

MATERNAL OUTCOMES BEFORE AND AFTER NEW OXYTOCIN PROTOCOL AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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DECLARATION

I, Adri Kotze (student no 1872203), declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



On this 26 day of November 2020 in Johannesburg.

DEDICATION

I dedicate this thesis to my parents: Piet and Christine, who have been a constant source of support and encouragement throughout my studies.

ABSTRACT

Background

Obstetric haemorrhage remains the third most common cause of death in South Africa, where 35% are due to postpartum haemorrhage at caesarean section. Uterotonic agents are used to prevent bleeding associated with uterine atony. Higher doses of oxytocin have previously been reported to reduce the incidence of uterine atony with varying protocols for administration.

Objectives

The primary objective was to describe the incidence of post-partum haemorrhage three months before and three months after implementation of the new high dose oxytocin protocol at Chris Hani Baragwanath Academic Hospital. Secondary objectives were to describe the socio-demographic, clinical characteristics, blood loss and associated morbidity.

Methods

This was a cross sectional retrospective record review three months before and three months after the implementation of a high dose oxytocin protocol. The study included all women that underwent caesarean section between 1 November 2016 and 30 April 2017 with a gestation of ≥ 24 weeks and who had a blood loss of $\geq 1\,000$ mL.

Results

A total of 4 604 Caesarean sections were performed during the study period. Of these, 2 162 were performed before the implementation of the new oxytocin protocol and 2 442 after. The incidence of post-partum haemorrhage was 4.8% (n=91) in the Before group and 3.9% (n=89) in the After group (p=0.17). There was a 17.9% change in incidence of postpartum haemorrhage between the groups after the protocol was implemented (p=0.17). There was no difference in the socio-demographic and clinical characteristics between the two groups. Pre-operative risk factors for postpartum haemorrhage between the two groups were similar, except for a higher trend of twin deliveries in the before group (15.5% versus 4.8%; p=0.07). There was no significant difference in uterine atony between the Before and After groups (21.8% and 30.1%, p=0.30). The most common intra operative finding in the Before and After groups was uterine tears (37.5% versus 27.4%, p=0.24). More women in the After group had anaemia at booking (25.9% and 41.9%; p=0.06). The median blood loss in both groups was 1 200 mL. There was no statistical difference in number of high care admissions, relook laparotomies, and hysterectomies between the groups.

Conclusion

There was no difference in the incidence of postpartum haemorrhage at caesarean section after the implementation of a high dose oxytocin protocol for prevention of postpartum haemorrhage. There was no difference in associated morbidity before and after implementing the new protocol.

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LIST OF ABBREVIATIONS

AOL	Augmentation of labour
APH	Ante-partum haemorrhage
APHUO	Ante-partum haemorrhage of unknown origin
BMI	Body mass index
CHBAH	Chris Hani Baragwanath Academic Hospital
CPD	Cephalopelvic disproportion
DIC	Disseminated intravascular coagulation
HB	Haemoglobin
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IMI	Intramuscular injection
IOL	Induction of labour
IU	International Units
IV	Intra-venous
IVI	Intra-venous infusion
NCCEMD	National Committee on Confidential Enquiries into Maternal Deaths
PPH	Post-Partum Haemorrhage
PPROM	Preterm prelabour rupture of membranes
PROM	Prolonged rupture of membranes
SOGC	Society of Obstetricians and Gynaecologists of Canada
SD	Standard deviation
UK	United Kingdom
WHO	World health organisation

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INTRODUCTION

Background

Since 2011, there has been a steady decline in maternal deaths due to obstetric haemorrhage in South Africa.^[1] However, it still remains the third most common cause of death.^[1] Primary post-partum haemorrhage (PPH) at caesarean section is defined as blood loss of $\geq 1\,000$ mL from the genital tract in the first 24 hours after delivery or any amount of blood loss causing significant haemodynamic instability.^[2,3] The Saving Mothers report for 2014-2016 found that bleeding associated with caesarean delivery caused 34.9% of all deaths related to obstetric haemorrhage with a case fatality rate of 30.6 per 100 000 caesarean deliveries.^[1,4] Lack of appropriate use of uterotonics and the delay in initiating second line uterotonics were some of the avoidable factors that were identified.^[1,5] Morbidity associated with PPH include, but are not limited to, hypovolemic shock, anaemia, multi organ failure, consumptive coagulopathy, disseminated intra vascular coagulation, blood transfusion with its related complications, admission to a high care or intensive care facility and hysterectomy.^[6,7]

The most important mechanism for haemostasis after delivery is adequate myometrial contraction causing occlusion of uterine blood vessels.^[2] Therefore, a key strategy to prevent PPH is the prophylactic use of uterotonic agents, especially in high risk women.^[8] Historically, 10 international units (IU) of oxytocin was given as a bolus as part of the active management of the third stage of labour at caesarean section.^[9] Recent evidence suggest that lower doses followed by an infusion, are as effective but associated with fewer side effects.^[9,10] Sartain JB, et al. compared the use of a 5 IU bolus to a 2 IU bolus of oxytocin followed by an infusion of 10 IU oxytocin per hour at elective caesarean section in low risk women.^[10] There were no differences in blood loss or uterine tone between the 2 groups.^[10] They found a significant increase in heart rate and decrease in mean arterial blood pressure in the 5 IU bolus group as well as a higher incidence of nausea in the 5 IU bolus group.^[10] Similarly, King KJ, et al. found no significant difference in blood loss when comparing a 5 IU bolus and high dose oxytocin infusion of 40 IU in 500mL over 30 min followed by an infusion of 2.5 IU/hr, to only using the high dose infusion alone.^[11]

Over the last decade, there have been several guidelines and interventions addressing the problem of obstetric haemorrhage, particularly during caesarean section in South Africa.^[8] These include two monographs produced by the National Committee on Confidential Enquiries into Maternal Deaths (NCCEMD).^[12,13] However, protocols differ between countries and institutions.^[14] Table 1 summarizes some of these guidelines.

Table 7: Summary of different guidelines for the use of uterotonics at caesarean section

	PPH Prophylaxis	PPH Treatment
Farina et al. Management of obstetric haemorrhage Oxytocin, ensuring appropriate use and balancing efficacy with safety. SA, 2015.^[8]	1. Oxytocin 2.5 IU IV slow bolus. 2. Oxytocin 7.5 IU in remaining IV fluid running in. 3. Oxytocin infusion 2.5 IU/hr for 8 hours.	1. Repeat oxytocin 2.5 IU IV slow bolus. 2. Oxytocin infusion 2.5 IU/hr. 3. Ergometrine 0.2 mg IV slow bolus repeated up to 0.6 mg <i>or</i> Syntometrine 0.1 mg/L IU IV slow bolus repeated up to 0.5 mg/5 IU <i>or</i> Misoprostol 400 - 600 µg sublingual or rectal. 4. Oxytocin infusion 5 IU/hr 5. Tranexamic acid 1 g IV
Heesen M et al. International consensus statement on the use of uterotonic agents during caesarean section. 2019.^[15]	<u>Elective caesarean:</u> Bolus 1 IU oxytocin; start oxytocin infusion at 2.5–7.5 IU/hr. If required after 2 min, give a further dose of 3 IU over ≥ 30 s. <u>Intrapartum caesarean:</u> 3 IU oxytocin over ≥ 30 s; start oxytocin infusion at 7.5–15 IU/hr.	1. Ergometrine 200– 500 µg: IMI, or slow IV in exceptional circumstances; may be repeated after 2 h. 2. Misoprostol 400–600 µg: sublingual, rectal, vaginal, oral; repeat after 15 min if required, maximum dose: 800 µg.
Royal College of Obstetricians and Gynaecologists, UK, 2016.^[3]	1. Oxytocin 5 IU by slow IV bolus. 2. Syntometrine may be used in the absence of hypertension in women at increased risk of haemorrhage . 3. Consider the use of IV tranexamic acid (0.5–1.0 g), in addition to oxytocin, in women at increased risk of PPH.	1. Oxytocin 5 IU by slow IV bolus may be repeated. 2. Ergometrine 0.5 mg by slow IV bolus or IMI. 3. Oxytocin infusion at 10 IU/hr. 4. Misoprostol 800 µg sublingually.
American College of Obstetricians and	Prophylactic oxytocin by dilute IV infusion (bolus dose of 10 IU) or	Recommends that uterotonic agents are the first-line treatment for PPH

Gynecologists Practice Bulletin number 183 Postpartum Hemorrhage, 2017. ^[16]	IMI (10 IU).	secondary to uterine atony but the selected agent is at the healthcare provider's discretion.
World Health Organization Recommendations for the prevention and treatment of postpartum haemorrhage, 2018. ^[17]	Only one of the following uterotonics should be used: 1. Oxytocin (10 IU, IMI/IV) 2. Misoprostol (either 400 µg or 600 µg, oral) 3. Ergometrine (200 µg, IMI/IV) 4. Syntometrine (5 IU/ 500 µg, IMI) In settings where multiple uterotonic options are available, oxytocin is the recommended uterotonic agent.	No specific regime of uterotonics mentioned.

* Agents not available in our setting, like Carbitocin, are excluded from this summary

Up until January 2017, hospitals attached to the University of the Witwatersrand used the following protocol for uterotonic administration at caesarean section.^[18]

1. Oxytocin 2.5 IU intravenous (IV) as a bolus after delivery of the baby.
2. Followed by an oxytocin infusion of 20 IU in one litre of Ringers-lactate to run over 8 hours (2.5 IU/hr).

If the uterus was still atonic a second bolus of oxytocin 2.5 IU was recommended followed by Syntometrine 1 ampule as an intramuscular injection (IMI) and misoprostol 800 µg rectally if the bleeding continued.

In February 2017 the Department of Obstetrics and Gynaecology changed this protocol in all the hospitals attached to the University of the Witwatersrand (Table 2). This new protocol

incorporated the use of Tranexamic acid and recommended a higher rate of oxytocin infusion after the initial bolus.

The aim was to describe the incidence of post-partum haemorrhage three months before and three months after implementation of the new high dose oxytocin protocol at Chris Hani Baragwanath Academic Hospital (CHBAH).

Objectives

The specific objectives of this study were:

1. To describe the incidence of PPH before and after implementation of the new protocol.
2. To describe the socio-demographic and clinical characteristics of women with PPH at caesarean section between 1 November, 2016 and 30 April 2017.
3. To describe blood loss and associated morbidity before and after implementing the new guidelines.

Table 8: New oxytocin protocol

	Prophylaxis	Cardiac patients and sever Pre-eclampsia
1	Oxytocin 2.5 IU IV bolus at delivery of anterior shoulder.	Oxytocin 2.5 IU IV slow bolus (over 30 s) at delivery of anterior shoulder.
2	Start oxytocin infusion 40 IU/1000mL Ringer's-lactate or Balsol at 125mL/hr in the dedicated oxytocin line (5 IU/hour).	Start oxytocin infusion 40 IU/200 mL at 25 mL/hr. (5 IU/hour).
3	If ongoing uterine atony, repeat oxytocin 2.5 IU IV bolus.	
4	Actively bleeding cases or ongoing uterine atony: I. Call for senior surgical and anaesthetic help. II. Syntometrine 1 ampoule IMI (into deltoid muscle) if no contra-indications. III. Tranexamic acid 1g IV. IV. Increase oxytocin to 80 IU/1 000 mL at 125 mL/hr.(10IU/hour). V. If no response, give Misoprostol 400 – 600 µg sublingual / rectal.	
5	Concurrent resuscitative (fluids/blood products etc.) and surgical (B-Lynch etc.) measures need to be taken to manage ongoing bleeding.	

***Women should come with an IV line (Line A) in situ, at 125 mL/hr or at 80 mL/hr for cardiac and hypertensive patients, dedicated for fluid resuscitation. Insert second IV line (Line B) pre-operatively. Line B must have a dial-a-flow for dedicated oxytocin administration. Line A can be removed in recovery once the woman is fully fluid resuscitated.**

METHODS

Setting

The CHBAH is an academic central hospital providing primarily tertiary care services in the Soweto district of Gauteng and is affiliated with the University of the Witwatersrand. The hospital has a 336 bed maternity unit, conducts approximately 23 000 deliveries a year and 640 caesarean sections.^[19] In 2016 the caesarean section rate was 41% and in 2017 it was 44%.

At CHBAH, two theatres are operational 24 hours a day. Due to the high volume of patients, there is often a long waiting list of caesarean sections (up to 20 emergencies at a time), which are constantly triaged.

Misoprostol is most often used for induction of labour (IOL) in women with an unfavourable cervix. A dose of 20 µg is given 2 hourly for 12 doses or until labour starts.^[20] Prandin gel is also available for induction of labour but is used far less often due to cost.

Women requiring augmentation of labour (AOL) with oxytocin receive 2 IU of oxytocin added to 200 mL of Normal saline.^[20] Infusion is started at a rate of 12mL/hr and increased by 12 mL/hr every 30 min until a minimum of 3 strong contractions are palpated.^[20] The maximum infusion rate is 120 mL/hr.^[20]

Study design

Cross sectional study with a retrospective record review of women that received oxytocin three months before and three months after the oxytocin protocol change.

Study population

The study included all women that underwent caesarean section between 1 November 2016 and 30 April 2017 with a gestation of ≥ 24 weeks and who had a blood loss of $\geq 1\,000$ mL. All cases where blood loss was not recorded in the theatre register were excluded. The medical records of women with a blood loss of $\geq 1\,000$ mL as recorded in the register were retrieved, reviewed and the relevant data recorded. When the medical record could not be located, or the records were incomplete (blood loss not recorded), the case was excluded from further analysis.

Data collection

Data was collected from the theatre registers. The PPH cases before and after the change in protocol were compared. Data obtained for analysis is further described in appendix 2.

Definitions

For the purpose of this study, the following definitions were used:

Primary PPH: blood loss $\geq$ 1 000 mL at caesarean section within 24 hours of delivery.^[2]

Pre-eclampsia: hypertension and one or more of the following:^[21]

1. Proteinuria ($>300\text{mg/day}$ or 1g/L on dipsticks or urine protein/creatinine $>30\text{mg/mmol}$).
2. Maternal organ dysfunction
 - I Renal impairment (creatinine $>90\text{ }\mu\text{mol/L}$).
 - II Liver involvement (transaminases twice upper limit of normal).
 - III Neurological complications (severe headache, hyperreflexia, altered mental state, eclampsia, blindness or stroke).
 - IV Haematological complications (thrombocytopenia, platelet count below $150000/\text{dL}$, diffuse intravascular coagulation (DIC), haemolysis).
3. Uteroplacental dysfunction (foetal growth restriction).

Gestational diabetes: diagnosis based on the International Association of the Diabetes and Pregnancy Study Group criteria after 75g oral glucose tolerance test.^[22]

- I Fasting glucose: ≥ 5.1
- II 1 hour: ≥ 10
- III 2 hour: ≥ 8.5

Antepartum haemorrhage: bleeding from genital tract after 22 weeks gestation.

Anaemia in pregnancy: haemoglobin concentration of less than 11 g/dL and a haematocrit of less than 35%.

Polyhydramnios: amniotic fluid index more than the 90th percentile for gestational age.

Massive blood transfusion: transfusion of ≥ 5 units Red packed cells.^[6]

Junior registrar: first and second year registrar.

Senior registrar: third and fourth year registrar.

Junior consultant: less than 5 years of experience.

Senior consultant: more than 5 years of experience.

Ethical approval

Ethical approval from the University of Witwatersrand Human Research Ethics Committee was obtained. Certificate clearance number: M180733. Approval was also obtained from the Chief Executive officers at CHBAH as well as the Obstetrics and Gynaecology department. Patient confidentiality were ensured at all times and anonymity was ensured by the use of study numbers.

Statistical analysis

Statistical analyses were conducted in R software (version 4.00; www.R-project.org). The normal distribution of the data was checked using the Shapiro–Wilk test and examining Q-Q plots. Data are reported as mean (SD) for parametric data and median (range) for non-parametric data and are presented descriptively in charts, tables or in text. Categorical data were compared using chi-squared contingency tests, or Fisher’s exact when the variable in any cell contained less than 5 samples. Continuous variables were compared using student t-test for parametric data and Mann-Whitney U tests for non-parametric data. Tests were two-tailed, and significance set at 0.05.

RESULTS

The incidence of PPH at caesarean section during the study period was 3.9 %, 4.8% (n= 91) in the Before group and 3.9% (n=89) in the After group. There was a 17.9% change in incidence of PPH after the protocol was implemented ($p=0.17$).

A total of 4 604 caesarean sections were performed during the study period with an overall caesarean section rate of 43.7% (40.9% Before versus 46.5% After, $p<0.05$). Of these, 2 162 (47%) were performed before the implementation of the new oxytocin protocol and 2 442 (53%) ($p<0.05$) After. When the incidence of PPH was calculated, significantly more cases had to be excluded in the Before group, 267 (12.3%) compared to the After group, 183 (7.5%), due to blood loss not recorded in theatre books ($p <0.05$). Thereafter, a further 32 (35.2%) in the Before and 26 (29.2%) in the After group were excluded from final analysis due to missing files or incomplete data.

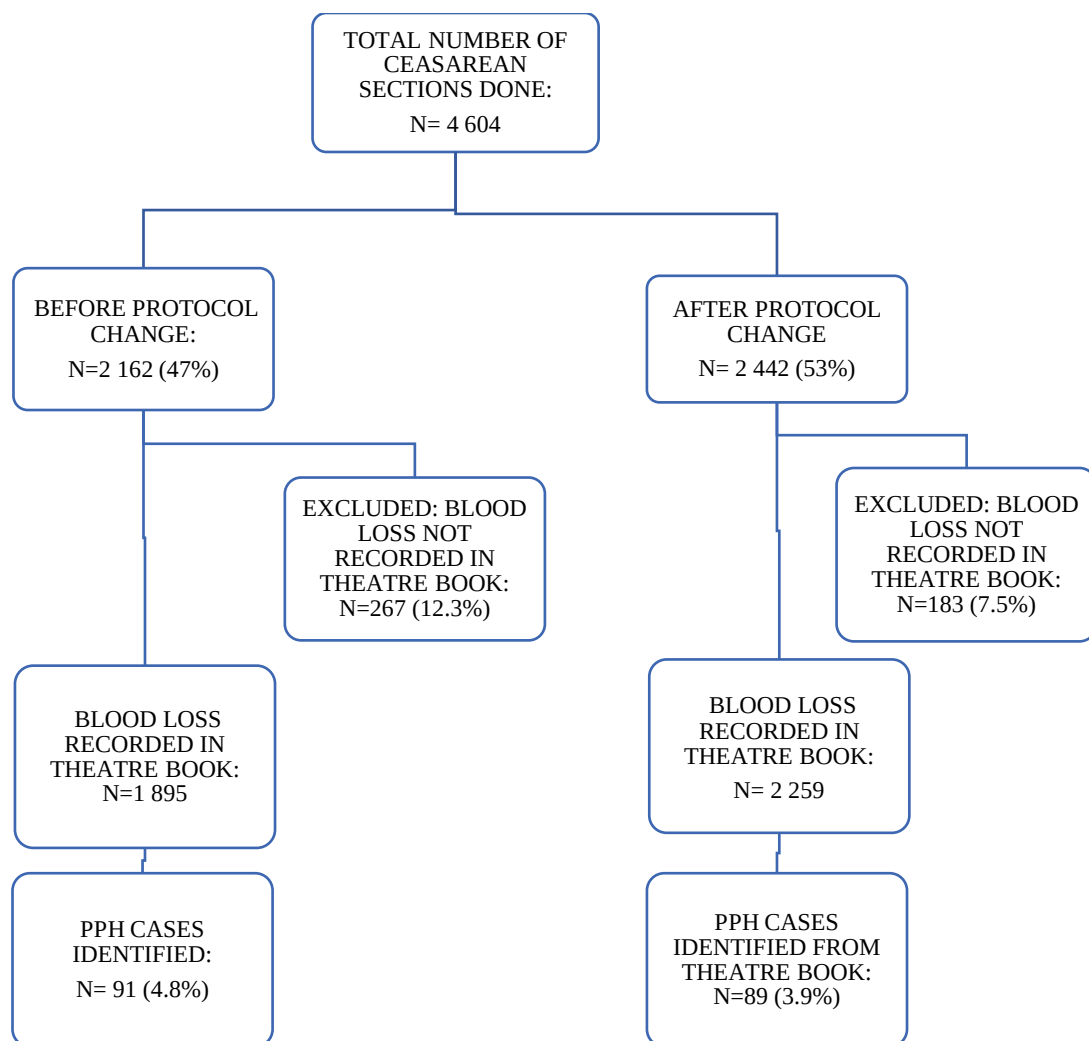


Figure 1: Flow chart of cases identified at caesarean section with postpartum haemorrhage

There was no difference between the two groups in terms of general socio-demographic and clinical characteristics, as reflected in Table 3.

Table 9: Socio-demographic and clinical variables

Socio-demographic and clinical variables	Before group n=59		After group n=63		p value
	N	No (%) Mean $\pm$ SD Median (range)	N	No (%) Mean $\pm$ SD Median (Range)	
Age	59	30.4 $\pm$ 5.5	63	28.7 $\pm$ 6.9	0.12
Height	25	157.7 $\pm$ 7.7	30	152.4 $\pm$ 30.2	0.36
Weight	47	75.7 $\pm$ 18.7	50	76.7 $\pm$ 17.5	0.78
Body mass index	27	31.3 $\pm$ 9.5	32	32.5 $\pm$ 8.7	0.62
Gravidity	59	3 (1-6)	63	3(1-6)	0.08
Parity	59	2 (0-4)	63	1 (0-1)	0.04
Booking gestation	52	20 (6-37)	58	19 (6-36)	0.35
Unbooked	53	1 (1.9%)	60	4 (6.7%)	0.38*
HIV	57	22 (38.6%)	61	23 (37.7%)	1.00**

* = Fisher's exact p value, **=Chi Square p value

No women reported a previous PPH. One woman reported having a history of ante-partum haemorrhage (APH). There were no cases of polyhydramnios. Other risk factors for PPH are compared in Table 4. In the Before group, 7 (11.9%) women had more than one previous caesarean section, and 6 (9.5%) in the After group (p=0.77) A general anaesthetic was given to 16 (27.6%) women in the Before, and 27 (42.9%) of women in the After group (p = 0.08).

Table 10: Comparisons of risk factors for postpartum haemorrhage in the Before versus After group

Risk factors for postpartum Haemorrhage	Before group n=59		After group n=63		p value
	n	No (%) Mean $\pm$ SD Median (range)	n	No (%) Mean $\pm$ SD Median (Range)	
Anaemia at booking	58	15 (25.9%)	62	26 (41.9%)	0.06**
Booking Hb in g/dL	57	11.8 $\pm$ 1.5	60	11.6 $\pm$ 1.7	0.51
Gestation at delivery	59	37.2 $\pm$ 3.2	61	36.9 $\pm$ 3.8	0.66
Diabetes	58	2 (3.4%)	62	0 (0%)	-
Twins	58	9 (15.5%)	63	3 (4.8%)	0.07*
Prolonged latent phase of labour	59	8 (13.6%)	63	16 (25.4%)	0.10**
Active phase of labour (>12hrs)	59	3 (5.1%)	63	7(11.1%)	0.22*
Augmentation of labour	59	6 (10.2%)	63	7 (11.1%)	0.86**
Induction of labour	59	6 (10.2%)	63	5 (7.9%)	0.67**
Multi-fibroid uterus	55	3 (5.4%)	63	4 (6.3%)	1.00*
PPROM	58	2 (3.5%)	63	2 (3.2%)	1.00*
PROM (>18hrs)	59	5 (18.5%)	63	5 (7.9%)	0.91**
Pre-eclampsia	58	10 (17.2%)	62	5 (8.1%)	0.13**
Received tocolysis	59	11 (18.6%)	63	12 (19.1%)	0.95**
Received MgSO4	59	4 (6.8%)	63	3 (4.5%)	0.71*
Previous caesarean section	59	16 (27.1%)	63	15 (23.8%)	0.67**

Hb=haemoglobin, PPRM= pre-term pre-labour rupture of membranes, PROM =prolonged rupture of membranes* = Fisher's exact p value, **=Chi Square p value

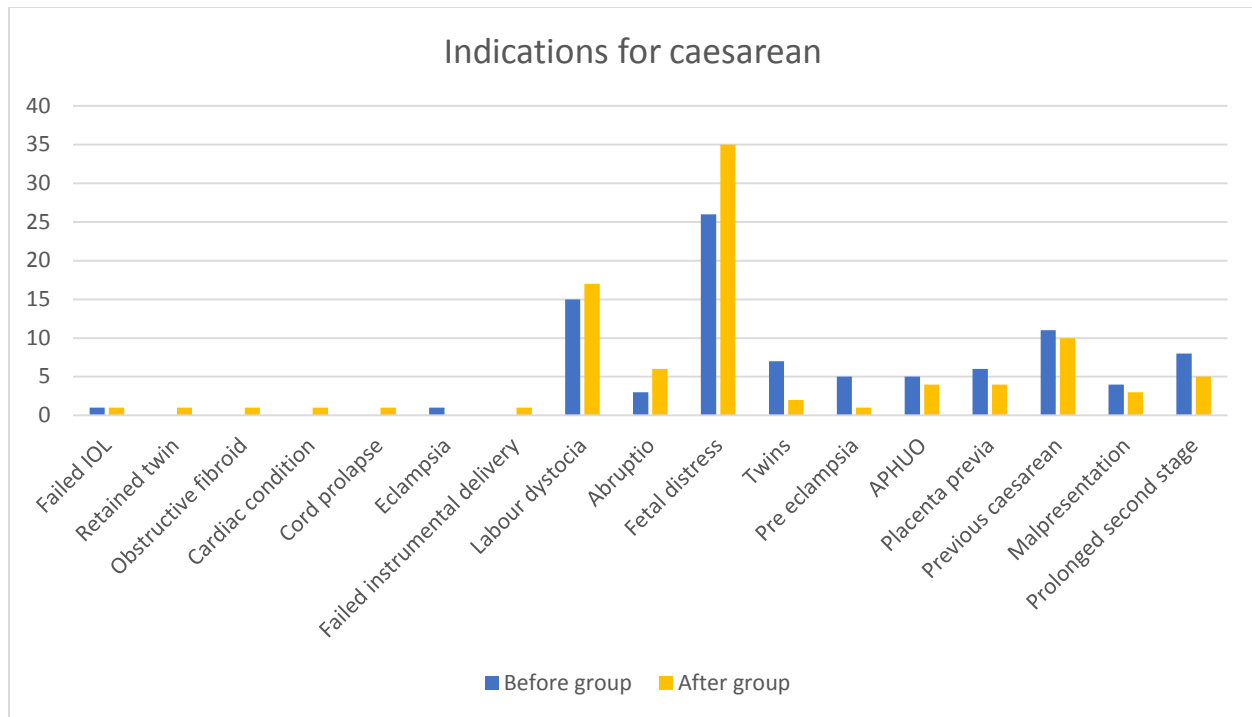


Figure 2: Indications for Caesarean section

APH/IO= Ante-partum haemorrhage of unknown origin

The most common indications for caesarean section are represented in Figure 2. In some cases, more than one indication for caesarean was given. Only one caesarean section was an elective delivery. Most of the caesarean sections were performed by registrars (Figure 3). All the caesarean sections done by interns were supervised by a registrar, medical officer or consultant. The median decision to incision time was 142.4 minutes in the Before group compared to 180 minutes in the After group. ($n_1 = 52$, $n_2 = 59$; $p = 0.16$). The median time of procedure in both groups were the same at 55 min ($n_1 = 36$, $n_2 = 46$; $p = 0.67$).

Uterine atony was reported in 12 (21.8%) of the women in the Before group compared to 19 (30.1%) in the After group ($p=0.30$). The most common intraoperative uterine pathology found were uterine tears, (21 (37.5%) Before; 17 (27.4%) After; $p = 0.24$). The most common surgical intervention was placement of figure of 8 sutures (16 (29.1%) Before; 14 (22.2%) After; $p = 0.39$). A B-Lynch suture was only placed in 3 (5.5%) women Before and 5 (7.9%) in the After group ($p=0.72$). Catheter balloon tamponade was placed in 3 (5.5%) of the Before and 7 (11.1%) of the After women ($p= 0.33$).

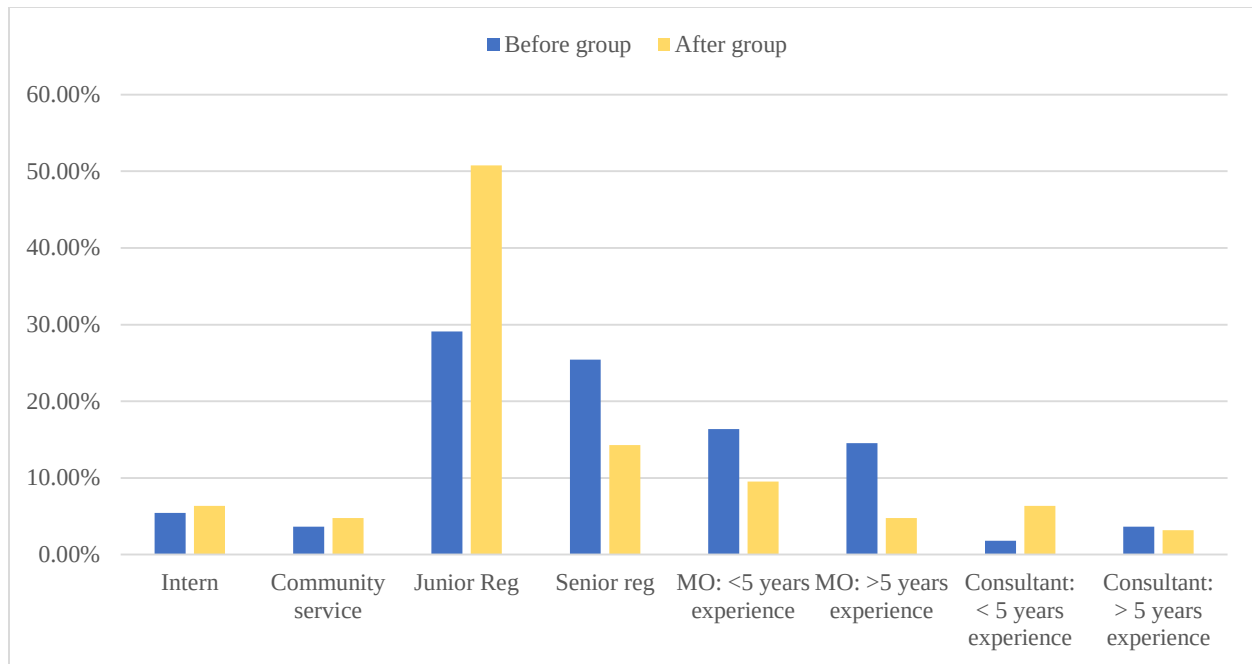


Figure 3: Experience of primary surgeon

The median blood loss in both groups were 1 200 mL with a range of 1 000-3 500 mL in the Before (n=59) and 1 000-3 200 mL in the After (n=63) group (p=0.61). There was no difference between the 2 groups in the need for a second oxytocin bolus (6 (11.1%) Before; 13 (21.3%) After; p=0.14). The use of tranexamic acid was similar in both groups (7 (13%) Before; 9 (15%) After; p=0.75). Misoprostol was given less often to women in the Before group (2 (3.7%) Before; 15 (25%) After, p<0.05).

Table 11: Comparison of morbidity variables

Morbidity		Before group n=59		After group n=63		p value
		N	No (%) Mean $\pm$SD Median (range)	n	No (%) Mean $\pm$SD Median (Range)	
High care	Admission	57	20 (35.1%)	63	31 (49.2%)	0.12**
	No of days	57	1 (1-5)	63	1(1-20)	0.84
Blood transfusion	No transfused	57	17 (29.8%)	63	27 (42.8%)	0.14**
	Massive	51	3 (5.3%)	61	2 (3.2%)	0.67*
	Units	57	2 (1-6)	63	2 (1-8)	0.92
Re-look laparotomy		55	2 (3.6%)	57	6 (9.5%)	0.28*
Hysterectomy primary surgery		56	1 (1.8%)	62	1 (1.6%)	1.00*
Hysterectomy at relook		57	0 (0%)	62	1 (1.6%)	-

* = Fischer's exact p value, **=Chi square

There were no maternal deaths secondary to bleeding at caesarean section amongst the cases examined. Only one patient was referred for ICU admission, however due to lack of resources this patient was admitted to high care instead.

In the Before group versus the After group, 51 (96.2%) versus 8 (13.3%) received an initial low dose oxytocin infusion of < 5 IU/hr ($p < 0.05$). In the Before group versus the After group 3 (5.7%) versus 52 (86.7%) received a higher dose of oxytocin as per the new protocol ($p < 0.05$). A sub-analysis was made, including all women in both groups, but comparing women who actually received high dose oxytocin infusion (≥ 5 IU/hr) compared to women who actually received low dose (< 5 IU/hr), despite the protocol in place at the time. Findings are summarized in Table 6.

Table 12: Sub-analysis comparing women who received high dose oxytocin to women who received low dose

		Low dose oxytocin		High dose oxytocin		P value
		N	No (%)	n	No (%)	
Antenatal risk factors	Anaemia	57	14 (24.6%)	56	26 (46.4%)	0.15**
Uterine findings	Atony	58	10 (17.2%)	56	20 (35.7%)	0.03**
	Tears	58	23 (39.7%)	55	12 (21.8%)	0.04**
Additional tocolytic agent	Repeat oxytocin bolus	59	6 (10.2%)	56	13 (23.2%)	0.06**
	Misoprostol	59	4 (6.8%)	56	13 (23.2%)	0.02**
Blood transfusion	Transfused	58	15 (25.9%)	56	26 (46.4%)	0.22**
Balloon tamponade		58	2 (3.4%)	56	8 (14.3%)	0.05*
High care admission		59	18 (30.5%)	56	28 (50%)	0.03**

* = Fischer's exact p value, **=Chi square

DISCUSSION

The overall incidence of PPH at caesarean section in our study was lower than the 6% estimated in the literature.^[23,24,25] There was no statistically significant difference in incidence of PPH at CHBAH between the Before (low dose oxytocin) and After (high dose oxytocin) groups (91 (4.8%) Before; 89 (3.9%) After, $p=0.17$). This finding may infer that a higher dose of oxytocin may not reduce the incidence of postpartum haemorrhage or the cause may be unrelated to uterine atony. At CHBAH, swabs are not routinely weighed and not all women have pre - and post-operative comparison of haematocrit. In addition, blood loss in theatre has previously been described to be underestimated if more than 600 mL so it is possible that blood loss in our study was underestimated.^[26]

In the women with PPH, socio- demographic variables like age, BMI, gestation at booking, and HIV status were similar in both comparison groups (Table 3). More women in the after group had anaemia at booking, the significance of which is described later. There was a trend towards a higher number of twin pregnancies in the Before group when compared to the After group. Twin pregnancies have previously been reported as a significant risk factor for uterine atony which has been attributed to overdistension of the uterus.^[2,11] In our study the trend to significance observed in twin pregnancies may suggest that a high dose of oxytocin may be more effective in preventing PPH when compared to a lower dose. Similar to our study, Munn et al., in labouring women, compared high dose oxytocin infusion (80 IU in 500 mL over 30min) to low dose oxytocin (10 IU in 500mL over 30 min) to prevent PPH at caesarean section.^[27] They found higher doses more effective in women with risk factors for uterine atony, specifically labour arrest and chorioamnionitis, but not in women who received magnesium sulphate.^[27]

Only one women in our review underwent elective caesarean section. It is well known that emergency caesarean section is associated with a higher risk of PPH than elective caesarean section.^[24] Magann et al. reported PPH in emergency caesarean to be 6.75% compared to 4.84% in elective caesarean ($p=0.007$).^[24] We also found that most of the caesarean sections were performed by registrars. Sheehan et al. evaluated oxytocin use at elective caesarean section in women with no known risk for PPH.^[28] They compared a bolus dose of 5 IU oxytocin followed by a 10 IU/hr oxytocin infusion with using just a 5 IU bolus dose.^[28] They found an overall

increase in incidence of major obstetric haemorrhage when the caesarean section was performed by a junior obstetrician, especially in the bolus only group. At CHBAH the most common intra operative finding was uterine tears (37.5% and 27.4% respectively). This may be attributed to several factors including experience of the surgeon, surgical technique, theatre delays, and high percentage of repeat caesarean sections. This finding may also account for no further reduction in uterine atony by use of a higher dose of oxytocin.

Some women in the After group did not receive the prophylactic high dose oxytocin infusion as indicated in the protocol. This could have been due to a delayed transition from the old to the new protocol by staff. In addition, some women in the Before group received a higher dose of infusion even though it was not standard practice at the time. A sub-analysis was performed, comparing all the women who received low dose, regardless of group, to those who received high dose (Table 6). This found that women who received high dose oxytocin infusion were more likely to have received a transfusion, additional uterotonics and more likely to be admitted to high care. Furthermore, in women who received high dose oxytocin there was a higher incidence of uterine atony being reported at caesarean. However, these findings could have been due to a reverse causation bias since the women in the Before group who received high dose oxytocin most likely had this as treatment, rather than prophylaxis of PPH, given that it was not the standard practice at the time.

Even though it is widely known that prophylactic oxytocin reduces the risk of PPH, there is still no consensus on the optimal dose.^[11, 14] Nevertheless, previous studies has found that the minimum effective dose of oxytocin to promote uterine contraction is up to eight times higher in women undergoing caesarean section due to labour arrest, than for women undergoing elective caesarean section.^[29,30] This is thought to be due to desensitization of oxytocin receptors during labour.^[30] However, Cecilia M, et al. argued that once an optimal number of oxytocin receptors are occupied, a further increase in oxytocin dose has no benefit in terms of uterine contractions but only increases the severity of side effects.^[31] Similar to our study, they found no difference in incidence of PPH when a low dose oxytocin infusion, 10 IU over 2-4 hours was compared to a higher dose of 30 IU over 8 hours.^[31] In their randomized control trial, mean blood loss, need for additional uterotonic and decrease in post-operative pack cell volume were all found to be

similar in both groups examined.^[31] They included both elective and emergency caesarean sections but excluded women known with high risk of PPH, and their sample size was small including only 271 women in total.^[31]

In the index study, there was no difference in the need for a second oxytocin bolus, or syntometrine between the two groups. We did find a significantly higher rate of misoprostol use in the After group, which could not be explained. It is also possible that just the implementation of a new protocol may have sensitized surgeons to the use of uterotonics other than oxytocin. In contrast to our study, Munn et al., found a significant decrease in the use of additional uterotonic agents when a high dose oxytocin infusion was used compared to a low dose oxytocin.^[27] Even though the use of tranexamic acid was only officially introduced into the new 2017 uterotonic protocol, the rate of use in the PPH cases examined were similar in both groups. The WOMAN trial found that death due to haemorrhage was reduced in women with PPH who received tranexamic acid, with no increase in adverse events.^[33] This trial was only published in 2017 however, so it may be that the use of tranexamic acid observed in our study might have stemmed from its already established benefit when used in trauma patients.

A lower number of women in the Before group received a blood transfusion compared to women in the After group (35.1% versus 49.2% ; $p=0.14$). Even though this was not statistically significant, this trend might be explained by the higher number of women in the after group who had anaemia at booking. However, estimated blood loss in both groups were similar. Duffield et al. also found no difference in blood loss or incidence of PPH when they compared high dose oxytocin infusion (15 IU/hr) to low dose oxytocin infusion (2.4 IU/hr) but they only included elective caesarean sections.^[33] Munn et al., on the other hand, included only labouring women in their study and also did not find any difference in blood loss when comparing a high dose to a low dose oxytocin infusion.^[27] We found no statistical difference when comparing other morbidity variables like B-lynch, high care admission, relook laparotomy, and rate of hysterectomy between the groups. Most of the studies found in the literature only include blood loss as a morbidity variable when comparing different oxytocin regimes.^[11,27,28,33] The studies by Munn et al. and Duffield et al., were underpowered to examine these morbidity outcomes.^[27,33] Munn et al. reported no need for blood transfusion or hysterectomy at caesarean section in their

study.^[27] Similarly, Duffield et al only transfused one woman in their study and no women required surgical intervention for PPH.^[33] Further studies are needed to investigate whether the infusion dose of oxytocin influences the incidence and severity of major haemorrhage-related morbidity, such as transfusion, intensive care admission, and major organ dysfunction.

Study limitations

The study period was initially set to be between 1 October 2016 and 31 May 2017. The theatre book for the month of May was so severely damaged that no accurate information could be obtained from it. Also, all maternity records from June 2017 onwards at CHBAH was captured on an electronic database which was not functioning at the time of data collection. No hard copies of those casefiles could be traced by the records department. Therefore, it was decided to shorten the study period by a month on each side, resulting in a smaller sample size. In some cases, blood loss was not recorded in the theatre books or the PPH casefiles could not be traced. Significantly more patients in the Before than the After group were excluded due to missing records, and significantly more caesarean sections were done in the After group. This might have influenced the results. Furthermore, we did not compare the incidence and severity of side effects experienced when a higher infusion dose of oxytocin was used, and our study was underpowered to compare morbidity outcomes. Blood loss in theatre was estimated visually, a method known to underestimate blood loss especially when more than 600 mL.^[32] Thus, the incidence of PPH might be underestimated.

CONCLUSION

The protocol with a higher dose of oxytocin did not decrease the incidence of PPH at caesarean section. This may infer that no further benefit is achieved with a higher dose and that causes other than atony, such as urine tears, contributed to the high incidence of PPH at the CHBAH. A higher dose of oxytocin may be beneficial in twin pregnancies, but a much larger sample size will be needed to evaluate this. We found no reduction in blood loss when a high dose oxytocin infusion was used and there was no difference in associated morbidity before and after implementing the new protocol. Due to the observed low incidence of PPH at caesarean section, a much larger prospective randomized controlled trial may better illicit the impact of high versus low dose oxytocin infusion on blood loss at caesarean section at CHBAH.

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APPENDIX 1: Approved protocol

Maternal outcomes before and after new Oxytocin protocol at Chris Hani Baragwanath Hospital.

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1. Introduction

1.1 Background

According to the Saving Mothers report of 2011-2013, obstetric haemorrhage is the second leading cause of maternal deaths in South Africa, accounting for 15.8% of all deaths.¹ A third of obstetric haemorrhage deaths are as a result of bleeding at or after caesarean section.¹ This report also found that deaths due to haemorrhage has increased in recent years, from 13.4% of all deaths from 2002-2004 to the 15.8% in the most recent report.¹ The risk of dying from a caesarean section was found to be 2.8 times higher than the risk of dying from a vaginal delivery.¹

An estimated 3.38% of all caesarean related deaths were from bleeding at caesarean section and 14% died from bleeding following the procedure.¹ It was found that the risk of dying from bleeding at or after caesarean section in South Africa was 1 in 3053.¹

It was reported that the use of uterotonics to prevent and treat uterine atony at caesarean section was underutilized. The recommendation made was to implement standard protocols for the use of uterotonic agents at caesarean section.

The Royal College of Obstetricians and Gynaecologists (UK) recommend a 5 IU intravenous bolus dose of oxytocin after delivery of the baby.² They further recommend an infusion of 40 IU oxytocin in 500 mL 0.9% saline at 125mL/hr for patients with post-partum haemorrhage (PPH).²

Up until February 2017, hospitals in the Witwatersrand university circuit were using the following protocol for administration of uterotonics at caesarean section:³

3. Bolus 2.5 IU oxytocin after delivery of the baby.
4. Followed by an oxytocin infusion of 20 IU in one litre Ringers-lactate to run over 8 hours.

If the uterus was still atonic a second bolus oxytocin was recommended followed by syntometrine 1 ampule IMI and misoprostol 800 µg rectally in a stepwise manner.

Protocols still differ widely between countries and institutions.

1.2 Oxytocin use at caesarean section

Oxytocin is a nine-amino acid peptide hormone produced by the hypothalamus and released by the posterior pituitary gland.⁴ It is one of the most important agents used to prevent post-partum haemorrhage. Oxytocin is also known to cause hemodynamic changes, which include tachycardia, hypotension and ST changes.⁵

Historically 10 IU oxytocin was given as a bolus after delivery of the baby. Recent evidence suggest that lower doses are as effective but associated with fewer of these side effects.⁶

An Australian study done by Sartain JB, et al. compared the use of a 5 IU bolus to a 2 IU bolus of oxytocin followed by an infusion of 10 IU oxytocin per hour.⁷ They found that there was a significant increase in heart rate and decrease in mean arterial blood pressure in the 5 IU group as well as a higher incidence of nausea in the 5 IU group.⁷ There were no difference in blood loss or uterine tone between the 2 groups.⁷ However, the study only included elective caesarean sections and excluded all women known to have a high risk for post-partum haemorrhage.

King KJ, et al. compared the use of a 5 IU bolus followed by an oxytocin infusion to only using the infusion alone.⁸ They used a high dose infusion of 40 IU in 500mL over 30 min followed by 20 IU in 1 litre over 8 hours.⁸ They found that there was no difference when comparing the need for the use of additional uterotonics over the next 24 hours.⁸ They also found no significant difference in blood loss between the two groups.⁸ However, the study lacked enough power to

compare side effects between the two groups and anaesthetic methods were not standardized. A strength was that they only included women with risk factors for post-partum haemorrhage.

The Elective Caesarean Section Syntocinon (oxytocin) Infusion Trial (ECSSIT) compared a bolus dose of 5 IU oxytocin followed by a 40 IU oxytocin infusion with using just a 5 IU bolus dose.⁹

They found that a bolus and infusion had no effect on the occurrence of major obstetric haemorrhage compared with a bolus of oxytocin alone.⁹ However, the need for another uterotonic agent was reduced in the bolus and infusion group.⁹ The use of an oxytocin infusion did not increase the occurrence of side effects.⁹ This study only included elective caesarean sections and excluded any woman with risk factors for PPH.

Carvalho JCA, et al. found that the ED90 of oxytocin is around 0.35 IU.¹⁰ ED90 is the minimum effective dose to promote uterine contractions in 90% of women. The study was performed with women undergoing elective caesarean section. The same group also conducted a study with women who underwent caesarean section due to labour arrest and received oxytocin during labour. Oxytocin ED90 of 2.9 IU was found in these cases.¹¹ An explanation for this could be the desensitization of oxytocin receptors in the myometrium after exposure to oxytocin during labour.

1.3 Other agents used for post-partum haemorrhage

1.3.1 Misoprostol

Misoprostol is a prostaglandin E1 analogue and has strong uterotonic activity through selectively binding prostanoid receptors.⁴ It is inexpensive, stable at room temperature and can be administered by oral, buccal, sublingual vaginal or rectal routes. Therefore a good option to use in a resource limited setting.

A meta-analysis published by Prata and Weidert reviewed the efficacy of misoprostol for the treatment of post-partum haemorrhage.

According to the article the use of misoprostol in addition to standard uterotonics, like oxytocin, is not supported in the evidence during vaginal delivery.¹² However, during caesarean deliveries,

it has been found that misoprostol as an adjunct to oxytocin has an important role in reducing intra and postoperative hemorrhage.¹²

1.3.2 Tranexamic acid

Tranexamic acid is a synthetic derivative of the amino acid lysine. It is used as an antifibrinolytic agent. It works by blocking lysine binding sites on plasminogen molecules, inhibiting the breakdown of fibrinogen and fibrin by plasmin. The WOMAN trial found that death due to haemorrhage was reduced in women with PPH who received tranexamic acid.¹³ There was no increase in adverse events.¹³

1.4 New protocol

In February 2017 the University of the Witwatersrand Obstetric department changed the protocol used during caesarean section in all the hospitals in their circuit.

Women should come with an IV line (Line A) in situ, at 125 mL/hr or at 80 mL/hr for cardiac and hypertensive patients, dedicated for fluid resuscitation. Insert second IV line (Line B) pre-operatively. Line B must have a dial-a-flow for dedicated oxytocin administration. Line A can be removed in recovery once the woman is fully fluid resuscitated.

Prophylaxis:

1. Oxytocin 2.5 IU IVI bolus at delivery of anterior shoulder (provided there is no twin).
2. Immediately start oxytocin infusion 40 IU/1000 mL Ringer's-lactate or Balsol at 125 mL/hr in the dedicated oxytocin line - (Equivalent to 42 drops/min from a 20

Dropper administration set)

3. If ongoing uterine atony, repeat oxytocin 2.5 IU IVI bolus. Actively bleeding cases or ongoing uterine atony:

- I. Call for senior surgical and / anaesthetic help
- II. Syntometrine 1 ampoule IMI (into deltoid muscle) if no contra-indications
- III. Tranexamic acid 1g IVI

IV. Increase oxytocin to 80 IU/1000 mL at 125 mL/hr

V. If no response, give Misoprostol 400 – 600 µg sublingual / rectal. Concurrent resuscitative (fluids/blood products etc.) and surgical (B-Lynch etc.) measures need to be taken to manage ongoing bleeding.

Cardiac and severe PET patients:

1. Oxytocin 2.5 IU IVI slow bolus (over 30 s) at delivery of anterior shoulder.
2. Immediately start oxytocin infusion 40 IU/200 mL at 25 mL/hr.

The aim of this study is to compare the incidence and morbidity of post-partum haemorrhage before and after the implementation of this new protocol at Chris Hani Baragwanath Hospital.

2.Study aim

The specific objectives of this study will be:

4. To describe the incidence of PPH before and after implementation of the new protocol.
5. To describe the socio-demographic and clinical characteristics of women with post-partum haemorrhage between 1 October 2016 until 31 May 2017.
6. To describe blood loss and associated morbidity before and after implementing the new guidelines.

3.Methods

3.1 Setting

Chris Hani Baragwanath Hospital is an academic institute associated with the University of the Witwatersrand. It is classified as a Central hospital in the Gauteng district and provides level 3 services. It is the 3rd largest hospital in the world with approximately 3200 beds.¹⁴ It is located in the Soweto area and serves a population of about 2 million people. The hospital has 336 obstetric beds and conducts more than 23000 deliveries a year. Baragwanath has a caesarean section rate of around 33.3% and does about 640 caesarean sections a month.¹⁵ All women are admitted via the 10-bed admission area from where they are transferred to one of the following operational areas:

- 1) First stage: A 13 bed short stay area for women in latent labour or awaiting blood results before being transferred to the antenatal wards.
- 2) Labour ward: Consist of 20 beds for women in active phase of labour, women who requires continuous foetal monitoring or women on augmentation of labour with oxytocin.
- 3) Antenatal ward: Three 30 bed antenatal wards for managing women with antenatal conditions such as hypertension, diabetes etc. Induction of labour is also initiated in these wards and women are transferred to labour ward once in active labour.
- 4) High care: A 7 Bed high care for women who need advance monitoring and nursing care. The unit also has one ventilator available that is used for critically ill patients awaiting ICU transfer.
- 5) Postnatal ward: Three 30 bed postnatal wards for all women who has delivered.

Misoprostol is most often used for induction of labour in women with an unfavourable cervix. A dose of 20 µg is given 2 hourly for 12 doses or until labour starts.¹⁶ Prandin gel is also available for induction of labour but is used far less often due to cost.

For women requiring augmentation of labour with oxytocin, the following regime is used: 2 units of oxytocin is added to 200 mL of Normal saline. Infusion is started at a rate of 12mL/hr and increased by 12 mL/hr every 30 min until a minimum of 3 strong contractions are palpated.¹⁶ The maximum infusion rate is 120mL/hr.¹⁶

Two theatres are operational 24 hours a day. Women can be booked for elective and emergency caesarean section from any of the operational areas. Due to the high volume of patients seen at Baragwanath, the theatre list can sometimes have up to 20 emergencies waiting. It is then up to the doctors in labour ward to prioritize the theatre list according to urgency and indication.

3.2 Study design Cross sectional study with a retrospective record review.

3.3 Study population All women that underwent caesarean section between 1 October 2016 and 31 May 2017.

3.4 Inclusion criteria All cases done for gestation of 24 weeks(600g) and higher.

3.5 Exclusion criteria Extra uterine pregnancies.

3.6 Definitions

Post-partum haemorrhage: More than a 1000 mL at caesarean section, more than 500 mL after normal vaginal delivery.

Gestational hypertension: New onset of hypertension after 20 weeks gestation with blood pressure >140/90 mmHg on 2 occasions 4 hours apart.

Chronic hypertension: Diagnosis of blood pressure pre-dating the pregnancy.¹⁷

Pre-eclampsia: Hypertension and one or more of the following:¹⁷

4. Proteinuria (>300mg/day or 1g/L on dipstix or urine protein/creatinine >30mg/mmol).
5. Maternal organ dysfunction
 - V Renal impairment (creatinine >90 µmol/L).
 - VI Liver involvement (transaminases twice upper limit of normal).
 - VII Neurological complications (severe headache, hyperreflexia, altered mental state, eclampsia, blindness or stroke).
 - VIII Haematological complications (thrombocytopenia, platelet count below 150000/dL, DIC, haemolysis).
6. Uteroplacental dysfunction (foetal growth restriction).

Preterm labour: Onset of labour before 37 completed gestational weeks.

Gestational diabetes: Diagnosis based on the International Association of the Diabetes and Pregnancy Study Group criteria after 75g oral glucose tolerance test.¹⁸

- IV Fasting glucose: ≥ 5.1
- V 1 hour: ≥ 10
- VI 2 hour: ≥ 8.5

Intra uterine growth restriction: A foetus whose weight is below the 10th percentile for its gestational age.

Antepartum haemorrhage: Bleeding from genital tract after 22 weeks gestation.

Early ultrasound: Antenatal ultrasound before 24 weeks gestation.

Late ultrasound: Antenatal ultrasound after 24 weeks gestation.

Anaemia in pregnancy: Haemoglobin concentration of less than 11 g/dL and a haematocrit of less than 35%.

Polyhydramnios: Amniotic fluid index more than the 90th percentile for gestational age.

3.7 Data collection

Data will be collected from the theatre registers. All the files for women with a blood loss of more than 1000 mL as recorded in the register will be collected. The PPH cases before and after the change in protocol will then be compared. Data, as described in appendix 1, will be obtained for analysis.

3.8 Sample size

If the incidence of PPH at caesarean section is estimated to be 6%,^{19,20,21} and the average number of caesarean sections per month at Chris Hani Baragwanath Hospital is 640, I expect to identify approximately 307 women who had had bloodloss of more than a 1000mL at caesarean section during my study period. With 154 women from 1 October 2016 to 31 January 2017, before the protocol change, and 154 from 1 February to 31 May, after the change.

4.Data analysis

Data will be entered into an excel spread sheet and then exported to Stata version 15 (StataCorp USA) for further analysis.

Analysis:

- 1) Crude incidence per caesarean section of post-partum haemorrhage will be calculated by dividing the number of PPH cases by the number of caesarean sections done at Chris Hani Baragwanath Hospital. Comparison of the incidence before and after the implementation of the new guidelines will be made.
- 2) Percentage change in incidence will be calculated as follows:

Incidence before-Incidence after/incidence before x 100/1.

- 3) Continuous socio-demographic and clinical variables such as age, gestational age, length of procedure etc., will be described using mean $\pm$ SD (If data normally distributed) or median (if not normally distributed).
- 4) Categorical socio-demographic and clinical variables such as booking status, HIV status etc. will be described using frequency, percentages and charts.
- 5) Comparison of continuous morbidity variables such as length of hospital stay, for PPH cases before and after implementation of the new guidelines will be done using student t-test (if normally distributed) or Mann Whitney U test (if not normally distributed).
- 6) Categorical morbidity such as Hysterectomy, relook laparotomy and B-lynch will be compared using Pearson's chi-square (if the expected cell is <5 Fishers exact will be used).
- 7) Statistical significant level will be set at P-value <0.05 .

5.Ethics:

The study will only commence after obtaining ethical approval from the University of Witwatersrand Human Research Ethics Committee. Approval will also be requested from the Chief Executive officers at CHBAH as well as the Obstetrics and Gynaecology department. Patient confidentiality and autonomy will be ensured at all times.

6.Project Timeline:

	April	May	June	July	August	September	October and November
Protocol Submission	X						
Ethics Submission				x			

Data Collection					X		
Data analysis						X	
Final write up						X	X

7.Funding:

Funding will be provided by the researcher. The main expense being printing cost.

8.Limitations :

Blood loss in theatre is often underestimated, and swab counting is only a crude estimate. Swabs and linen are not routinely weighed, and I anticipate that this might influence my results.

Furthermore, the majority of caesarean sections performed at Baragwanath hospital is done by junior doctors. A high incidence of puerperal haemorrhage could potentially be attributed to surgical skills. However, I would expect that this was also true before the protocol change and that the surgical skills in the two groups would be similar.

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APPENDIX 2: Data collection sheet

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APPENDIX 3: Ethics Clearance Certificate



R14/49 Dr A Kotze

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M180733

NAME: Dr A Kotze
(Principal Investigator)
DEPARTMENT: School of Clinical Medicine
Department of Obstetrics and Gynaecology
Chris Hani Baragwanath Academic Hospital

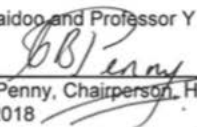
PROJECT TITLE: Maternal outcomes before and after the new
Oxytocin protocol at Chris Hani Baragwanath
Academic Hospital

DATE CONSIDERED: 27/07/2018

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr P Naidoo and Professor Y Adam

APPROVED BY: 
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 28/11/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore reports and re-certification will be due early in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

30/11/2018

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4: Author Guidelines from the South African Medical Journal.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

This should be 250-400 words, with the following recommended headings:

- Background: why the study is being done and how it relates to other published work.
- Objectives: what the study intends to find out

- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- **Objectives (within Introduction/Background):** a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- **Design (within Methods):** including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- **Setting (within Methods):** level of care, e.g. primary, secondary, number of participating centres.
- **Participants (instead of patients or subjects; within Methods):** numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- **Interventions (within Methods):** what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- **Main outcome measures (within Methods):** those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.

- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the $\pm$ symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).

- Please make your article concise, even if it is below the word limit.
- Qualifications, **full** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. μ not u for micro, α not a for alpha, β not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

APPENDIX 5: Turnitin plagiarism report

Turnitin Originality Report

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"International consensus statement on the use of uterotonic agents during
caesarean section", Anaesthesia, 2019

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Dean Leduc, Vyta Senikas, André B. Lalonde, Dean Leduc et al. "Active
management of the third stage of labour: Prevention and treatment of

postpartum hemorrhage", International Journal of Gynecology & Obstetrics, 2010

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1% match (publications)

L. C. Stephens, T. Bruessel. "Systematic Review of Oxytocin Dosing at Caesarean Section", Anaesthesia and Intensive Care, 2019



