EFFECT OF MISOPROSTOL AS AN ADJUNCT TO OXYTOCIN DURING CAESAREAN DELIVERY IN WOMEN AT RISK OF POSTPARTUM HEMORRHAGE

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LIST OF ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynaecologists
BMI	Body mass index
CI	Confidence Interval
CS	Caesarean section
EBL	Estimated blood loss
Et al	and others
eg	for example
FBC	Full blood count
FIGO	International Federation of Gynaecology and Obstetrics
GSH	group screen and hold
Hb	Hemoglobin
HRPZ II	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
IM	Intramuscular
IV	Intravenous
IU	International Unit
JEPeM	Jawatankuasa Etika Dan Penyelidikan Manusia
mcg	microgram

MDG	Millennium Development Goal
ml	mililiter
n	number
MMR	maternal mortality ratio
MREC	Medical Research
MOH	Ministry of Health
PAC	Patient Assessment Center
PPH	Postpartum Hemorrhage
OR	Odd Ratio
RCOG	Royal College of Obstetricians & Gynaecologists
WHO	World Health Organization
>	more than
<	less than

DEFINITION

1. Caesarean section

   A birth of a fetus via laparotomy and then hysterotomy.

2. Spinal anaesthesia

   A form of regional anaesthesia involving the injection of a local anaesthetic into the subarachnoid space.

3. Postpartum hemorrhage

   Bleeding from genital tract of greater than 500 ml after vaginal delivery or blood loss greater than 1000ml after caesarean section.

   PPH is classified as either primary or secondary PPH. Primary PPH occurs within 24 hours following birth while secondary PPH occurs after 24 hours of delivery until 42 days postpartum.

4. Parity

   Number of live born and stillbirth woman has delivered at more than 24 weeks gestation or birth weight more than 500g .

   Nulliparous= parity 0

   Multipara = parity 1-4

   Grandmultipara = parity ≥5

5. Polyhydramnios

   Amniotic fluid index ≥ 25 cm.

6. Body mass index

   Weight (kg)/ height $(m)^2$ before pregnancy, categorized as :

   - Underweight BMI <18.5
   - Normal BMI 18.5-24.9
   - Overweight BMI 25-29.9
   - Obese BMI >30

7. Big baby

   Clinical and ultrasound estimation of fetal weight ≥ 4kg.

8. Pfannenstiel incision

   A long horizontal abdominal skin incision made below the line of the pubic hair and above the mons pubis, down to and through the rectus sheath.

ABSTRAK

ABSTRAK

KEBERKESANAN MISOPROSTOL SEBAGAI UBAT TAMBAHAN BAGI OXYTOCIN SEMASA PEMBEDAHAN CAESAREAN KE ATAS WANITA YANG BERISIKO MENGALAMI PENDARAHAN BERLEBIHAN SEMASA DAN SELEPAS BERSALIN

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Pengenalan: Pembedahan Caesarean adalah merupakan salah satu prosedur pembedahan yang terdapat banyak komplikasi. Salah satu komplikasi yang serius adalah pendarahan berlebihan ketika bersalin disebabkan kegagalan rahim mengecut secara efektif. Misoprostol merupakan ubat yang dapat membantu pengecutan rahim dan menghentikan pendarahan dan boleh digunakan di dalam pembedahan.

Objektif: Untuk menilai sama ada kombinasi misoprostol dan oxytocin lebih berkesan mengurangkan pendarahan semasa dan selepas bersalin secara pembedahan caesarean berbanding penggunaan oxytocin sahaja di kalangan wanita yang mempunyai faktor-faktor risiko yang diketahui untuk mengalami pendarahan berlebihan selepas bersalin. Untuk mengenalpasti penggunaan ubat pengecutan rahim tambahan, pemindahan darah atau pembedahan tambahan yang diperlukan dan mengenal pasti komplikasi dan kesan sampingan yang berkaitan dengan ubat-ubatan tersebut.

Metodologi: Kajian prospektif berbentuk ujian rawak terkawal telah dijalankan di Hospital Raja Perempuan Zainab II bermula pada Disember 2016 sehingga April 2017. Kajian melibatkan 156 wanita yang mempunyai faktor-faktor risiko yang diketahui untuk mengalami pendarahan berlebihan selepas bersalin secara pembedahan caesarean elektif. Mereka dibahagi secara rawak kepada 2 kumpulan untuk menerima sama ada sublingual misoprostol 400 mcg + IV oxytocin 5 IU bolus atau IV oxytocin 5 IU bolus sahaja selepas bayi dilahirkan. Jumlah kehilangan darah semasa dan selepas pembedahan, pengurangan tahap haemoglobin, ubat pengecutan rahim tambahan, pemindahan darah, pembedahan tambahan dan kesan sampingan berkaitan dengan ubat-ubatan terapi dikenalpasti dan direkodkan.

Keputusan: Seramai 156 wanita telah diambil menyertai kajian ini. Data demografi ibu dan faktor risiko adalah sama di antara 2 kumpulan tersebut. Purata paras haemoglobin sebelum pembedahan ialah 11.3 g/dl bagi kumpulan misoprostol + oxytocin berbanding 11.5 g/dl bagi kumpulan oxytocin. Paras hemoglobin pesakit sebelum pembedahan adalah di antara 8.1-14.1 g/dl. Anggaran jumlah pendarahan semasa pembedahan bagi kumpulan oxytocin adalah lebih banyak dari kumpulan misoprostol + oxytocin (654.5 ml±259.9 berbanding 524.3 ml±253.9, p= 0.010). Anggaran jumlah pendarahan selepas pembedahan bagi kumpulan oxytocin adalah statistik lebih tinggi dari kumpulan misoprostol + oxytocin (90 ml±29.6 versus 77.1 ml±23.7, p= 0.003). Ia juga menunjukkan bilangan pendarahan berlebihan yang dilihat dalam kumpulan oxytocin lebih tinggi berbanding kumpulan misoprostol + oxytocin (19(24.4%) versus 9(11.5%), p = 0.037). Insiden Pendarahan berlebihan dalam kajian ini ialah 17.9%. Daripada 19 pesakit yang mengalami pendarahan berlebihan dalam kumpulan oxytocin, 7 (36.8%) pesakit telah diberi satu suntikan hemabate 250mcg berbanding kumpulan misoprostol+oxytocin, hanya

2 (22.2%) pesakit memerlukan satu suntikan hemabate 250mcg. Hanya 4 pesakit yang mengalami pendarahan berlebihan memerlukan pemindahan darah.

Kesimpulan: Kombinasi sublingual misoprostol dan oxytocin lebih banyak mengurangkan kehilangan darah semasa dan selepas bersalin secara pembedahan caesarean berbanding oxytocin sahaja di kalangan wanita yang mempunyai faktor-faktor risiko pendarahan berlebihan semasa dan selepas pembedahan caesarean. Ia juga selamat untuk digunakan. Oleh yang demikian misoprostol harus dianggap sebagai alternatif yang baik untuk ubat pengecutan rahim lain dalam mengelakkan pendarahan berlebihan semasa dan selepas pembedahan bersalin.

Professor Dr Nik Mohamed Zaki Nik Mahmood: Supervisor

Dr Zainal Abidin Hanafiah: Co-Supervisor

ABSTRACT

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EFFECT OF MISOPROSTOL AS AN ADJUNCT TO OXYTOCIN DURING CAESAREAN DELIVERY IN WOMEN AT RISK OF POSTPARTUM HEMORRHAGE

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Introduction: The caesarean section was a recognized risk factor for PPH. The common cause of PPH during caesarean delivery includes uterine atony result in complications including both maternal and fetal morbidity and mortality. Oxytocin is the first choice of uterotonic agent for prevention of PPH during caesarean delivery. The use of additional uterotonic agent is common in women with known risk factor for PPH. Misoprostol has been evaluated as an alternative to oxytocin and has also been used in combination with oxytocin.

Objectives: To evaluate whether a combination of misoprostol and oxytocin more effectively reduces blood loss during and after caesarean delivery than does oxytocin alone among women with known risk factors for postpartum hemorrhage. To document the use of additional uterotonic drugs, the need of blood transfusion or additional surgical intervention for PPH and to identify the complication and adverse effects related to drugs therapy.

Methodology: A prospective single blinded randomised control trial was conducted in Hospital Raja Perempuan Zainab II from December 2016 until April 2017. The study included 156 women with known risk factor for PPH undergoing elective caesarean section under spinal anaesthesia. They were assigned randomly into 2 groups to receive either sublingual misoprostol 400mcg+ IV oxytocin 5 IU bolus or IV oxytocin 5 IU bolus just after delivery of baby. The outcome measures were intraoperative and postoprerative blood loss, reduction in haemoglobin, additional uterotonic agents, blood transfusion, additional surgical intervention for PPH and adverse effects relate to drugs therapy.

Results: A total of 156 women were recruited and completed this study. The maternal demographic data and risk factors were similar between the 2 groups. The mean for preoperative haemoglobin was 11.3 g/dl in misoprostol+oxytocin group compared to 11.5 g/dl in oxytocin group. The range of preoperative haemoglobin was 8.1-14.1 g/dl. The estimated blood loss intraoperatively in oxytocin group was statistically significantly higher than the misoprostol+oxytocin group (654.5 ml±259.9 versus 524.3ml±253.9, p = 0.010). Estimated blood loss postoperatively in oxytocin group was statistically significantly higher than the misoprostol+oxytocin group (90 ml±29.6 versus 77.1 ml±23.7, p =0.003). It also showed statistically significant higher number of PPH seen in oxytocin group compared to misoprostol+oxytocin group (19(24.4%) versus 9(11.5%), p= 0.037). The incidence of PPH in this study was 17.9%. Out of 19 patient with PPH in oxytocin group, 7 (36.8%) patients required additional single dose IM hemabate 250 mcg compared to misoprostol group, only 2 (22.2%) patients required single dose IM hemabate 250mcg. Only 4 patients with PPH required blood transfusion. However, no significant difference was demonstrated between the 2 groups in term of reduction in hemoglobin

level (p=0.750), any additional uterotonic drug (p=0.083) and blood transfusion (p=0.310). No additional surgical intervention required for both groups.

Conclusion: Combination of sublingual misoprostol and oxytocin more effectively reduces blood loss during and after caesarean delivery than does oxytocin alone among women with risk factors for PPH. It also appears safe and well tolerated in this population. Therefore misoprostol should be considered as a good alternative to other uterotonics in prevention of PPH following caesarean delivery.

Professor Dr Nik Mohamed Zaki Nik Mahmood: Supervisor

Dr Zainal Abidin Hanafiah: Co-Supervisor

INTRODUCTION

1.0 INTRODUCTION

1.1 CAESAREAN DELIVERY

Caesarean delivery defines as a birth of a fetus via laparotomy and then hysterotomy (Cunningham *et al*, 2014). It is one of the commonest surgical procedures performed in obstetric practice.

The number of CS has been rising tremendously over the years due to various indications. This surgical procedure has been proven to result in complications, including both maternal and fetal morbidity and mortality. Complications include post partum hemorrhage (PPH), visceral injury, extended tear resulting in broad ligament hematoma, the need for blood transfusion, infection and venous thromboembolism. Long term complications include placenta previa and placenta accreta. Fortunately, some of the complications can be minimized by proper pre operative assessment, appropriate indications, performed by skilled doctors and measurements taken prior to or during operative procedures.

Caesarean section rate is defined as the total number of caesarean deliveries over the total number of deliveries, and is usually expressed in percentage. The global CS rate was estimated around 15%, but higher in developed countries such as Latin America and Caribbean, but lower in other developing countries (Betran AP *et al.*, 2007). In Asia, the CS rate was 15.9% and more specifically in South East Asia, the rate was 6.8%. In Malaysia, the CS rates have been gradually increasing in trend. The caesarean section rate in Malaysian public hospitals has increased to 15.7% (in 2006) from 10.5% in the year 2000 (Ravindran J, 2006). The CS rate from the 14 tertiary hospitals in

Malaysia was 23.08% in 2010 (Sharmala Devi Karalasingam *et al*., 2010). The study also reported 18.71% of patients were delivered via caesarean section in Hospital Raja Perempuan Zainab II Kota Bharu, Kelantan.

1.2 POSTPARTUM HEMORRHAGE

Obstetric hemorrhage is one of the leading causes of preventable maternal mortality and accounts for 25% of maternal deaths in developing country (Mukherjee S *et al*., 2009). The risk of developing PPH has been estimated around 1 in 1000 deliveries (Drief J, 1997). The incidence of PPH affects approximately 2% of all women who give birth (WHO, 2012).

Post partum hemorrhage is defined as bleeding from genital tract of 500ml or more after vaginal delivery, or greater than 1000ml after caesarean section, or any blood loss sufficient enough to cause haemodynamic instability in postpartum patient (MOH Malaysia, 2016). Bleeding is considered major once the blood loss is 1000ml or more (Mavrides E *et al*., 2016).

PPH can be further divided into primary and secondary PPH. Primary PPH occurs within 24 hours following birth, while secondary PPH reflects to any abnormal bleeding from the birth canal which happens after 24 hours of delivery till 42 days postpartum.

PPH is associated with high risk of morbidity and mortality to the mother. Catastrophic bleeding will lead to coagulopathy, hysterectomy, renal failure, cardio respiratory

collapsed, complications from massive blood transfusion and intensive care admission (Devine, 2009).

Maternal mortality rate (MMR) is the number of women who died from any cause related to or aggravated by pregnancy or its management (excluding accidental or incidental causes) during pregnancy or childbirth or within 42 days of termination of pregnancy, irrespective of the duration of pregnancy, per 100,000 live births.

According to the report produced by Kaur J *et al* (2011), the common causes of MMR were the direct causes, including PPH (17.4%), obstetric thromboembolism (17.4%) and hypertensive disorders in pregnancy (18.1%). Of the 14 million women who have PPH each year, about 2% die, with an average interval from onset of bleeding to death of 2 to 4 hours (Abou Zahr, 1998). Since the introduction of the Millennium Development Goal 5 (MDG 5) to our setting in 1990, the incidence of maternal mortality has reduced due to the implementation of comprehensive strategies. The main objective of MDG 5 is to achieve a reduction of MMR by three quarters (11 per 100,000 populations) from 1990-2015.

The main causes of PPH are the '4 Ts' which includes tone (70%), trauma (20%), tissue (10%) and thrombin (<1%) (MOH Malaysia, 2016). Table 1.1 showed summary of common causes and risk factors of PPH.

Table 1.1: The causes of PPH (Mavrides E *et al*, 2016)

The four Ts	Risk factors/notes
<u>Tone: abnormalities of uterine contraction.</u>	
Overdistension of uterus.	Polyhydramnios, multiple gestation, macrosomia.
Intra-amniotic infection.	Fever, prolonged rupture of membranes.
Functional/anatomic distortion of uterus.	Rapid labour, prolonged labour, fibroids, placenta praevia, uterine anomalies.
Uterine relaxants.	Magnesium and nifedipine Terbutaline, halogenated anaesthetics, glyceryl trinitrate.
Bladder distension.	May prevent uterine contraction.
<u>Tissue: retained products of conception.</u>	
Retained cotyledon or succenturiate lobe.	
Retained blood clots.	
<u>Trauma: genital tract injury.</u>	
Lacerations of the cervix, vagina or perineum.	Precipitous delivery, operative delivery.
Extensions, lacerations at caesarean section.	Malposition, deep engagement.
Uterine rupture.	Previous uterine surgery.
Uterine inversion.	High parity with excessive cord traction.
<u>Thrombin: abnormalities of coagulation</u>	
Pre-existing states:	Haemophilia A. Idiopathic thrombocytopenic purpura. von Willebrand's disease.
Acquired in pregnancy.	Gestational thrombocytopenic. Pre-eclampsia with thrombocytopenia (HELLP).

Disseminated intravascular coagulation.	a) Gestational hypertensive disorder of pregnancy with coagulopathy. b) in utero fetal demise. c) severe infection. d) abruption. e) amniotic fluid embolus.
Therapeutic anticoagulation.	History of thromboembolic disease.
History of previous PPH.	

The common causes of PPH during cesarean delivery include uterine atony, bleeding from the uterine incision or extensions of this incision and placenta accreta/increta/percreta. Uterine atony can be isolated or associated with one or more of the other causes of hemorrhage. Cervical and vaginal lacerations typically occur during cesarean delivery when the operator attempts to dislodge a fetal head wedged deep in the pelvis. Serious hemorrhage from the uterine incision is generally caused by lateral extension, which can result from excessive traction when creating the incision or from tears resulting from delivery of the fetus through an incision that is too small (Allan J Jacobs, 2011)

The caesarean section was a recognized risk factor for PPH. Briley et al (2014) demonstrated how prepregnancy and pregnancy-acquired factors may be mediated through intrapartum events, including caesarean section, elective (aOR 24.4, 95% CI 5.53-108.00) or emergency (aOR 40.5, 95% CI 16.30-101.00), and retained placenta (aOR 21.3, 95% CI 8.31-54.7) which increased the incidence of postpartum haemorrhage.

Prevention of postpartum haemorrhage begins early in high risk women, as early as in preconception period. Prevention and optimization of anemia allows better tolerability to variable severity of PPH. WHO defined anaemia in pregnancy as haemoglobin level below 11 g/dl. It divided into mild (Hb 10.0-10.9 g/dl), moderate (Hb 7.0-9.9 g/dl) or severe anaemia (<7.0 g/dl). Hb <9.0 g/dl was associated with greater blood loss (90.6 ml , p <0.01) average at delivery and 24 hours postpartum period compared to nonanaemic women (Kavle JA *et al*, 2008). Iron deficiency anaemia is the commonest cause of anaemia in pregnancy. Treatment with oral iron reduces the incidence of anaemia (RR 0.38 95% CI 0.26-0.55) (Reveiz *et al*, 2007).

The use of oxytocin and cord traction is the recommended method to prevent PPH in caesarean section (WHO,2012). Oxytocin is the first choice of uterotonic agent for prevention of PPH during caesarean delivery. It is as effective as ergot alkaloids or prostaglandins and has fewer side effects (Janice M Anderson 2007, Mc Donald S *et al* 2004, Gulmezoglu AM 2004).

Uterine atony is responsible for most cases of PPH about 70%. The majority of these could be avoided through the use of prophylactic uterotonics drugs during the third stage of labour and in conjunction with uterine massage. Prophylactic administration of oxytocin reduces rates of postpartum hemorrhage by 40%.

1.3 OXYTOCIN

Oxytocin (Pitocin®, Syntocinon®) is a sterile, clear, colorless aqueous solution that contains 10 units of oxytocin /mL in 1 ampoule. Oxytocin stimulates the upper segment

of the myometrium to contract rhythmically following delivery, constricting spiral arteries and decreasing blood flow through the uterus. It is used for prevention as well as treatment of PPH.

The study by Mc Donald S et al (2004) involved 9332 women reported that syntometrine, oxytocin 5 IU and oxytocin 10 IU have similar efficacy in preventing PPH in excess of 1000ml. 5 IU oxytocin by slow bolus IV injection is currently recommended for all caesarean section (MOH Malaysia 2016, Mavrides E *et al* 2016).

The combination of an oxytocin infusion after an initial IV bolus of oxytocin after caesarean delivery reduces the need for additional uterotonic agents but does not affect the overall occurrence of major obstetric haemorrhage (WHO, 2012).

Oxytocin can be administered via intravenous or intramuscular route. The onset of action depends on the route of administration. It has rapid immediate onset of action via intravenous compare to intramuscular administration (within 3-5 minutes). The peak concentration is within 40 minutes. Oxytocin has a plasma half-life of about 1 to 6 minutes. Following intravenous administration of oxytocin, uterine response subsides within 1 hour compare to intramuscular injection the uterine response persists for 2 to 3 hours. It has rapid excretion largely by the kidney and the liver. Only small amounts are excreted in urine unchanged.

The side effects include transient vasodilatation and hypotension, nausea, vomiting and painful contraction. Overdose or prolonged use of oxytocin infusion for >24 hours can cause water intoxication.

1.4 MISOPROSTOL.

The use of additional uterotonic agent is common in women with known risk factor for PPH. Misoprostol has been evaluated as an alternative to oxytocin and has also been used in combination with oxytocin.

The usefulness of misoprostol, a synthetic prostaglandin E1 analog marketed for the prevention and/or treatment of peptic ulcers, in the active management of the third stage of labour in developing countries was first reported by El-Refaey in 1996. Misoprostol is an effective myometrial uterine stimulant, selectively binding to EP-2/EP-3 prostanoid receptors. Because of its uterotonic effects, misoprostol has been demonstrated to be effective for both the prevention and treatment of PPH. Misoprostol is the cheapest uterotonic drugs and requires no refrigeration or syringe. With its ease of administration and storage, there has been increasing evaluation and promotion of misoprostol in developing countries.

Misoprostol can be administered via sublingual, oral, vaginal and per rectal. Compared with other routes of administration, sublingual and oral misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. The misoprostol tablet is very soluble and can dissolve in 20 minutes when it put under the tongue. Sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes. The avoidance of first-pass metabolism via the liver achieves a higher peak concentration by sublingual administration. Following a single dose of 400 mcg sublingual misoprostol, the plasma misoprostol level increases rapidly, onset of action within 8-11 minutes and peaks at

about 30 minutes, decline by 120minutes after administration (O.S. Tang *et al*, 2007). This characteristic makes sublingual misoprostol more suitable than other routes of administration for clinical applications requiring a rapid onset of action, such as that required for the prevention of PPH.

Misoprostol generally is well tolerated. The frequency of side effects does not appear to be affected by patient age in adults. The most common side effects associated with misoprostol involve the gastrointestinal tract (e.g., diarrhea, nausea, vomiting and abdominal pain). Less common or rare side effect include bleeding from vagina, constipation, cramps in lower abdomen or stomach area, gas, headache, heartburn and indigestion. Symptoms of overdose include convulsions (seizures), drowsiness, fast or pounding heartbeat, fever, low blood pressure, tremor and troubled breathing.

There are limited research on the optimal dose, route of admission and efficacy done for patient with known risk factors for PPH in Malaysia. Therefore the purpose of this study will contribute to produce more local data for decision and use of misoprostol for high risk patient to prevent postpartum hemorrhage. Hopefully the knowledge will be valuable and give benefit to patient, hospital care and country.

Cost savings could also be gained from avoiding the use of additional uterotonic drugs such as carboprost, carbetocin and also expensive haematological agents such as Factor VIIa, which are establishing its place in the treatment of massive PPH in modern obstetrics despite extreme costs.

LITERATURE REVIEW

2.0 LITERATURE REVIEW

Many risk factors for PPH have been reported. A study including 154,311 deliveries compared 666 cases of PPH to controls without hemorrhage by Sheiner E *et al* (2005) found that factors significantly associated with hemorrhage include retained placenta/membranes (odds ratio [OR] 3.5, 95% CI 2.1-5.8), failure to progress during the second stage of labor (OR 3.4, 95% CI 2.4-4.7), morbidly adherent placenta (OR 3.3, 95% CI 1.7-6.4), lacerations (OR 2.4, 95% CI 2.0-2.8), instrumental delivery (OR 2.3, 95% CI 1.6-3.4), large for gestational age newborn (>4000 g) (OR 1.9, 95% CI 1.6-2.4), hypertensive disorders (preeclampsia, eclampsia, HELLP [Hemolysis, Elevated Liver enzymes, Low Platelets] syndrome) (OR 1.7, 95% CI 1.2-2.1), induction of labor (OR 1.4, 95% CI 1.1-1.7) and prolonged first or second stage of labor (OR 1.4, 95% CI 1.2-1.7).

In another large series study by Mhyre JM *et al* (2013), the most common risk factors associated with need for massive transfusion during hospitalization for delivery were abnormal placentation (1.6/10,000 deliveries, adjusted OR [aOR] 18.5, 95% CI 14.7-23.3), placental abruption (1.0/10,000, aOR 14.6, 95% CI 11.2-19.0), severe preeclampsia (0.8/10,000, aOR 10.4, 95% CI 7.7-14.2), and intrauterine fetal demise (0.7/10,000, aOR 5.5, 95% CI 3.9-7.8).

Other risk factors include personal or family history of previous PPH, obesity, high parity, Asian or Hispanic race, precipitous labour, uterine over distention (e.g: multiple gestation, polyhydramnios, macrosomia), uterine infection, uterine inversion, inherited bleeding diathesis, acquired bleeding diathesis (e.g: amniotic fluid embolism, abruptio

placenta, sepsis, fetal demise), and use of some drugs such as uterine relaxants and drugs that affect coagulation (possibly including antidepressants) (Bateman BT *et al* 2010, Cheng YW *et al* 2009, Wetta LA *et al* 2013, Kramer MS *et al* 2013, Sharp GC *et al* 2014, Bruning AH *et al* 2015, Oberg AS *et al* 2014, Giannella L *et al* 2013).

In postpartum hemorrhage, treatment can be divided into pharmacological (uterotonic drugs/ prostaglandins), mechanical methods (tamponade balloon) and surgical methods. Studies have shown that active management of third stage of labour reduces blood loss and risk of PPH. Four Cochrane reviews addressed prophylaxis in the third stage of labour in women delivering vaginally. The Active Versus Expectant Management in the Third Stage of Labour included five trials and found that active management (which includes the use of uterotonic drugs, early cord clamping, and controlled cord traction) was associated with lower maternal blood loss with reduced risks of PPH and prolonged third stage (Mousa HA *et al*, 2007).

Active management of third stage of labour reduces the risk of PPH by 60% (Prendiville WJ *et al*, 1988), the need of blood transfusion (McCormick M.L *et al*, 2002) and subsequently maternal morbidity and mortaliy (WHO 2012). Oxytocin and other prostaglandins have been used in prevention of PPH. Four randomized control trials have compared different uterotonic drugs for prophylaxis in women delivering via Caesarean Section, and recommended 5 IU oxytocin via slow bolus intravenous injection (Mavrides E *et al*, 2016). A longer acting oxytocin derivative, Carbetocin is licensed in the UK specifically for the indication of prevention of PPH in the context of caesarean delivery. Randomized controlled trial suggested that a single dose of carbetocin 100mcg is at least as effective as oxytocin by infusion (Dansereau J *et al*,

2006). However it has not been recommended for routine use due to the paucity of data and its high price.

Misoprostol is being advocated for wide use in prevention and treatment of PPH, and is recommended for such in certain settings by the World Health Organization, the Clinical Practice Obstetrics Committee; Society of Obstetricians and Gynecologists of Canada (Leduc 2009) and the American College of Obstetricians and Gynecologists (ACOG 2006). The Royal College of Obstetricians and Gynecologists Green-Top Guideline no 52 of 2009 (revised 2011) recommends misoprostol 1000 mcg rectally for treatment of PPH when other interventions fail (RCOG 2009). Guidance for the use of misoprostol for the prevention (FIGO 2012a) and treatment (FIGO 2012b) of PPH has been issued by the International Federation of Gynecology and Obstetrics.

A paper published in Cochrane Database Systemic Review title Prostaglandin for preventing postpartum hemorrhage conducted by Tuncalp O *et al* (2012) included 72 trials (52,678 women). Oral or sublingual misoprostol compared with placebo is effective in reducing severe PPH (blood loss>1000 ml). Seven trials involved 6225 women with oral misoprostol not totalled due to significant heterogeneity. One trial involving 661 women with sublingual misoprostol noted RR 0.66; 95% CI 0.45- 0.98. Need for blood transfusion (oral: RR 0.31; 95% CI 0.10-0.94; four trials, 3519 women).Compared with conventional injectable uterotonics, oral misoprostol was associated with higher risk of severe PPH (RR 1.33; 95% CI 1.16- 1.52; 17 trials, 29,797 women) and use of additional uterotonics, but with a trend to fewer blood transfusions (RR 0.84; 95% CI 0.66 to 1.06; 15 trials; 28,213 women). Additional uterotonic data were not totalled due to heterogeneity. Misoprostol use is associated

with significant increases in shivering and a temperature of 38º C compared with both placebo and other uterotonic. Therefore an injectable uterotonic is the drug of choice for routine third stage management when the placenta is delivered. Oral or sublingual misoprostol may be used where no injectable uterotonic is available.

A double blind randomised controlled trial study conducted by Bellad MB *et al* (2012) involved a total of 652 patients, compared the postpartum measured blood loss with 400 mcg sublingual misoprostol and after standard care using 10 IU intramuscular (IM) oxytocin. The mean blood loss with sublingual misoprostol was 192 +/- 124 ml (n = 321) and 366 +/- 136 ml with oxytocin IM (n = 331, P <= 0.001). The incidence of PPH (blood loss >500ml) was 3.1% with misoprostol and 9.1% with oxytocin (p = 0.002). No woman lost >=1000 ml of blood. 9.7% and 45.6% of women experienced a haemoglobin decline of >10% after receiving misoprostol and oxytocin (p < 0.001). Side effects were significantly greater in the misoprostol group than in the oxytocin group. This study demonstrated Sublingual misoprostol is more effective than intramuscular oxytocin in reducing PPH, with only transient side effects being greater in the misoprostol group.

A paper published in International Journal Gynaecology Obstetrics by P. Chaudhuri *et al* (2010) title rectally administered misoprostol versus intravenous oxytocin infusion during cesarean delivery to reduce intraoperative and postoperative blood loss. They compare the efficacy of rectally administered misoprostol with intravenous oxytocin infusion in preventing uterine atony and blood loss during cesarean delivery. 200 women undergoing cesarean delivery who did not have risk factors for postpartum hemorrhage were randomly allocated to receive either 800 µg of rectal misoprostol or

an intravenous infusion of oxytocin. A total of 96 and 94 women were analyzed in the misoprostol and oxytocin groups, respectively. Intraoperative and postoperative blood loss was significantly lower in the misoprostol group than in the oxytocin group (503 vs 592 ml, $p = 0.003$ and 74 vs 114 ml, $p = 0.045$, respectively). The incidence of shivering was higher in the misoprostol group (8.3% vs 1.1%, $p= 0.018$; RR 7.83; 95% CI 0.99‑61.42). However the difference of intraoperative blood loss between 2 groups was only 89ml and postoperative blood loss was only 40 ml, although statistically significant. Therefore rectal misoprostol appears to be an effective alternative to intravenous oxytocin in preventing blood loss for routine use during cesarean delivery.

Another prospective, randomized, double-blind, placebo-controlled trial was performed at a tertiary care centre in Kolkata, India by P. Chaudhuri and Majumdar A (2014) to evaluate whether a combination of misoprostol and oxytocin more effectively reduces blood loss during and after caesarean delivery than does oxytocin alone among women with known risk factors for PPH. Both groups contained 198 women. Mean intraoperative blood loss was significantly lower in the misoprostol group (505.4±215.5 ml) than in the placebo group (587.3±201.5 ml; P<0.001). Mean postoperative blood loss was slightly lower in the misoprostol group (96.9±57.3 ml) than in the placebo group (103.4±58.4 ml; P=0.07). Shivering and pyrexia were more frequently associated with misoprostol (P<0.05 for both). They concluded that misoprostol as an adjunct to oxytocin seemed to more effectively reduce blood loss than did oxytocin alone. However the difference of intraoperative blood loss between 2 groups was only 82ml and postoperative blood loss was only 6ml, although statistically significant. Therefore misoprostol+oxytocin group was having similar outcome compared to oxytocin only group.

Another prospective double-blind randomized clinical trial study conducted by Pakniat H Khezri (2015) to compare the effect of combined oxytocin-misoprostol versus oxytocin and misoprostol alone in reducing blood loss at caesarean delivery showed that the mean blood loss during surgery was significantly lower in group oxytocin-misoprostol (received 200-mcg misoprostol plus 5 IU bolus intravenous oxytocin, group MO) compared to other groups (P = 0.04) (received 20 IU infusion of oxytocin , group O) or 400-mcg sublingual misoprostol tablets , group M). The use of combined lower dose of misoprostol-oxytocin significantly reduced the amount of blood loss during and after the lower segment caesarean section compared to higher dose of oxytocin and misoprostol alone, and its use was not associated with any serious side effects.

A randomized controlled trial to look for the effect of sublingual misoprostol versus intravenous oxytocin on reducing blood loss at cesarean section in Nigeria by K.M. Owonikoko et al (2011) involved 100 women with term singleton pregnancy undergoing elective or emergency cesarean section under spinal anesthesia. They compare the effectiveness and safety of sublingual misoprostol with i.v. oxytocin infusion administered after delivery in reducing blood loss at cesarean section in Nigeria. One hundred women in Nigeria were randomly allocated to receive either misoprostol 400 mcg sublingually or i.v. infusion of 20 units oxytocin soon after delivery of the baby. Estimated blood loss at surgery and within the first 4 h post-operation were measured in both groups. No significant difference was found in mean blood loss between the oxytocin and misoprostol groups. Similarly, no significant difference occurred between preoperative and postoperative hematocrit levels and need for additional oxytocin in both groups. There was significantly less blood loss in the first 4 h after surgery in the misoprostol group than in the oxytocin group (58.2 ± 20.7

vs 80.5 ± 26.8; P-value = 0.02). However the difference of blood loss amount was small and only 22ml. The incidence of adverse effects like shivering/pyrexia was significantly higher in the misoprostol group than in the oxytocin group (27/50 vs 1/50, P < 0.001). Therefore sublingual misoprostol was as effective as i.v. oxytocin infusion in reducing blood loss at cesarean section. It offers several advantages over oxytocin, including long shelf life, stability at room temperature, and oral administration, which make it a suitable uterotonic agent in low-resource areas.

A study by N. Eftekhari et al (2009) title the effect of sublingual misoprostol versus intravenous oxytocin in reducing bleeding after caesarean section was conducted in 100 singleton pregnant women underwent a caesarean delivery under general anaesthesia. Patients were randomly divided into two equal groups. One group received two tablets of misoprostol 200 μg sublingually and the second group took intravenous infusion of 20 units of oxytocin at the rate of 10 ml/min immediately after delivery until full contraction of the uterine. The amount of blood loss was lower in misoprostol group comparing with oxytocin group (608.91 ml vs 673.9 ml, *p*= 0.048) and this difference was statistically significant. The need to give additional oxytocin therapy in oxytocin group (36) was significantly higher than misoprostol group (14, p 0.032). It seems that the efficacy of sublingual misoprostol is equivalent to that of low dose intravenous oxytocin in reducing postpartum haemorrhage at caesarean section. Misoprostol has some other advantages like long shelf -life, stability at room temperature and oral use.

Another previous study by N. Vimala et al (2006) to compare the effectiveness of 400 mcg sublingual misoprostol administered immediately after delivery of the neonate at cesarean section, with 20 units intravenous oxytocin infusion in prevention of uterine

atony and thereby reducing blood loss at cesarean section. One hundred women with singleton term pregnancy undergoing elective or emergency lower segment cesarean section under spinal anesthesia were included in this study. The mean blood loss estimated was significantly lower in misoprostol group compared to oxytocin group (819 ml versus 974 ml; p = 0.004). The number of women who had blood loss exceeding 500 ml and the change in hemoglobin, however, was comparable between the two groups. There was a need for additional oxytocic therapy in 16% and 18% after use of misoprostol and oxytocin respectively (p = 0.673). The incidence of side effects such as pyrexia, shivering and metallic taste was significantly higher in misoprostol group compared to oxytocin group. The sublingual misoprostol appears to be as effective as intravenous infusion of oxytocin in reducing blood loss at cesarean section.

J. Hamm et al (2005) did a randomized study regarding buccal misoprostol to prevent hemorrhage at cesarean delivery. A total of 352 patients who underwent cesarean delivery were assigned randomly to either 200-µg misoprostol or placebo placed in the buccal space. A dilute intravenous oxytocin infusion was given to all patients at delivery of the placenta. The mean estimated blood loss between the misoprostol and placebo groups was 749± 173 ml versus 725±212 ml, respectively (*p* 0.250). More women in the placebo group required 1 additional uterotonic agent (76/179 women [43%] vs 45/173 women [26%]; *p* 0.010; relative risk, 1.3; 95% CI, 1.10-1.50). There were no differences between the groups in the incidence of maternal adverse events.There was not a difference between the groups in the incidence of postpartum hemorrhage or a difference in preoperative and postoperative hemoglobin level. Buccal misoprostol reduces the need for additional uterotonic agents during cesarean delivery.

OBJECTIVES

3.0 OBJECTIVES

3.1 General and specific objectives

General Objective

To study whether a combination of misoprostol and oxytocin more effectively reduces blood loss during and after caesarean delivery than does oxytocin alone among women with known risk factors for postpartum hemorrhage.

Specific Objectives

a) To determine proportion of postpartum hemorrhage among women with known risk factor in both groups.
b) To compare the amount of blood loss during intraoperative and postoperative periods between control and study groups.
c) To determine the need for additional uterotonic drugs (within 24 hours), blood transfusion (until discharge) or additional surgical intervention need for primary PPH (within 24 hours) between control and study groups.
d) To identify the complication and adverse effects related to drugs therapy (within 24 hours).

3.2 Study hypothesis

Combination of misoprostol and oxytocin more effectively reduces blood loss during and after caesarean delivery than does oxytocin alone among women with known risk factors for postpartum hemorrhage

METHODOLOGY

4.0 METHODOLOGY

4.1 Study Design

This study was a randomized controlled single blinded study, which was conducted in Department of Obstetrics & Gynaecology, Hospital Raja Perempuan Zainab II Kota Bharu from December 2016 until April 2017.

4.2 Study Setting

Labour room, maternity operation theatre and obstetric ward at Department of Obstetrics & Gynaecology, Hospital Raja Perempuan Zainab II Kota Bharu with the collaboration of the consultants, specialists, medical officers, house officers and nursing staffs of the department. Hospital Raja Perempuan Zainab II (HRPZ II) is a government tertiary referral hospital, located in Kota Bharu town. The department of Obstetrics and Gynaecology was one of the earliest departments in HRPZII.

The department has 1 labour suite equipped with 15 beds, 1 pregnancy assessment centre (PAC) which was equipped with 3 beds, 1 maternity theatre, 5 wards with 144 beds with 1 specialist clinic. The total number of deliveries remained in the range of 12,000 -13, 000 per year. 18.7% of patients were delivered via caesarean section.

4.3 Study population

All pregnant women who were planned for elective caesarean section as mode of delivery for this index pregnancy were assessed by the medical officer/ specialist/ consultant in charge in ward. Explanation regarding the research study was given for patients who fulfill the inclusion criteria. Patients who had understood the research study and consented were recruited as subjects for the study.

4.4 Inclusion Criteria and Exclusion Criteria

4.4.1: Inclusion criteria

- Women undergoing elective caesarean section under spinal anaesthesia.
- Had at least 1 risk factor for PPH
    1. multiple pregnancy
    2. polyhydramnios
    3. big baby
    4. obesity BMI>30
    5. grandmultipara (parity ≥5)
    6. severe preeclampsia
    7. previous lower segment caesarean scar
    8. history of PPH
- Willing and able to give written consent.

4.4.2: Exclusion criteria

- Woman with any contraindication for the use of misoprostol or oxytocin and those with cardiovascular, hepatic or hematologic disorders.
- Concomitant placenta previa or morbidly adherent placenta.

4.5 Sample size determination

Sample size for the study is calculated using the Power and Sample size (PS) software.

$\alpha = 0.05$, power= 0.8, m = ratio of control to intervention group = 1:1

δ = 100 ml; detectable mean difference of estimated blood loss(ml) in misoprostol group and control group

σ = 201.5 ml; the standard deviation of blood loss(ml) in the Misoprostol group *(chaudhuri, p. 2014)*

Total = 65 samples in each group.