

Effects of 5 IU oxytocin bolus and 20 IU oxytocin infusion compared to 5 IU oxytocin bolus and normal saline infusion in the control of blood loss during and after ante-partum lower segment caesarean section: a randomized controlled trial

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Abstract

Introduction Obstetric haemorrhage is the leading cause of maternal mortality worldwide and in most cases it relates to uterine atony. Even though an oxytocin bolus is used routinely, additional infusion of oxytocin may be required if haemorrhage occurs.

Objectives To compare the effects of 20 IU oxytocin infusion and 5 IU bolus with 5 IU bolus and 500ml normal saline on the control of blood loss in ante-partum lower segment caesarean section.

Methods A double-blind randomized controlled trial was conducted in the Teaching Hospital, Peradeniya, Sri Lanka. Ninety two pregnant women, forty six from each group were randomized to receive either intravenous slow 5 IU oxytocin bolus over 1 minute and additional 20 IU oxytocin infusion in 500 ml of 0.9% saline solution over 4 hours (Group-A) or 5 IU oxytocin bolus over 1 minute and 500 ml of 0.9% Saline over 4 hours (Group B). Visual assessment of mean blood loss was done by the surgeon and anaesthetist. Blood loss was calculated based on the body weight and haematocrit before and 48 hours after delivery.

Results Calculated mean blood loss (456.0ml vs 569.8ml) was significantly less in group A ($p=0.046$). Visual estimation of blood loss by surgeon (476.9 vs 552.1) ($p=0.01$) and anaesthetist (492.7 vs 557.2) ($p=0.03$) were also significantly less in group A.

Conclusion Additional oxytocin infusion at ante-partum caesarean section reduces blood loss during and after caesarean section significantly.

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Introduction

Caesarean section is one of the most commonly performed major operations in women throughout the world [1]. The caesarean section rate in Sri Lanka in 2013 was 31.3% [2]. Operative morbidity due to caesarean section includes haemorrhage, anaemia, blood transfusion and the risks associated with receiving donor blood products [3, 4]. In extreme cases it may result in hysterectomy, admission to an intensive care unit or even maternal death [5]. According to a WHO report which was published in 2014 major obstetric haemorrhage is the leading cause of maternal mortality worldwide and in most cases it relates to uterine atony [6]. According to the Annual Health Bulletin 2013, postpartum haemorrhage is the leading cause of maternal mortality in Sri Lanka [7].

Intravenous oxytocin has a very short half-life (4-10 minutes) hence an oxytocin infusion can maintain uterine contractility throughout surgery and in the immediate postpartum period [8]. That is the most susceptible period when most primary haemorrhages occur. Reduction of blood loss will be instrumental in bringing down the post-operative morbidity [9, 10]. It will also assist in averting potential problems in blood transfusion [11]. The third stage at the caesarean section has not been duly managed [12]. The current practices of oxytocin administration are not uniform [13]. The value of routine oxytocin in the third stage of vaginal birth has been well established and it has been assumed that these benefits apply to caesarean section as well [14, 15].

In line with latest guidelines by the Royal College of Obstetricians and Gynaecologists on actively managing labour in its third stage, a slow intravenous bolus dose of 5 IU of oxytocin is recommended to be administered after delivery [16]. This dose is based on the principles of active management of the third stage of labour. During routine use of an intravenous oxytocin bolus, additional oxytocin is administered in case of a haemorrhage. This practice is on the rise either selectively or as a routine even when there is no need [17]. It is also observed that the administration of a oxytocin bolus is carried out sometimes with and sometimes without the additional dosage [18]. In Sri Lanka there is a wide variation in the use of an oxytocin infusion in addition to the bolus following caesarean section. Most clinicians intervene in the event of uterine atony by administering an additional uterotonic agent. However, there is very limited evidence to guide practice.

Studies have compared use of an oxytocin infusion in addition to the bolus during caesarean section. However, the evidence is inadequate to recommend oxytocin infusion over IV bolus injection [19]. One study compared the effects of a 5 IU oxytocin bolus and placebo infusion versus a 5 IU oxytocin bolus and 30 IU infusion on the control of blood loss at elective caesarian section and it reported that mean estimated blood loss was lower in the oxytocin infusion arm (5 IU oxytocin bolus and 30 IU infusion) compared to placebo (5 IU oxytocin bolus and placebo infusion) and fewer women had a major haemorrhage or required an additional uterotonic agent [20]. However, another study which compared 5 IU oxytocin bolus and 40 IU infusion to placebo revealed that there was no significant difference in mean blood loss [21]. Therefore, this study aims to compare a standard 5 IU bolus of oxytocin and an additional 20 IU oxytocin infusion (bolus and infusion) with a 5 IU bolus of oxytocin and placebo infusion (bolus only), to determine whether the use of an inexpensive and widely used drug can further improve prevention of hemorrhage at caesarian section.

Method

A double-blind, placebo controlled randomized trial was conducted in an obstetric unit at Teaching Hospital, Peradeniya, Sri Lanka, which is a leading tertiary care hospital in the country. Pregnant women, who were at term, with singleton pregnancies and had a planned elective caesarian section were selected for the study. Sample size was calculated based on the measured blood loss in women following

caesarian section, taking mean blood loss with the use of oxytocin as 900 ml (SD = 500ml). Assuming that adding 20 IU infusion in addition to bolus will further reduce blood loss by 300 ml, a sample of 46 subjects in each group was required to detect the difference at 90% power at 5% significance (Figure 1).

Exclusion criteria were women who were in established labour, had multiple pregnancies, established or suspected cases of chorioamnionitis, both minor and major degree placenta praevia and established or suspected cases of placental abruption, previous history of postpartum haemorrhage and coagulation disorders, and women with a history of or had ultrasonically proven fibroids.

Randomization was done using computer-generated random numbers. Sequentially numbered and sealed, opaque envelopes coded with the appropriate dose regimen were prepared by the supervisor. Anaesthetist who gave anaesthesia during the caesarian section and the investigator were blinded. Principles of allocation concealment and double blinding were followed. An anaesthetist, who was not involved in the management of women during and after the caesarian section received an envelope when the woman was sent to operating theatre. According to the information in the sealed envelope, either the placebo or active infusion was prepared and given to the anaesthetist who gave the anaesthesia and was involved in management. While inserting the cannula before anaesthesia 3ml of blood was taken from each woman in a Vacutainer plastic tube (Hunan Liyang Medical instrument factory, China) with ethylene diamine tetra acetic acid and sent for assessment of full blood count. Full blood count was checked by using Mindray BC-3000 plus Haematology Analyser (Mindray, Shenzhen, China). Haemoglobin concentration, packed cell volume, platelets and other blood cells concentration were assessed. All patients who underwent spinal anaesthesia received an intravenous bolus of 500 ml normal saline before spinal anaesthesia. Surgical and anaesthetic techniques were standardized to both groups of study. Before caesarian section, a 16Fr Foley catheter was inserted and the abdomen was cleaned with povidone iodine solution. Pfannenstiel incisions were performed in all patients. Routine caesarian section was performed with transverse lower uterine segment incision followed by delivery of the foetus and placenta. The placenta was delivered by controlled cord traction. A 5 IU intravenous bolus of oxytocin over 5–10 seconds was injected to each woman by the anaesthetist when the umbilical cord clamping was being done. Then in group A patients, 20 IU oxytocin in 500 ml of 0.9% normal saline solution was continued at a rate of 125

ml/hour for four hours and in group B patients 500 ml of 0.9% normal Saline solution at a rate of 125 ml/hour was continued for four hours. If the uterus remains atonic despite the trial intervention, the obstetrician or anaesthetist could use an additional uterotonic agent by replacing the trial infusion with a known oxytocin infusion or by using other additional agents. The uterine atony was detected by the surgeon during surgery and by skilled birth attendants in the postnatal ward. Pulse rate, respiratory rate, blood pressure and oxygen saturation percentage were monitored every 15 minutes during the procedure.

Identical standard of postpartum care was provided for both groups who were managed in the same postnatal ward by the same staff. Vital signs (pulse rate, respiratory rate, blood pressure and oxygen saturation percentage) were checked every 15 minutes in the first 2 hours, every 30 minutes in second 2 hours and hourly for another 2 hours and continued 4 hourly for 24 hours. Urine output was monitored hourly for 6 hours. The need for additional uterotonic agents for the management of intraoperative and postoperative uterine atony was recorded. Full blood count was repeated at 48 hours postoperative. Preoperative PCV, haemoglobin and post-operative PCV and haemoglobin values were recorded. The blood loss was calculated through the difference in the haematocrit values assessed prior to and 48 hours after caesarean section according to the following formula [22, 23]. Calculated blood loss = estimated blood volume x (preoperative packed cell volume - postoperative packed cell volume) / preoperative packed cell volume. Estimated blood volume in ml was estimated by multiplying the woman's weight in kilograms x 85.

Blood loss estimation was done using above formula as a quantitative objective measure to estimate blood loss because it is widely accepted that clinicians underestimate blood loss visually and that gravimetric methods include liquor in addition to blood, which limits accuracy [24, 25, 26]. Disposable waterproof drapes with pockets that capture blood and liquor were not used due to financial constraints. Visual estimation and accepted calculation method were chosen to estimate blood loss [20,21]. Need for additional uterotonic and occurrence of adverse effects such as nausea, vomiting and arrhythmias was recorded.

Ethical approval was obtained from the Ethical Review Committee, Faculty of Medicine, University of Peradeniya, Sri Lanka. Trial was registered in the Sri Lanka Clinical Trial Registry (SLCTR/2013/019, 29th May 2013). Prior approval was

obtained from the Director, Teaching Hospital, Peradeniya, Sri Lanka. Strict confidentiality of the data was ensured. Women were recruited to the trial in the third trimester when they got admitted for a planned elective caesarian section. An investigator or an assistant approached eligible women and explained about the study. Consenting women were recruited after explaining about the intervention and associated risks. Written informed consent was obtained from all participants.

Descriptive statistics were used to summarize the data. Measures of dispersion and 95% confidence intervals were calculated. For comparisons of continuous variables Student's T test was used when the data were normally distributed. For variables with a skewed distribution median, inter-quartile range, Mann-Whitney U test were used. Chi-square test was used to look for associations between categorical variables. Relative risk (RR) with 95% confidence interval (CI) was calculated. A p-value of less than 0.05 was considered as statistically significant.

Results

Ninety two mothers were recruited for the study (46 in each group). Demographic details of the sample are presented in Table 1. There were no significant differences in age, BMI, parity or period of amenorrhoea between the treatment groups. Table 2 shows that the oxytocin bolus and infusion group (intervention group) had significantly lower mean calculated blood loss, lower visual estimation of blood losses by surgeon (476.9 vs. 552.1) ($p=0.01$) and by the anaesthetist (492.7 vs. 557.2) ($p=0.03$). However, there was no significant difference in occurrence of major obstetric haemorrhage ($p=0.153$), change in haemoglobin concentration or packed cell volume. There was no significant difference in need for additional uterotonic agent or interventions following blood loss (Table 3). None of the participants needed surgical intervention, uterine artery ligation, B-lynch / compression sutures, total or subtotal hysterectomy or internal iliac artery ligation. There was no significant differences in mean duration of surgery between the intervention group 30.4 minutes (SD=11.6) and the control group 30.0 minutes (SD=11.6), ($p=0.4$). There was no significant difference in mean length of stay in theatre and recovery in the intervention group 116.6 minutes (SD=56.0) and the control group 112.6 minutes (SD=46.8) ($p=0.08$). Side effects of oxytocin such as nausea and vomiting were reported in two subjects in the intervention group and in one subject in the control group.

Discussion

In this trial, women delivered by caesarian section had significantly less blood loss during and after caesarian section when 20 IU oxytocin infusion was given in addition to 5 IU oxytocin bolus compared to those who received 5 IU oxytocin and a normal saline infusion.

A study carried out to assess effects of 40 IU of oxytocin infusion in addition to slow intravenous 5IU bolus found no difference in the occurrence of major obstetric haemorrhage (blood loss more than 1000 ml) between the groups [21]. The need for an additional uterotonic agent in the bolus and infusion group was lower than in the bolus only group. There were no significant difference in any of the secondary outcomes such as mean calculated blood loss, mean fall in haemoglobin and mean measured blood loss. Even though that study standardized the surgical technique, different surgeons both junior and senior obstetricians, carried out the caesarian sections [21]. But in our study the caesarian sections were done by one surgeon.

Another double-blind, placebo-controlled study was done on 720 women to assess the effects of a 5 IU oxytocin bolus and placebo infusion versus 5 IU oxytocin bolus and 30 IU infusion, on the control of blood loss at elective lower segment caesarean section. Blood loss was estimated based on the haematocrit values before and 48 hours after delivery. Mean estimated blood loss and the proportion of women with blood loss estimated to be greater than 1000 ml were significantly less in the oxytocin infusion group. They used lactated Ringer's solution as placebo and caesarian sections were performed by different surgeons. Even though it was done with a larger sample size, it has also yielded similar outcomes as our study [20]. Another study compared the blood loss at elective lower segment caesarian section with administration of oxytocin 5 IU bolus versus oxytocin 5 IU bolus and oxytocin 30 IU infusion [24]. A randomized trial among 115 women has showed that additional oxytocin infusion at elective caesarian section may reduce blood loss and maternal morbidity [27].

The amount of blood loss in our study (120 ml) was not clinically significant. The intervention did not affect occurrence of major obstetric haemorrhage or the need for additional uterotonic agents or blood transfusion. Use of an oxytocin infusion after an initial bolus did not increase the occurrence of side effects. The sample was not calculated to detect differences in occurrence of major obstetric haemorrhage, need for additional uterotonics or blood transfusion. Therefore, valid conclusions cannot be drawn about these

outcomes. Women with risk factors associated with postpartum haemorrhage were excluded because of the different preventive measures undertaken in these women. In this study blood loss at the time of caesarean section was visually estimated and total blood loss was calculated by using preoperative and postoperative packed cell volume. But if the blood loss was measured by using the weighing method it may have been more accurate. The strength of our study is that all caesarian sections were performed by a single surgeon and techniques of surgery and anaesthesia were standardized.

In conclusion, additional oxytocin infusion at ante-partum caesarean section reduces blood loss during and after caesarean section significantly. The implementation of these findings in clinical practice merits special attention. One option is to administer oxytocin bolus and infusion to all women who undergo antepartum caesarian section. This may help circumvent the problem of having to determine the time of administering uterotonic agent. The negative side of this approach is that some women who do not need an infusion may receive it. Another option is to administer the additional oxytocin infusions during antepartum caesarian section to selected women.

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Conflicts of interest

There are no conflicts of interest.

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Table 1. Demographic and clinical characteristics of the intervention and control groups

Demographic characteristics	Oxytocin bolus and infusion	Oxytocin bolus and placebo infusion	P value
	Mean (SD)	Mean (SD)	
Age	30.7 (4.5)	29.9 (4.7)	0.41
BMI	26.8 (3.4)	27.1 (3.3)	0.66
Period of amenorrhoea	38.6 (0.95)	38.7 (0.96)	0.83
	Median (inter quartile range)		
Parity	2 (1)	1 (1)	0.78

Table 2. Comparisons of blood loss between intervention and control groups

	Oxytocin bolus and infusion	Oxytocin bolus and placebo	p
	Mean (95% CI)	Mean (95% CI)	
Drop in Hb (mg/dL)	1.37 (1.1 – 1.6)	1.40 (1.1 – 1.7)	0.92
Drop in PCV	3.28 (2.7 – 3.9)	4.08 (3.4 – 4.7)	0.07
Calculated blood loss ml	455 (381 – 531)	569 (485 – 654)	0.046

Table 3. Comparison of interventions following blood loss in the intervention and control groups

Measures (% within group)	Oxytocin infusion	Oxytocin placebo	p
Blood transfused	3 (6.5)	4 (8.7)	0.694
Condom catheter inserted	1 (2.2)	2 (4.3)	0.557
Misoprostol	8 (17.4)	4 (8.7)	0.216

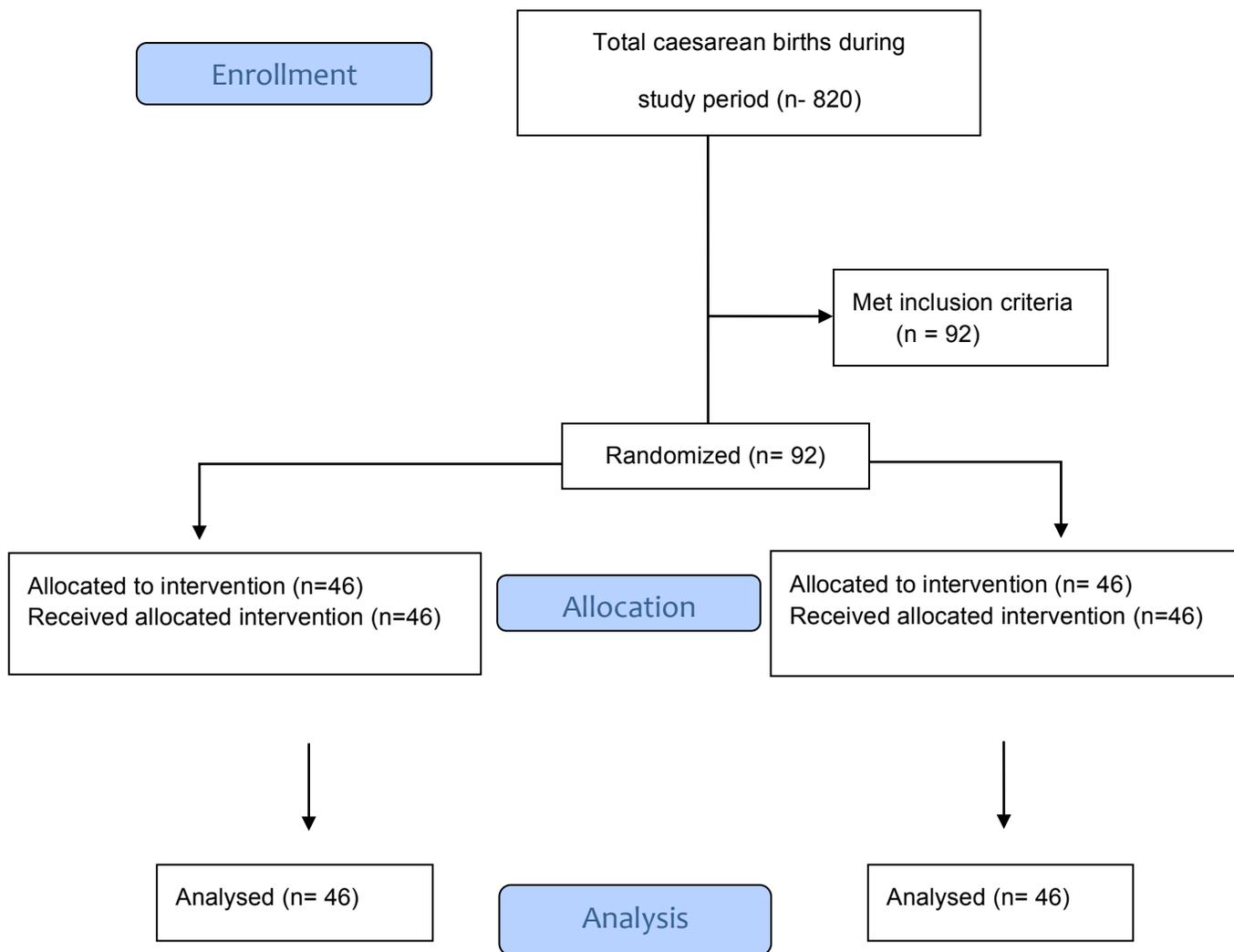


Figure 1. CONSORT flow chart



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