

Effectiveness of intramyometrial oxytocin versus intravenous oxytocin bolus administration during elective caesarean section – a randomized control trial

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Abstract

Introduction: Intravenous oxytocin (IVO) is recommended during elective caesarean section to prevent postpartum haemorrhage. However, compared to IVO intramyometrial oxytocin (IMO), may result in better contractility with minimal haemodynamic side effects. Limited number of studies are available on IMO use at elective Caesarean section (CS).

Objective: To evaluate the effectiveness of prophylactic IMO against IVO, in term singleton mothers at elective CS.

Methods: Sixty five term singleton mothers undergoing elective CS at the Teaching Hospital, Kandy from 1st February 2015 to April 2015 were randomized to IMO and IVO. Prior to umbilical cord clamping, either IMO 5 IU divided half to each cornu or routine IVO 5 IU was administered. Blood loss was assessed using gravimetric methods and allowable blood loss calculation. Surgeon assessed uterine tone at 2,5,10 and 15 minutes following injection and gave a score of 1 to 5. Haemodynamic parameters, side effects, haemoglobin and haematocrit were recorded.

Results: Thirty three were in IMO group while 32 were in IVO group. There was no significant difference between IVO and IMO groups in relation to mean blood loss, (303.83, SD 103.77ml vs 267.65 SD 93.53 ml, $p=0.43$), uterine contractions at 2 and 5 minutes and side effects. Calculated allowable blood loss in IMO group was significantly less than IVO group ($p=0.04$) and contraction scores at 10 and 15minutes were significantly higher in IMO group. There was no difference in haemodynamic parameters in each group.

Conclusion: IMO oxytocin was not more effective than IVO during elective CS.

Key words: oxytocin, intramyometrial, caesarean, blood loss

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Introduction

Caesarean section (CS) is a major obstetric surgery which has been in practice for several years. Postpartum haemorrhage (PPH) following CS is an important cause of maternal mortality and morbidity associated with the procedure. The main cause of maternal mortality worldwide is postpartum haemorrhage, which is responsible for nearly 25% of maternal deaths world wide¹. Uterine atony is considered as the commonest cause of PPH, which is preventable by active management in the third stage, which includes the use of an uterotonic as oxytocin, controlled cord traction and early cord clamping. It results in less blood loss compared to expectant management and is capable of reducing PPH by nearly 60%³.

Oxytocin is a neuropeptide which causes contraction of the uterus. Towards term the number of oxytocin receptors increase along, with their receptor sensitivity. As a pharmacological agent oxytocin can be administered as intravenous, intramuscular, intraumbilical and intramyometrial routes. However, oxytocin is associated with side effects which are likely to be more common in intravenous route due to rapid entry of oxytocin into the systemic circulation. Intramyometrial oxytocin (IMO) may minimize side effects if used in the treatment of post-partum haemorrhage as it acts locally. However, carboprost (prostaglandin F2 α) is the only drug currently recommended to use intramyometrial in management of PPH due to uterine atony⁴. Studies have shown that intramyometrial carboprost may not be more effective than intramyometrial oxytocin⁵.

Oxytocin has a high therapeutic index and in addition to treatment of PPH its use as a prophylactic uterotonic agent is justified as well. Oxytocin is considered as the initial option for prevention of uterine atony in patients undergoing caesarean sections. The National Institute of Clinical Excellence (NICE) guidelines in United Kingdom recommend intravenous administration of 5 International Units (IU) of oxytocin during caesarean section⁷. However intravenous oxytocin during caesarean section is associated with side effects such as tachycardia, hypotension, decreased cardiac output which are dose related and can lead to haemodynamic instability especially in an already haemodynamically compromised patients⁸. Other side effects of oxytocin include nausea and vomiting, arrhythmias and hyponatremia⁹. Therefore, the most appropriate dose and route of administration need to be determined which would provide adequate uterine contractions to

prevent uterine atony and prevent PPH whilst causing minimal unwanted effects.

Limited studies are available on the use of IMO and their effectiveness. A study conducted in 1990 comparing intramyometrial carboprost (prostaglandin F2 α) 125 μ g with IMO 20IU in relation to blood loss found similar effectiveness in both drugs⁵. In a multicenter study conducted in the United Kingdom on caesarean hysterectomy it was found that IMO was administered in 9% of cases as a medical measure for preventing caesarean hysterectomy and control of bleeding¹⁰. Another randomized control study by Dennehy et al in 1998 found that IMO 20IU caused a transient hypotension which was more severe when compared to IVO 5IU bolus. The study further concluded that the uterine contractility caused by intravenous and intramyometrial oxytocin was similar and the use of IMO be cautioned in the treatment of uterine atony as it may aggravate the preexisting hypotension in PPH¹¹.

A randomized control study by Divya Mangala et al comparing effectiveness of IVO with IMO before and after delivery of the placenta concluded that IMO administered, before delivery of the placenta is more effective in increasing uterine contractility than IVO infusion and is associated with reduced blood loss. IMO was also shown to have reduced side effects such as hypotension, nausea and vomiting. In regards to haemodynamic parameters the authors observed that the blood pressure decrease and heart rate increase associated with IMO, was less than IVO infusion¹². Akinaga et al in a randomized trial administering IMO vs IVO 0.07IU/kg reported a delayed effect in the IMO group with up to 10 minutes delay in achieving a satisfactory uterine contraction compared to IVO. There was no difference in the blood loss and haemodynamic effects, with IMO effects manifesting later than IVO, similar to contractility³. A systematic review incorporating above studies by Guerra-Callilung et al revealed limited conflicting evidence that IMO significantly reduced PPH (RR 0.4; 95% CI 0.19 to 0.82) and maternal adverse drug event (RR 0.1, 95% CI 0.01 to 0.75) compared to IVO¹⁴.

At caesarean section the operator has free access to the uterus, enabling direct injection of oxytocin into the myometrium, a favourable option compared to intravenous administration. Unfortunately, there is limited data available on the routine use of intramyometrial oxytocin as a prophylactic agent during

cesarean section. Further research on uterotonic agents, their mode of administration and timing is recommended by the World Health Organization¹⁵. The objective of this study was to assess the effectiveness of intramyometrial oxytocin compared to intravenous oxytocin at elective caesarean section with regards to blood loss, uterine contractility and side effect profile.

Methods

A double blind, parallel group, randomized control clinical trial was conducted with 1:1 allocation ratio. A study done by Divya Mangala et al, was utilized to set the power at 90% and a significance level of 5% and accordingly a sample size of 68 was calculated with 34 participants in each arm. A random number allocation sequence was generated. Term mothers at 37-41 weeks of gestation with an uncomplicated pregnancy who were undergoing elective CS at Teaching Hospital, Kandy between March 2015 to June 2015 were included for the study. Patients with placenta previa, polyhydramnios, fibroids, maternal heart disease, hypertensive disease, multiple pregnancy, diabetes mellitus, suspected fetal macrosomia, previous failed spinal anaesthesia were excluded from the study.

The parity, gestation, indication for caesarean section and significant risk factors were recorded along with basic demographic details. Baseline systolic and diastolic blood pressures were recorded. Pre-operative haemoglobin and haematocrit was done. One group of patients received intravenous oxytocin 5IU at the time of delivery of the baby, while the other group received 5IU of intramyometrial oxytocin diluted in 9ml of 0.9% saline 5ml to each cornu of the uterus following delivery while awaiting placental separation.

At the time of recruitment, a sealed envelope labelled as either A or B was provided to each participant by a trained medical officer who allocated patients to each group. Immediately prior to the procedure the medical officer, in the presence of the anaesthetist prepared a sealed plastic bag containing two syringes of 5 ml and 10 ml each, for concealment of allocation. The 5 ml syringe was used for intravenous administration and the 10 ml syringe for intramyometrial administration. The IVO group received a bag with a 5 ml syringe containing 5IU of oxytocin for intravenous administration with a 10ml syringe containing sterile 0.9% saline for intramyometrial injection, 5ml each to both cornu. The IMO group received a plastic bag with a 5ml syringe of sterile 0.9% saline for intravenous

administration and a 10ml syringe containing 5IU of oxytocin for intramyometrial injection. Each participant was given two injections at the time of surgery. The surgeon, investigators as well as the patient were blind to the treatment received. The anaesthetist was not blind either to the drug, dose or the route each drug was administered at all times, in view of patient safety.

Prior to the surgery haemodynamic parameters were recorded by the anaesthetist. Blood loss up to the uterine incision was collected to a separate suction apparatus. The amniotic membrane was ruptured and suction carried out separately. Upon delivery of the baby the surgeon administered the intramyometrial preparation, prior to umbilical cord clamping over 2 minutes while the anaesthetist administered the intravenous preparation over 2 minutes. Blood loss following administration of intravenous and intramyometrial preparations was collected to a separate suction apparatus. The tone of the uterus was assessed by the surgeon at 1, 5 and 10 and 15 minute intervals following administration of oxytocin. The surgeon assessed the uterine tone using a standardized technique of digital palpation of the fundus and body of the uterus at above intervals and gave a score of 1 to 5, which was recorded. The same surgeon conducted the surgery and assessment in all patients, using the same technique to minimize variation. Presence of chest pain, nausea and vomiting during the surgery was recorded by a medical officer. The per vaginal blood loss within 1 hour after the surgery was assessed. The need for a second uterotonic agent or additional surgical measures such as compression sutures, balloon tamponade within 24 hours was noted.

Blood loss was estimated by using gravimetric methods and allowable blood loss (ABL) calculation. Volume of blood in the suction apparatus was measured directly and care was taken to prevent admixture of amniotic fluid by using separate suction canisters. Dry weights of gauze towels and swabs were assessed pre-operatively. Soaked weights of towels and swabs were measured immediately during the surgery. By subtracting the dry weight, blood in soaked towels were calculated. (1 gram = 1 ml of blood). Pre-operative and post-operative haematocrit was used to calculate the allowable blood loss.

The blood loss and the haemodynamic parameters between the two groups were compared following calculation of means using independent sample t test or Mann Whitney U test depending on their distri-

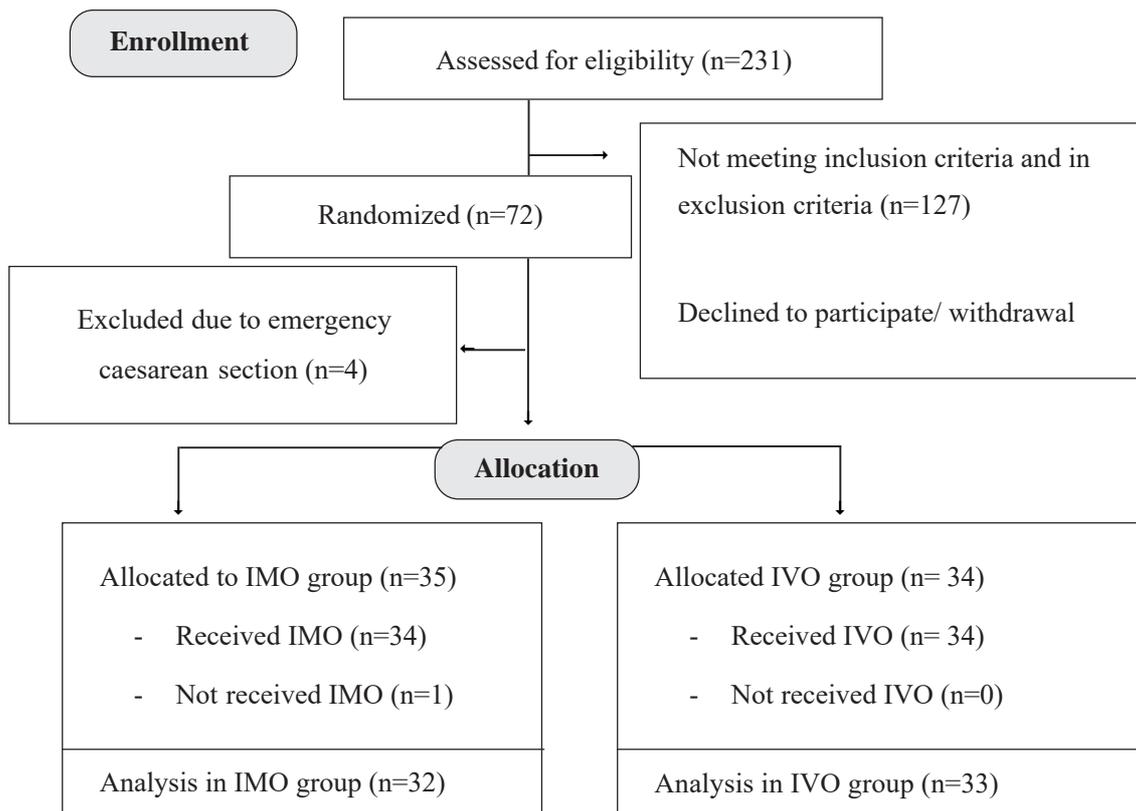
bution. Uterine tone scores were assessed using Mann Whitney U test. The need for additional uterotonic agents and occurrence of side effects were assessed using Chi square tests. Ethical approval for the study was obtained from Ethical Review Committee, Kandy Teaching Hospital and administration approval from the Director, Teaching Hospital, Kandy.

Results

231 patients undergoing elective caesarean section were assessed for eligibility to participate in the study of which only 104 were eligible. 28 women did not provide consent while 4 patients withdrew participation. From the remaining, 4 patients underwent emergency CS while awaiting elective CS. Due to lack of complete data, 3 women were not included in the

final analysis. There were 32 women in the intramyometrial oxytocin (IMO) group and 33 in the intravenous oxytocin (IVO) group.

Majority of participants were in the age group of 31-35 years in both IVO (45.5%) and IMO (43.8%) groups and were in their second pregnancy. The median gestation was 39 weeks. The mean blood loss measured through gravimetric methods was similar in both groups with 303.83 (103.77) ml in the IVO group and 267.65 (93.53)ml in the IMO group (mean difference 36.17 ml; p=0.14, 95% CI for difference -85.19 to 12.84). The calculated mean allowable blood loss in the IMO group 180.8 (178.28) ml, was significantly less than in the IVO group 275.06 (200.66)ml (mean difference 94.6ml; p=0.04, 95% CI 0.48 to 188.87) (Figure 2).



IMO - intramyometrial oxytocin, IVO - intravenous oxytocin

Figure 1. Flow diagram of participants in the study for intramyometrial oxytocin (IMO) and intravenous oxytocin (IVO) groups.

Table 1. Basic demographic and obstetric characteristics of the participants

	Intravenous oxytocin bolus group (n=33)	Intramyometrial oxytocin group (n=32)
Age (mean)	30.73 (±4.46)	30.72 (±4.82)
<25 years	4 (12.1)	6 (18.8)
26-30 years	10 (30.3)	7 (21.9)
31-35 years	15 (45.5)	14 (43.8)
36-40 years	4 (12.1)	4 (12.5)
>41 years	0 (0)	1 (3.1)
Parity		
1	13 (39.4%)	10 (31.3%)
2	13 (39.4%)	16 (50%)
3	6 (18.2%)	4 (12.5%)
4	1 (3%)	2 (6.3%)
Period of gestation* (weeks)	39 (1.5)	39 (1.5)
Mean weight (kg)	61.93 (±6.4)	61.37 (±7.7)
Mean birth weight (kg)	2.96 (±0.31)	2.88 (±0.39)

Data presented as n (%) and mean (standard deviation) *median (inter quartile range). All observations had p<0.05

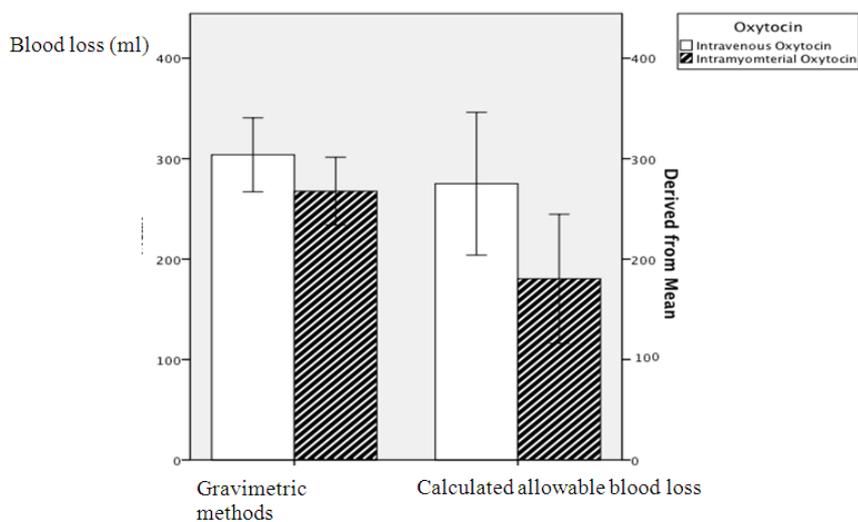


Figure 2. Mean blood loss following oxytocin administration at caesarean section between intravenous and intramyometrial groups.

Strength of uterine contraction was similar at 1 and 5 minutes in both groups. However, at 10 and 15 minutes IMO group was stronger with a median score of 3 compared to IVO group ($p=0.002$). The need for additional uterotonics, mechanical compression was 16 (48.5%) vs 8 (25%) and 1 (3%) vs none ($p=0.98$) in IVO and IMO groups respectively. There was no difference in overall side effects by either route of administration. Commonest side effect in IVO group was chest pain (21.2%)

while in the IMO group it was nausea (21.9%) (Table 2).

Haemodynamic parameters were similar in both groups. Increase in heart rate, decrease in systolic blood pressure (SBP) and decrease in diastolic blood pressure (DBP) were 9.36 (15.30) beats per minute (bpm) vs 9.46 (13.06) bpm, 14.03 (19.74) mmHg vs 13.9 (17.12) mmHg, 10.54 (18.03) mmHg vs 8.56 (11.35) mmHg in IVO and IMO groups. Observed changes were highest at 5 minutes in both groups (Figure 3).

Table 2. Side effects following IVO and IMO administration

Side effect	IVO group (n=33)	IMO group (n=32)	P value
Nausea	5 (15.2)	7 (21.9)	0.48
Vomiting	4 (12.1)	2 (6.3)	0.66
Chest pain	7 (21.2)	3 (9.4)	1.74
Arrhythmias	1 (3)	0 (0)	0.98
Need for vasopressors	4 (12.1)	1 (3.1)	1.85

Data given as number (percentage%), IVO- intravenous oxytocin, IMO- intramyometrial oxytocin

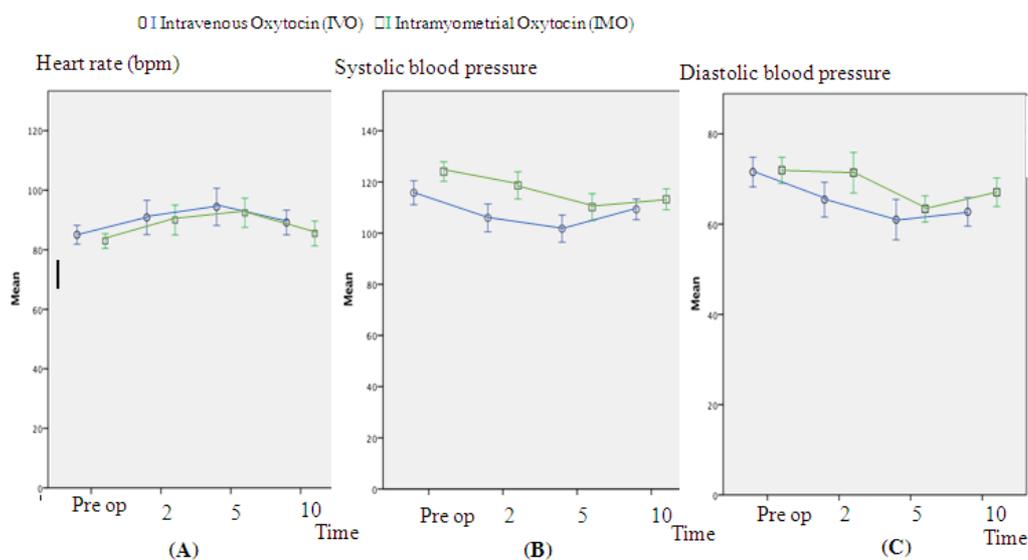


Figure 3. Mean heart rate (A), Systolic blood pressure (B) and diastolic blood pressure (C) with time following oxytocin administration in IVO and IMO groups.

Discussion

Our results do not show any difference between IVO and IMO in terms of blood loss assessed through gravimetric methods, side effect profile and haemodynamic parameters. However, IMO was more effective than IVO with regards to uterine contractility especially at 10 and 15 minutes following administration and resulted in less allowable blood loss.

At the onset of the study it was expected that IMO would be superior to IVO in the reduction of blood loss at the time of surgery, due to its more localized action directly on the myometrium. Furthermore, IMO due to less systemic availability was expected to cause less side effects and haemodynamic disturbance compared to IVO. Yet the findings from this study indicate that such localized effects are not apparent in the doses of oxytocin studied.

At caesarean section oxytocin is administered as part of active management to ensure adequate uterine contraction and thereby minimize blood loss due to uterine atony. Our findings of similar blood loss between the two groups was observed in the double blind randomized control trial conducted by Akinaga et al. However, the authors acknowledge their study may be underpowered to assess any true difference in blood loss between the two groups as they had considered systolic blood pressure to calculate sample size rather than blood loss itself which was measured as a secondary outcome. Furthermore, in this study, IMO resulted in a delay in causing effective uterine contractions for 10 minutes, compared to IVO which required only 2 minutes. They postulated, the delayed contractility with IMO may have contributed to a higher blood loss in the IMO group³. In our study too although a similar delayed effect after 10 minutes was observed with IMO, uterine tone scores were higher than IVO, although it did not translate into a resultant decrease in overall blood loss. Akinaga et al in their study, used a continuous low dose oxytocin infusion routinely, in both groups, after the initial bolus dose, which was not used in our study. This might have contributed as a confounding factor for the final contractility in their study.

Conversely a prospective randomized control study conducted by Divya Mangala et al demonstrated IMO 5IU given prior to placental separation to be superior, in regards to blood loss than both, intravenous 20 IU oxytocin infusion and IMO 5IU administered after

separation of the placenta¹². Although the intra myometrial dose used in the current study was similar the intra venous group differed from Divya Mangala et al as a bolus dose was used rather than an infusion, therefore limiting comparability. Though similar gravimetric methods were utilized in both studies, the current study did not show such a difference in blood loss between the two groups as observed by Divya Mangala et al except through allowable blood loss calculation. Allowable blood loss calculation may not be as accurate as gravimetric methods and the volume of intravenous fluid administered needs to be considered. The difference observed between the two studies may be due to the different intravenous doses used.

When considering haemodynamic parameters Denney et al observed more severe hypotension with 20IU of IMO compared to 5IU of IVO with comparable contractility in both groups. The resulting increase in heart rate and decrease in SBP was highest at 1 minute following administration and was considered to be due to an immediate absorption of oxytocin into the systemic circulation¹¹. The IMO group in their study received a relatively large dose of intramyometrial oxytocin compared to intravenous oxytocin, which may be the cause for the significant severe side effects observed. Akinaga et al in their study demonstrated a more stable heart rate and SBP in their IMO group with a much smaller dose of IMO. Although the occurrence of hypotension was similar in both groups, IMO had a delayed effect on haemodynamic parameters as well, similar to its effect on contractility. The mechanism for this delayed effect according to the authors were possibly due to low blood concentrations of oxytocin after intra myometrial injection¹³. However, blood concentrations of oxytocin were not assessed in the study. In contrast Divya Mangala et al observed a significantly lesser decrease in blood pressure in IMO group compared to IVO infusion¹². Such a significant difference was not observed between the two groups in our study, which may be due to the fact that we used only oxytocin bolus for intravenous administration. The infusion used by Divya Mangala et al may have caused persistently high oxytocin concentrations in blood causing more haemodynamic effects. In our study too the decrease in systolic and diastolic blood pressures were highest at 5 minutes in IMO group which may further strengthen the argument of a delayed effect on haemodynamic parameters with IMO proposed by Akinaga et al.

IMO was administered by Akinaga et al only to fundus of the uterus, while it was injected to each cornu separately in our study, which was similar to the technique used by Divya Mangala et al. The technique of administration adopted in this study may result in a quicker and more even spread of oxytocin throughout the myometrium potentiating its local effect on contractility. Therefore, it is reasonable to explore the effect of different techniques of intramyometrial oxytocin. Surprisingly, less side effects such as nausea and vomiting were not observed in the IMO group, as expected and observed in Divya Mangala et al. Although administered locally, IMO may be entering the systemic circulation contributing to similar side effect profile as IVO. On the other hand, as only an intravenous bolus oxytocin dose was used rather than an infusion, the side effects in the intravenous arm may be too low to show a significant difference with IMO.

The strength of the study lies in its double blind nature and randomization. Both groups were matched for confounding variables and recommended standard doses of oxytocin were used. However, primary outcome of assessing blood loss using gravimetric methods and calculation methods may not be accurate. Allowable blood loss calculation may be affected by fluids infused peri operatively while gravimetric methods may be affected by amniotic fluid mixing with blood. Despite measures taken to minimize admixture of amniotic fluid, it cannot be completely prevented. Another limitation is the subjective assessment of uterine tone by surgeon. Sarna et al in a study to assess effect of intravenous oxytocin on uterine tone at elective caesareans used a similar technique of assessing uterine tone by digital palpation post oxytocin¹⁶. In our study a linear scoring system was utilized to add limited objectivity to assessments. As a single surgeon conducted the surgeries it minimized interobserver variation in assessment. An intrauterine pressure gauge would have provided a more objective and accurate measurement of uterine tone following oxytocin. However, using an intrauterine pressure gauge may act as a confounding factor for assessing blood loss, which was the primary outcome of the study and due to its limited availability, it was not used in the present study. Assessment of oxytocin concentration in the blood to identify the oxytocin available in the systemic circulation would have been better to assess systemic availability of oxytocin as well.

In conclusion there was no difference in blood loss between either route, although IMO achieved higher

contraction scores with a slight delay in effect. Both routes of administration in the given dose had no difference in their effects on haemodynamic parameters and side effects. Further research on the effectiveness of IMO including the optimum technique of administration, with more accurate blood loss assessment is recommended. Oxytocin should be continued to be administered intravenously at the time of caesarean section until further evidence of effectiveness of intramyometrial oxytocin is available.

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