

This study utilised rectal misoprostol in addition to oxytocin bolus to control blood loss during Caesarean section as PPH still ranks high as a cause of morbidity and mortality especially in sub-Saharan Africa. It also determined the efficacy and the side effects profile of the participants. The mean blood loss during CS in this study was found to be lower in the misoprostol group when compared with oxytocin group. The difference was however not statistically significant. This finding is similar to studies within and outside Nigeria.<sup>28,36,37and 87</sup> Systematic review of randomised controlled trials also reported a significantly less blood loss in the misoprostol group compared with the oxytocin group.<sup>10,30</sup> However, Owonikoko et al<sup>29</sup> reported more blood loss in the misoprostol group than the oxytocin group that was not statistically significant.<sup>29</sup> This might not be unrelated to the method of blood loss estimation in the study where visual estimation by the anaesthetist and surgeon was taken into consideration unlike the use of calibrated jar as well as gravimetric measurement utilised in this study. In addition, there are variations in the actual volumes of blood loss in this study and others. For example, the mean blood loss in this study was  $550.59 \pm 170.54\text{ml}$  (range 276-1233ml) in the misoprostol group and  $585.07 \pm 163.44\text{ml}$  (315-1400ml) in the oxytocin group, it was not significant. Sood et al<sup>28</sup> in India reported  $598 \pm 108\text{ml}$  and  $651 \pm 118\text{ml}$  in the misoprostol and oxytocin group respectively while Fazel et al<sup>86</sup> reported  $578 \pm 185\text{ml}$  in the misoprostol group and  $620 \pm 120\text{ml}$  in the oxytocin group. Owonikoko et al<sup>29</sup> reported a slightly higher volume of blood loss as  $650 \pm 251\text{ml}$  in the oxytocin group and  $667 \pm 213\text{ml}$  in the misoprostol group. Although the actual volumes of blood loss in these studies were comparable, the difference in the actual volumes might be related to the different methods of blood loss estimation. For example Fazel et al<sup>86</sup> in their study assumed certain amount of blood in each soaked gauze and abdominal packs and only utilised gravimetric measurement for the patients

draping. This study utilised gravimetric measurement on all the small and large gauze as well as the draping.

The mean post operative blood loss for 24 hours after surgery was  $98.77 \pm 26.40$  ml (46-206ml) and  $99.47 \pm 24.45$ ml (61-258ml) in the misoprostol and oxytocin group respectively. Although most studies stopped blood loss estimation at 4 hours post operatively, primary PPH might still occur after 4 hours and up to 24 hours post operatively hence the reason for 24 hours used in this study. Adinakin et al in the study of effect post operative rectal misoprostol blood loss after CS reported  $100.08 \pm 24.85$ ml and  $108.20 \pm 29.93$  ml in the first 4hours post operatively.<sup>87</sup> This amount of blood loss in a 4 hour period might be related to the fact that the rectal misoprostol was administered post operatively and requires approximately 40 min to reach peak serum concentration for its action to be felt.<sup>39</sup> Owonikoko et al found a significant difference in the mean post operative blood loss in misoprostol group compared with the oxytocin group.<sup>29</sup> The blood loss in the post operative period was  $22.7 \pm 14.2$  ml and  $42.2 \pm 22.1$ ml in the study by Ugwu et al,<sup>36</sup> the reason for the low volume recorded cannot not be explained despite the gravimetric method of blood loss estimation as utilised in this study.

This present study showed a drop in haematocrit of  $3.58 \pm 1.8$  % in the misoprostol group and  $3.72 \pm 1.61$ % in the oxytocin group. The observed difference was not significant ( $p= 0.620$ ). Similar change in haematocrit was reported in Nigerian studies.<sup>29,36,87</sup> Hua et al in a randomised control trial found that mean difference in the haemoglobin level was also lower in the misoprostol group when compared to the oxytocin group.<sup>10</sup> Sood et al in study in India found similar lower drop in the haemoglobin concentration in the misoprostol group.<sup>28</sup> The lower drop in the haematocrit in this study and haemoglobin concentration in other studies might be related to the fact that the blood loss in the misoprostol group was lower for almost similar pre operative haematocrit and

haemoglobin concentration in both groups. It might therefore be expected to have a higher change from pre operative haematocrit to the post operative in the oxytocin group.

Surgeries were carried out by senior registrars and consultants. The mean duration of surgery was comparable in both groups ( $66.07 \pm 17.24$  minutes and  $66.19 \pm 16.29$  minutes in misoprostol and oxytocin group respectively). This duration of CS was similar to what was reported by Ugwu et al and Adinakin et al.<sup>36,87</sup> Fazel et al<sup>86</sup> in their study however reported a lower mean duration in both groups and might be related to the fact that women with previous abdominal surgeries in which access to the peritoneal cavity might be delayed were excluded from the study. In this study the modal indication for CS was for 2 previous CS scars. Twenty out of 75 participant in the misoprostol group (26.7%) required use of additional oxytocics while 22 patients (29.3%) in the oxytocin group required additional oxytocics after the study drug has been utilised. None of the patient in the post partum period required additional oxytocics. Some studies have corroborated this finding.<sup>28,36</sup> Adinakin et al<sup>87</sup> also reported that there was no need for additional oxytocics in the post operative period. The finding was not in congruence with study by Owonikoko et al where the oxytocin group required less additional oxytocics.<sup>29</sup> Conde-Agudelo et al in the systematic review and meta analyses found that use of additional oxytocics was less in the patients that utilised combined misoprostol and oxytocin than oxytocin alone.<sup>30</sup> This might be related to the fact that oxytocin and misoprostol utilizes different mechanism of action which has additive effect on uterine smooth muscle contractility.<sup>39,81</sup>

The need for blood transfusion as a measure of the effectiveness of particular oxytocics in the control of blood loss was more in the oxytocin group in this study though it was not statistically significant. Different studies have reported varying needs for blood transfusion albeit low transfusion rate. For example, Owonikoko et al reported only a patient in the misoprostol arm that

required blood transfusion.<sup>29</sup> Ugwu et al on the other hand reported that a patient each in each arm of study group required blood transfusion.<sup>36</sup> Hua et al found no statistically significant difference in the need for blood transfusion in the two groups.<sup>10</sup> while Fazel et al had no patient that required blood transfusion.<sup>86</sup> The need for blood transfusion was also found to be low in this study probably due to the fact that the patients selected had elective CS and patients had been optimised before surgery. The distribution of blood loss as a measure of efficacy revealed that misoprostol in combination with bolus oxytocin reduced blood loss to <500ml more than oxytocin (16% versus 8% respectively). However, participants in the misoprostol group had more patients that had blood loss >1000ml than in the oxytocin group (5.3% versus 1.3% respectively).

The frequency of shivering as a side effect of medication used was significantly more in misoprostol group than the oxytocin group (38.7% versus 16.2%  $p = .002$ ) in this study. Sood et al<sup>28</sup> reported similar finding in which 21.1% of participants in the misoprostol group had shivering and 9.5% of the participants in oxytocin group had shivering. Other studies reported similar findings in which frequency of occurrence of shivering was significantly more in the misoprostol group compared to the oxytocin group<sup>10,29,36-38,86</sup> In contrast Adinakin et al<sup>87</sup> reported a non significant shivering between the misoprostol and the oxytocin group. In fact the oxytocin group had more shivering than the misoprostol group in that study and might be related to the sample size of 25 participants in both study arms.<sup>87</sup> Shivering might also be subjective symptom and the onset of which might be delayed.

In this study, the frequency of pyrexia was significantly higher in the misoprostol group compared to oxytocin (17.3% versus 4%;  $p = 0.020$ ). Similar finding were noted in most of the other studies reviewed.<sup>29,30,36-37</sup> Misoprostol is known to be thermogenic increasing temperature via the prostaglandin mediated shift in hypothalamic set point of the thermoregulatory pathway. However,

Fazel et al <sup>86</sup> in Iran and Adinakin et al <sup>87</sup> in Nigeria reported no statistically significant difference in the occurrence of pyrexia between the misoprostol group and the oxytocin group though the frequency of occurrence of pyrexia was more in the misoprostol group. Rectally administered misoprostol have a steady rise of serum concentration and a lower peak serum concentration.<sup>39</sup>This might be responsible to the finding by Fazel et al <sup>86</sup> and Adinakin et al.<sup>87</sup>

In this study, there was no significant difference in the occurrence of nausea and vomiting between the two arms of the study but symptoms occurred more in the misoprostol group compared to the oxytocin group. This finding is similar to the findings in other studies<sup>28,29,86</sup>.

Although the side effects were more in the misoprostol group, they were mild, transient and self limiting without any debilitating sequel in any of the participants of the study.

**CONCLUSION:** In this study, pre delivery rectal misoprostol in addition to bolus oxytocin was comparable to oxytocin bolus and oxytocin infusion currently used in my centre for the control of blood loss during and after Caesarean Section. The efficacy of rectal misoprostol and oxytocin with oxytocin bolus and oxytocin infusion were similar. A drop in the haematocrit was lower in the misoprostol group than the oxytocin group. The side effects were more in the misoprostol group than the oxytocin group. These side effects were self limiting and transient.

**RECOMMENDATION:** The use of pre delivery rectal misoprostol with bolus oxytocin is safe for the prevention of excessive blood loss during and after Caesarean section. This can be adapted to practice in the control of blood loss during elective CS.

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## **APPENDIX 1- INFORMATION SHEET**

### **A COMPARISON OF COMBINED RECTAL MISOPROSTOL AND OXYTOCIN WITH OXYTOCIN ALONE IN THE CONTROL OF BLOOD LOSS DURING ELECTIVE CAESAREAN SECTION: A RANDOMISED CONTROLLED TRIAL.**

#### **BRIEF DESCRIPTION OF THE STUDY**

This study will be carried out in the department of Obstetrics and Gynaecology University of Ilorin Teaching Hospital on patients planned for an elective Caesarean section at term (37 completed weeks and above). It is to compare the effectiveness of administration of 600µg rectal misoprostol and 5IU of oxytocin bolus with the use of 5IU of oxytocin bolus and 201U of oxytocin in 500ml of 0.9% saline infusion that is currently being practised in the control of haemorrhage during Caesarean section at UITH.

#### **WHAT IS REQUIRED FOR YOUR PARTICIPATION**

Your participation requires you be given either 5IU of intravenous oxytocin (bolus) with 600µg of misoprostol passed into your anus and a 2ml of placebo fluid (aqua water) added into 500mls of 0.9% saline infusion for 4 hours after the delivery of your baby or 5IU of oxytocin with 3 placebo tablets (no active ingredient) inserted into your anus and 201U of oxytocin (2ml) added into 500ml of 0.9% saline as infusion for 4 hours following delivery of your baby to prevent blood loss during Caesarean section. Your blood sample will also be taken before and 24 hours after the procedure to determine the drop (if any) in your blood level. Your blood loss intraoperatively will be assessed and you will be observed closely to determine any side effects of the drugs administered. All of these clinical variables will be analysed afterwards. The study will not expose you to any risk or increase the cost of your treatment.

## **CONFIDENTIALITY**

The information obtained about you will remain confidential

## **BENEFIT TO PARTICIPANT**

Your participation in this study will contribute to knowledge that will help in formulating protocols that will be used in managing patients in future to prevent excessive blood loss during and after your Caesarean section. There will be no extra cost for your participation.

## **CONSENT TO PARTICIPATE AND RIGHT TO WITHDRAW**

Your participation in this study is voluntary and you have the right to withdraw at any stage if you so wish. There will be no penalty if you decide to withdraw from the study. However, I will appreciate your willingness to participate. You are free to ask any question (s) to clarify any uncertainties about the study from the researcher and the trained research assistants.

**RESEARCHER: DR AHMED AO (MBBS)**

**ADDRESS: DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, UITH, ILORIN**

**APPENDIX II- CONSENT FORM**

**A COMPARISON OF COMBINED RECTAL MISOPROSTOL AND OXYTOCIN WITH OXYTOCIN ALONE IN THE CONTROL OF BLOOD LOSS DURING ELECTIVE CAESAREAN SECTION: A RANDOMISED CONTROLLED TRIAL.**

I ..... Of  
.....

Hereby, consent to participate in the above research study after proper information on the nature and pattern of study and its benefit (s) to me and the society at large. All information obtained in this study is strictly confidential. If the study is published, there should be no information that will identify me as a participant.

Signed ..... OR Right thumb print .....

Date .....

I confirm that I have explained to you the purpose and nature of the study.

Researcher .....

OR

Research assistant .....

Signed ..... Date.....

Witness .....

Signed ..... Date .....

**APPENDIX III- INFORMATION DATA SHEET  
 A COMPARISON OF COMBINED RECTAL MISOPROSTOL AND OXYTOCIN WITH  
 OXYTOCIN ALONE IN THE CONTROL OF BLOOD LOSS DURING ELECTIVE  
 CAESAREAN: A RANDOMISED CONTROL TRIAL.**

- RANDOM NUMBER .....
- A OR B .....
- DATE OF ADMISSION .....
- DATE OF SURGERY .....
- TIME OF RECTAL DRUG ADMINISTRATION .....
- TIME OF COMMENCEMENT OF SURGERY .....
- TIME OF DELIVERY OF THE FETUS .....
- TIME OF BOLUS OXYTOCIN ADMINISTRATION .....
- TIME OF END OF SURGERY .....
- DURATION OF SURGERY .....
- 24 HOURS POST SURGERY .....
- PREOPERATIVE HAEMATOCRIT (%) .....

**SOCIO-DEMOGRAPHIC CHARACTERISTICS**

- AGE (YEARS) ..... TRIBE .....
- OCCUPATION ..... 1) UNEMPLOYED 2) ARTISAN 3) TRADER 4) CIVIL  
SERVANT 5) PROFESSIONAL 6) OTHERS
- EDUCATIONAL STATUS ..... 1) PRIMARY 2) SECONDARY 3) TERTIARY 4)  
QURANIC 5) NONE
- PARITY .....
- LMP ..... EXPECTED DATE OF DELIVERY .....
- ESTIMATED GESTATIONAL AGE .....

## EVENTS DURING CAESAREAN SECTION

- INDICATION FOR SURGERY .....
- TYPE OF ANAESTHESIA
  - I. SAB.....
  - II. EPIDURAL .....
  - III. COMBINED SPINAL EPIDURAL .....
  - IV. GENERAL ANAESTHESIA .....
- TYPE OF SKIN INCISION .....
- TYPE OF INCISION ON THE UTERUS .....
- AMNIOTIC FLUID VOLUME (ml) .....
- ESTIMATED BLOOD LOSS DURING CS (ml) .....
- NEED FOR BLOOD TRANSFUSION Yes .....No.....
- IF YES, NUMBER OF BLOOD TRANSFUSED .....
- NEED FOR ADDITIONAL OXYTOCICS Yes..... No.....
- IF YES
  - i. Oxytocin ..... Units .....
  - ii. Misoprostol.....Dose.....
  - iii. Ergometrine .....Dose .....
  - iv. Others .....
- NEED FOR PERIPARTUM HYSTERECTOMY. Yes .....No.....
- CADRE OF SURGEON Senior Registrar..... Consultant .....
- TOTAL INTRAOPERATIVE FLUID GIVEN (ml) .....

## POSTPARTUM ASSESSMENT

- POSTPARTUM BLOOD LOSS (immediate postoperative period to 24hrs post operation)  
(ml).....
- Use of additional oxytocics. Yes ..... No .....
- If yes, oxytocin.....units .....
- Misoprostol ..... dose.....
- Ergometrine ..... dose .....
- Need for blood transfusion. Yes ..... No .....
- If yes, number of units .....
- Need for Intensive Care Unit (ICU) Admission. Yes ..... No.....
- Indication for ICU admission .....
- Total blood loss (intra and postoperative blood) [ml].....
- 24hrs postoperative haematocrit (%) .....
- Difference between the pre and the postoperative haematocrit (%).....

## SIDE EFFECT PROFILE

- Nausea (Yes/ No)..... Time of onset .....
- Shivering (Yes/No) ..... Time of onset.....
- Vomiting (Yes/No) ..... Time of onset .....
- Temperature before administration oxytocic ( $^{\circ}\text{C}$ ).....
- Temperature 1 hour after administration of oxytocic ( $^{\circ}\text{C}$ ) .....
- Temperature 4hours after administration of oxytocic ( $^{\circ}\text{C}$ ).....
- Temperature change ( $^{\circ}\text{C}$ ) .....

- Pyrexia (temperature  $\geq 38.0^{\circ}\text{C}$ ) Yes ..... No.....
- Time of onset .....
- Other side effects .....