Effectiveness of intramyometrial Oxytocin versus intravenous Oxytocin bolus administration during elective Cesarean section

A randomized controlled trial

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Abstract

Introduction

Oxytocin is recommended during elective caesarean section as a bolus to reduce uterine atony and prevent postpartum haemorrhage. Intravenous use of oxytocin bolus is associated with hameodynamic side effects and is occasionally, insufficient by itself alone to maintain uterine tone following delivery. Due to free accessibility of the uterus at the time of Caesarean section intramyometrial oxytocin may be an effective alternative, to intravenous oxytocin with minimal side effects due to its more localized action. Limited studies have been conducted on this regard and available studies show conflicting results on its effectiveness.

Objective

To assess the effectiveness of prophylactic intramyometrial oxytocin and intravenous oxytocin at the time of Caesarean section in terms of blood loss, contractility and side effects.

Methods

A double blind randomized control clinical trial was conducted at Teaching Hospital Kandy. Sixty five mothers with singleton pregnancies >37 weeks of gestational age undergoing elective Caesarean section under spinal anasthesia were randomized to intramyometrial oxytocin (IMO) (n=33) and intravenous oxytocin (IVO) (n=32). Oxytocin 5IU was administered by either route before umbilical cord clamping at the time of delivery. Blood loss was assessed using gravimetric methods and allowable blood loss calculation. Uterine tone was assessed by the surgeon and a score of 1 to 5 given at 2,5,10 and 15 minutes following drug administration. Hameodynamic parameters and occurrence of side effects were recorded. Pre operative and post operative haemoglobin and haematocrit was checked.

Results

In both groups majority were in the age group of 31- 35 years with a median gestation of 39 weeks. Blood loss was similar between the two groups with a blood loss of 267.65 (±93.53)ml in the IMO group and303.83 (±103.77)ml in the IVO group (p= 0.43). The uterine contraction was similar between the two groups at 2 minutes and 5minutes, but significantly higher in the IMO group at 10 minutes and 15 minutes. There was no difference in the need for additional uterotonic agents or occurrence of side effects between the two groups. Both routes of administration resulted in similar haemodynamic changes, with the increase in heart rate highest at 5 minutes in both groups. The decrease in systolic and diastolic blood pressures were highest at 5 minutes following administration by either route, with a less decrease in diastolic blood pressure by the intramyometrial route at 5 minutes.

Conclusion

IMO oxytocin was similarly effective as IVO, in terms of blood loss and hameodynamic changes. Despite IMO causing stronger uterine contractions from 10 minutes onwards following administration, it did not result in lesser blood loss compared to IVO. Further studies on the effectiveness of intramyometrial oxytocin in specific subgroups and the optimum technique of administration are recommended to establish if IMO has a place in routine clinical practice.

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Abbreviations

PPH	Post partum haemorrhage
IVO	Intravenous Oxytocin
IMO	Intra myometrial Oxytocin
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

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SECTION - 1

Introduction

Background and Justification

Cesarean section is considered as a major obstetric surgery which has been in practice for several years. Post partum haemorrhage (PPH) is a major cause attributed to the increased maternal mortality and morbidity associated with Cesarean sections. Uterine atony is considered as a prime factor leading to post partum haemorrhage. The correct use of an uterotonic agent such as Oxytocin during cesarean sections is vital for the prevention of PPH. Routinely following delivery of the baby active management of 3rd stage in labour, which includes the use of an uterotonic agent, controlled cord traction and early cord clamping results in less blood loss compared to expectant management(1).

Oxytocin is a nanopeptide 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 and is a commonly used uterotonic agent. Oxytocin is associated with increased risk of tachycardia, hypotension, nausea and vomiting, and burning chest pain. These side effects are likely to be more common in intravenous route due to rapid entry into the systemic circulation. Intramyometrial oxytocin (IMO) may be used in the treatment of post-partum haemorrhage. However intramyometrial Carboprost (prostaglandin F2alpha) is the only drug recommended in management of PPHdue to uterine atony(2). Studies have shown that intramyometrial Carboprost may not be more effective than intramyometrial Oxytocin(3). Therefore the use of intramyometrial Oxytocin for prevention of PPH is justifiable. Furthermore it is likely to have a reduced side effect profile compared to intravenous Oxytocin(IVO) due to localized administration.

At Caesarean section (CS) the operator has free access to the uterus enabling direct injection of Oxytocin into the myometrium a favourable option compared to intravenous administration. Limited data is 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 Organization(4). Although a study was available comparing Oxytocin infusion and intramyometrial' use only two studies have compared the recommended Oxytocin intravenous bolus dose with intramyometrial route. In one of these studies too the intramyometrial dose used may be higher than actually required. Furthermore the effectiveness of intramyometrial oxytocin in the Sri Lankan population is unknown. Therefore it was worthwhile to study and assess the effectiveness of intramyometrial Oxytocin against intravenous route during Cesarean sections in the Sri Lankan population. The null hypothesis of the study wasthat intramyometrial Oxytocin was not as effective as intravenous Oxytocin bolus during routine Caesarean section.

SECTION - 2

Literature Review

According to the World Health Organization 830 women die each day due to pregnancy, child birth and related complications. The global maternal mortality ratio(MMR) in 2015 was estimated as 239 maternal deaths in 100,000 live births, in developing countries where 99% of maternal deaths take place(5). With regards to achieving the sustainable developmental goal3, which is to reduce MMR to less than 70 per 100,00 live births by the year 2030prevention of PPH is highly important(5). The main cause of maternal mortality worldwide is postpartum haemorrhage which is responsible for nearly 25% of maternal deaths world wide(6). Uterine atony is considered as the commonest cause of PPH, which is preventable by active management in the third stage(AMTS) which includes the use of an uterotonic agent, in addition to controlled cord traction and early cord clamping. These measures are capable of reducing PPH by nearly 60%(7).

Oxytocin has a high therapeutic index and in addition to treatment of post partum haemorrhage its use as a prophylactic utero tonic agent is justified as well(8). Oxytocin can be considered as an initial option for the prevention of uterine atony in patients undergoing Cesarean sections. The NICE guidelines in United Kingdom recommend the intravenous administration of 5IU of Oxytocin during a Cesarean section(9). However intravenous Oxytocin during Cesarean sections is associated with side effects such as tachycardia, hypotension, decreased cardiac output which are dose related and can lead to haemodyamic instability especially in a already haemodynamically compromised patients(10). Other side effects of Oxytocin include nausea and vomiting, arrhythmias and hyponatremia(11). 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 while causing minimal discomfort to the patient by minimum unwanted effects.

Limited studies are available on the use of intramyometrial Oxytocin and their effectiveness. There were no systematic reviews on intramyometrial Oxytocin use in literature. A study conducted in 1990 compared intramyometrial Carboprost (prostaglanidin F2α) 125 μg with intramyometrial Oxytocin 20IU in relation to blood loss. The effectiveness of Carboprost was similar to that of intramyometrial Oxytocin (3). In a multicenter study conducted in the United Kingdom on Cesarean hysterectomy it was found that intramyometrial Oxytocin was administered in 9% of cases as a medical measure for preventing Cesarean hysterectomy and control of bleeding. This method was more commonly used than uterine packing (6%) and internal iliac artery ligation(4%)(12).

Another randomized control study conducted by Dennehy et al in 1998 found that intramyometrial Oxytocin dose of 20IU caused a transient hypotension which was more severe when compared to intravenous 5IU Oxytocin bolus. The study further concluded that the uterine contractility caused by intravenous and intramyometrial Oxytocin was similar and the use of intramyometrial Oxytocin should be cautioned in the treatment of uterine atony as it may aggravate the preexisting hypotension in PPH(13).

Another prospective randomized control study compared the effectiveness of intravenous Oxytocin infusion with Intramyometrial Oxytocin both before and after delivery of the placenta in approximately 150 women delivering by elective Cesarean section. This study concluded that intramyometrial Oxytocin administered during Cesarean section, before delivery of the placenta is more effective in increasing uterine contractility than intravenous Oxytocin infusion and is associated with reduced blood loss. Intramyometrial Oxytocin was also shown to have reduced side effects such as hypotension, nausea and vomiting. In regards to haemodyanmicparamteresthe authors observed that blood pressure decrease and heart rate increase associated with IMO was less than IVO infusion(14).

A double blind randomized trial on IMO and IVO during elective Caesarean section was conducted by Akinaga et al involving 40 women. Half were given IMO and other half were administered IVO 0.07IU/kg after umbilical cord clamping. Both groups received a slow infusion of Oxytocin 0.1U/kg thereafter. The authors reported a delayed effect in in the IMO group with up to 10 minutes delay in achieving a satisfactory uterine contraction. The IVO group in contrast achieved a satisfactory contraction within 2 minutes. However, there was no difference in the blood loss between the two groups. They further observed the haemodynamic effects were similar between the two groups with IMO effects manifesting later than IVO, similar to the effect on contractility(15).

SECTION -3

Objectives

The study was conducted to test the hypothesis that intramyometrial oxytocin is more effective than intravenous oxytocin.

3.1 General Objective

To assess the effectiveness of intramyometrial injection of oxytocin to intravenous oxytocin bolus during elective Caesarean section.

3.2 Specific Objectives

1. To compare the changes in blood loss between those who received intramyometrial injection of oxytocin and those who received intravenous oxytocin bolus during Cesarean section, by utilizing haemoglobin, haematocritt, and gravimetric estimation methods

2. To compare the occurrence of side effects such as nausea and vomiting, changes in haemodynamic parameters during intravenous oxytocin bolus against intramyometrial oxytocin.

3. To compare the contractility of the uterus between those who received intravenous oxytocin bolus to those who received intramyometrial oxytocin.

SECTION-4

Material and Methods

4.1 Study Design

Aplacebo controlled, double blind, parallel group, clinical trial with balanced randomizationcontrol (1:1) was conducted.

4.2 Study Setting

The study was conducted at Teaching Hospital, Kandy. This is a tertiary care hospital in the Central Province of Sri Lanka, governed by the Ministry of Health. There are approximately 420 deliveries per month with a total Caesarean section rate of 30% per month of which 10% are elective Caesarean sections.

4.3 Study population

Mothers undergoing elective Caesarean section between January 2015 to April 2015at Teaching Hospital Kandy were assessed for eligibility to participate in the study using the following inclusion and exclusion criteria.

4.3.1 Inclusion criteria

Term mothers at 37-41 weeks of gestation with an uncomplicated pregnancy who are awaiting elective Cesarean section were included for the study.

4.3.2 Exclusion criteria

All emergency Cesarean sections

Diagnosed Placenta Previa

Diagnosed Polyhydroamnios

Patients refusing spinal anesthesia

Uterine fibroids complicating pregnancy

Diagnosed Heart disease

Diagnosed hypertensive disease in pregnancy

Multiple pregnancy

Diabetes mellitus in pregnancy

Suspected fetal macrosomia

Refused or failed spinal anesthesia

Patients who developed hypotension as a result of spinal anesthesia and require ephedrine within 10min of delivery.

The decision for elective Cesarean section was made by a Consultant Obstetrician and Gynaecologist in the ward or antenatal clinic. Once the decision was made the mother was approached by a nursing officer in the unit to to ask if they were willing to participate in the study. If yes, a medical officer described the study including the procedures, risks / benefits and voluntary participation and withdrawal.

4.4 Sampling

4.4.1 Sample selection

Pregnant women who were undergoing Elective Caesarean section who fulfilled the above inclusion criteria were selected for the study.

4.4.2 Sampling technique

Patients were allocated randomly into two groups using computer generated random number tables and block randomization by in ward medical officers. Investigator, surgeon and patients were blind to the randomization process. 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.

4.4.3 Sample size calculation

$$N = \frac{2c}{\delta^2} + 1 \qquad \delta = \frac{\mu 1 - \mu 2}{\sigma}$$

C = 10.5 for power of the study90%

μ1= mean of group 1

μ2 = mean of group 2

σ = common standard deviation

$$(\delta)0.8 = \frac{606 - 460}{171.8} \qquad N = \frac{2x10.5}{0.8^2} + 1 = 34 \text{ per group}$$

Power of the study	90%
Mean of group 1	606
Mean of group 2	460
Common standard deviation(SD)	171.8

Data of the similar study done by DivyaMangala et al, was utilized to set the power of the study at 90% and a significance level of 0.05 to minimize α and β errors, a sample size of 68 was calculated with 34 participants for each of the two groups.

4.5 Method

Each mother underwent a detailed medical history and examination. The parity, gestation, indication for Cesarean section and significant risk factors were recorded along with basic demographic details. Baseline systolic and diastolic blood pressures were recorded. The pre-operative haemoglobin and haematocrit estimation were be done on the day prior to surgery. Informed written consent was obtained prior to the Caesarean section.

At the time of recruitment, a sealed envelope containing a labeled tag as either A or B was provided to each participant. A medical officer not participating in the surgery nor involved in the study analysis, in the presence of the anesthetist prepared a sealed plastic bag containing two syringes of 5ml and 10ml each for concealment of allocation within the theatre. The 5ml syringe was used for intravenous administration and the 10ml syringe for intramyometrial administration. These were prepared immediately prior to the Cesarean section in the presence of the anesthetist who was not blinded.

One group received a bag with a 5ml 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 other 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 blinded to the treatment received. The anesthetist was not blinded to the drugs administered, dose and the route each drug was administered at all times, in view of patient safety.

Prior to the surgery systolic and diastolic blood pressures and heart rate were recorded by the anesthetist. Spinal anesthesia was given by administering heavy bupivacaine 0.5%to the T12- L1 space and patient was positioned supine with a left tilt of 15° to avoid supine hypotension. The surgeon conducted a lower segment Cesarean section. 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 clampingover 2 minutes while the anesthetist administered the intravenous preparation over 2 minutes. Blood loss following administration of intravenous and intramyometrial preparations was collected to a separate suction apparatus. The contractility of the uterus was assessed by the surgeon at 1,5 and 10 and 15min intervals following administration of Oxytocin and recorded in a scale of 1 to 5. The same surgeon conducted the surgery in

all patients using the same technique to minimize variation. The anesthetist recorded the heart rate, blood pressure with the monitor. Presence of chest pain, nausea and vomiting during the surgery was recorded by a medical officer. The per vaginal blood loss within 1hr after the surgery was assessed.

Each patient underwent haemoglobin and haematocrit estimation on the 1st post-operative day. Further the volume of IV fluids infused post operatively was recorded. The need for a second uterotonic agent or additional surgical measures such as compression sutures, balloon tamponade within 24hrs was noted.The need to use of additional antiemeticswas recorded as well. Blood loss was estimated by using gravimetric methods and heamoglobin and haematocrit. 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 = 1ml of blood). Pre and post operative haematocrit was used to measure the allowable blood loss using the following formula.

Allowable blood loss (ABL) = EBV x (Hi-Hf)/Hi

EBV = body weight x 65ml/kg

Hi – initial Haematocrit

Hf – Final Haematocrit

e. Outcome measures

Primary outcome:

The primary outcome of the study was to compare the blood loss in the two study populations. However visual estimation of blood loss is considered to be inaccurate and is advised to be avoided in research studies(16). Visual methods underestimated blood loss when compared to simulated volumes(6). The best method for assessment of blood loss includes photometric measurement of alkaline heamatin(17) or the use of dilution techniques. Considering these factors the pre operative and post operative haematocritt values which are more objective were used to calculate allowable blood loss in addition to gravimetric methods using guidelines specified in article by Bose et al in British Journal of Obstetrics and Gynaecology(18).

Secondary outcome:

Patients vital parameters such as pulse rate, systolic and diastolic blood pressures, mean arterial pressures were recorded as the haemodynamic parameters.The need for additional uterotonic agents within 24 hours of delivery and additional surgical maneuvers such as balloon tamponade were assessed as an indicator of insufficient contractility. Contractility of the uterus was assessed by the surgeon at 1,5,10 and 15min intervals and was rated on a scale of 1 to 5.Presence of nausea, vomiting, chest pain, palpitations and the need for additional antiemeticswere recorded as further secondary outcomes.

f. Statistical analyses and plan of presentation of results

Data obtained were analyzed using IBM SPSS statistics software version 24. Basic demographic features were analyzed using independent sample t test. The blood loss, changes in 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 distribution. Uterine tone scores were assessed using Mann Whitney U test.The need for additional uteto tonic agents and occurrence of side effects were assessed using

Chi square tests. In each statistical test a p value less than 0.05 was considered to be statistically significant.

g. Ethical considerations

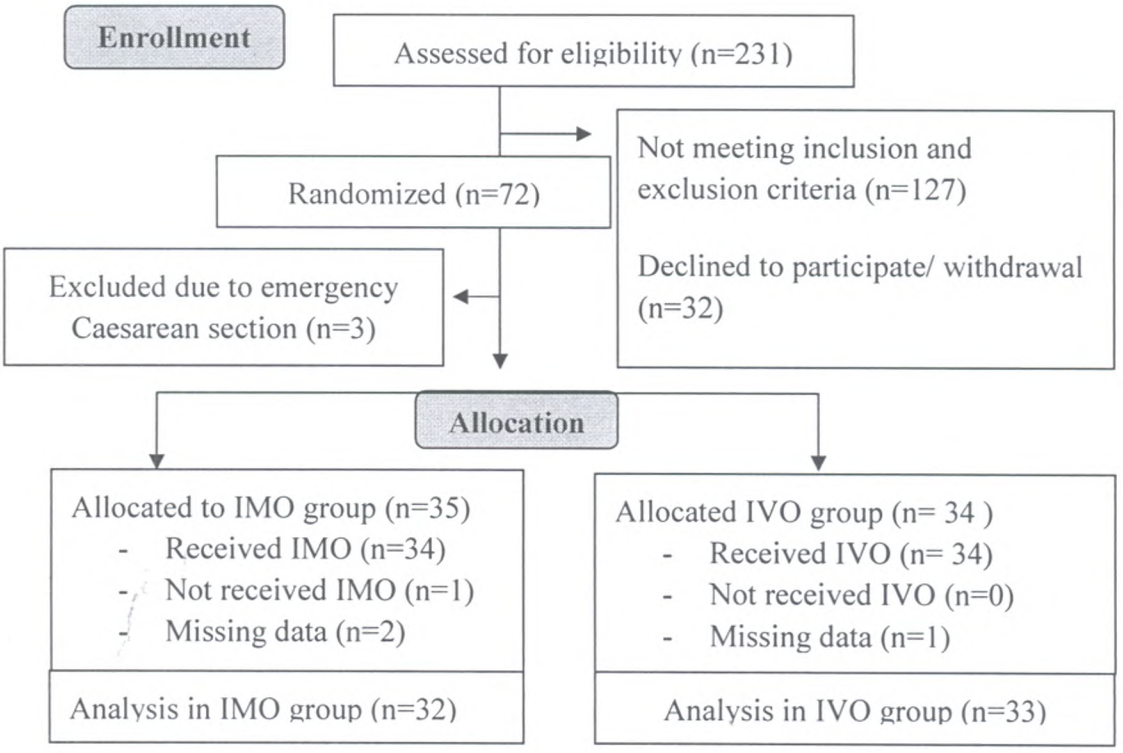
Antenatal mothers admitted to ward 05, teaching hospital Kandy, and who are eligible were approached by the investigator and information regarding the study was provided. Any clarifications and questions regarding the study posed by expected participants were explained by the investigator at that time. Participation for the study was voluntary and informed written consent was obtained. The participants were made aware that they may withdraw from the study at any point. The management of the patients were not compromised on their decision to accept or decline participation. Although the participants were blinded to the treatment and placebo, as the participants were given 0.9% saline as placebo solution and in small volumes, they were not adversely affected. Furthermore anesthetist were not blinded to the drugs received ensuring patient safety throughout the study. Ethical approval for the study was obtained from Ethical Review Committee, Kandy Society of Medicine. Permission to conduct the study was obtained from the Director, Teaching Hospital Kandy and consultant of the respective unit. Data obtained from the study was entered into a computer data base and was kept confidential with access only to the investigator.

SECTION – 5

Results

Within the study period of January 2015 to April 2015, 231 patients were assessed for eligibility to participate in the study. However only 104 were eligible to participate in the study. 28 women did not provide consent while 4 patients withdrew from the study after providing consent. From the remainingparticipants 3 patients had to undergo emergency Caesarean section while awaiting elective Caesarean section. 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 while 33 were in the intravenous Oxytocin (IVO) bolus group.

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



IMO – intramyometrial oxytocin, IVO- intravenous oxytocin

There were no significant differences in the demographic characteristics such as age, parity, period of gestation, maternal and neonatal weights between the two groups. (Table 1). 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 first or second pregnancy. The median gestation was 39 weeks.

Table1: 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), $p<0.05$

There was no statistically significant difference in total blood volume, pre operative haemoglobin, haematocrit, pulse rate, systolic and diastolic blood pressures between the two groups (Table 2).

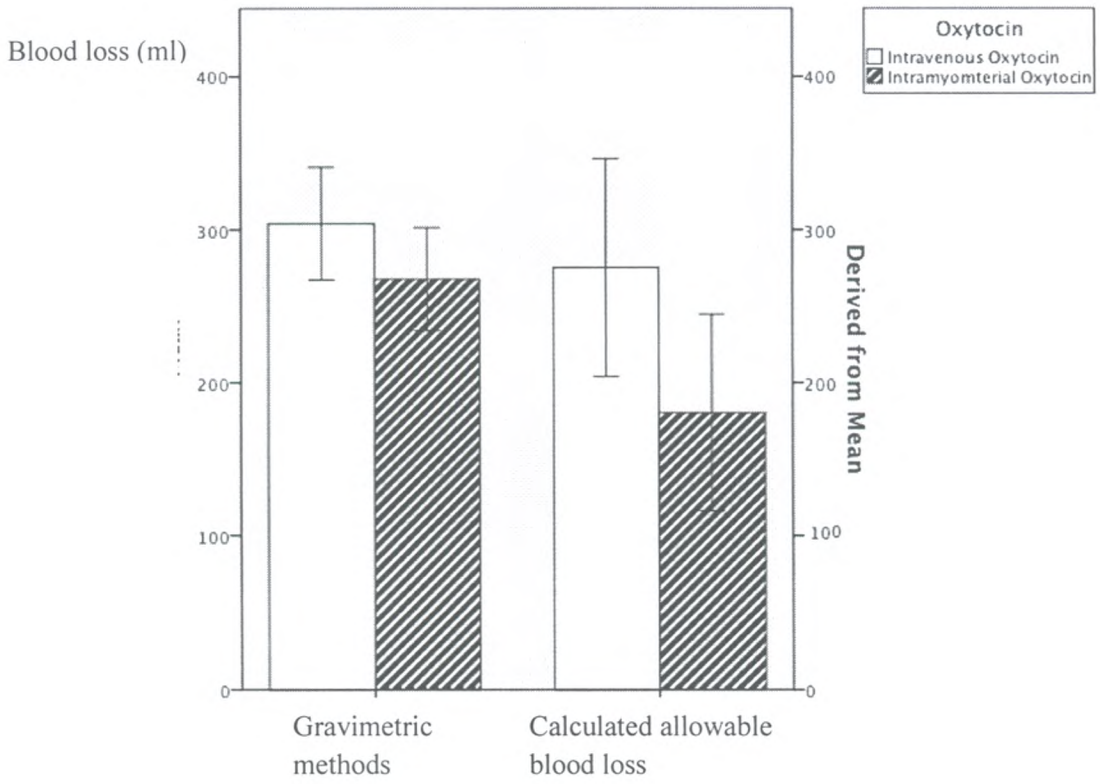
Table 2: Baseline clinical and laboratory haemodynamic parameters between the two groups

	IVO bolus group (n=33)	*IMO group (n=32)*	*P value*
Total blood volume (ml)	4120.60 (±476.52)	4143.75 (±573.11)	0.56
Pre operative Haemoglobin (g/dl)	11.54 (±0.98)	11.66 (±0.95)	0.61
Pre operative Haematocrit(%)	36.61 (±2.94)	36.32 (±3.16)	0.97
Preoperative pulse rate (bpm)	85.03 (± 8.97)	82.94 (±6.81)	0.33
Pre operative SBP (mmHg)	115.79 (±13.23)	124.06 (±10.64)	0.21
Pre operative DBP (mmHg)	71.55 (±9.26)	71.94 (±8.01)	0.22

Data presented as mean(± standard deviation)

The primary outcome, which was the mean blood loss between the two groups were comparable. Blood loss estimated through gravimetric methods was 303.83 (±103.77)ml in the IVO group and 267.65 (±93.53)ml in the IMO group, although it was not statistically significant(p= 0.43). The mean allowable blood loss calculated using the haematocrit in the IVO group was 275.06 (±200.66)ml while in the IMO group it was 180.8 (±178.28)ml, which was not statistically significant as well(p= 0.09). Blood loss >500ml occurred in 4 (12.1%) in the IVO group while only in 1 (3.1%) in the IMO group (p=0.17). There was a statistically significantdecrease of the post operative haemoglobin valuesin the IVO group of 0.93 (±1.02)g/dl,compared tothe IMO group which had a decrease of 0.57 (±0.70)g/dl (p=0.02). The mean decrease in haematocrit in pre operative and post operative samples were similar between the two groups.In the IVO group it was 2.48 (±1.73)% and in the IMO group it was 1.58 (±1.46)% (p=0.16).

Figure 2 : Blood loss following oxytocin administration at Caesarean section between the two groups, measured through gravimetric methods and calculated allowable blood loss



The strength of uterine contractions, which was used as a secondary outcome measure on effectiveness of oxytocinmeasured at 1 and 5minutes following injection of Oxytocinwere similar in both groups (Table 3). However, at both 10 and 15 minutes in the IMO group the median score was increased to 4 and contractility was significantly higher,in the IMO group than IVO group which had a median score of 3 at these time intervals.

Table 3: Median contraction scoresbetween the two groups following oxytocin

Time interval	**IVO group (n=33)**	**IMO group (n=32)**	**P value**
1min	3	3	0.09
5 min	3	4	0.20
10min	3	4	0.002
15min	3	4	0.002

The need for additional uterotonics and mechanical compression by tamponade or compression sutures, which were secondary measures of effectiveness was similar between the two groups. In the IVO group 16 (48.5%) required additional uterotonic agents, while in the IMO group only 8 (25%) required further uterotonics (p=0.05). Mechanical means of uterine tamponade was required in 1 patient (3%) in the IVO group and none in the IMO group (p=0.98).

The side effects of Oxytocin by different routes were compared as a secondary outcome measure on the effectiveness of IMO and IVO which is summarized in table no 3. The commonest side effect observed in the IVO group was chest pain (21.2%) while in the IMO group it was nausea (21.9%). The side effect profile of oxytocin by either route of administration was similar to each other.

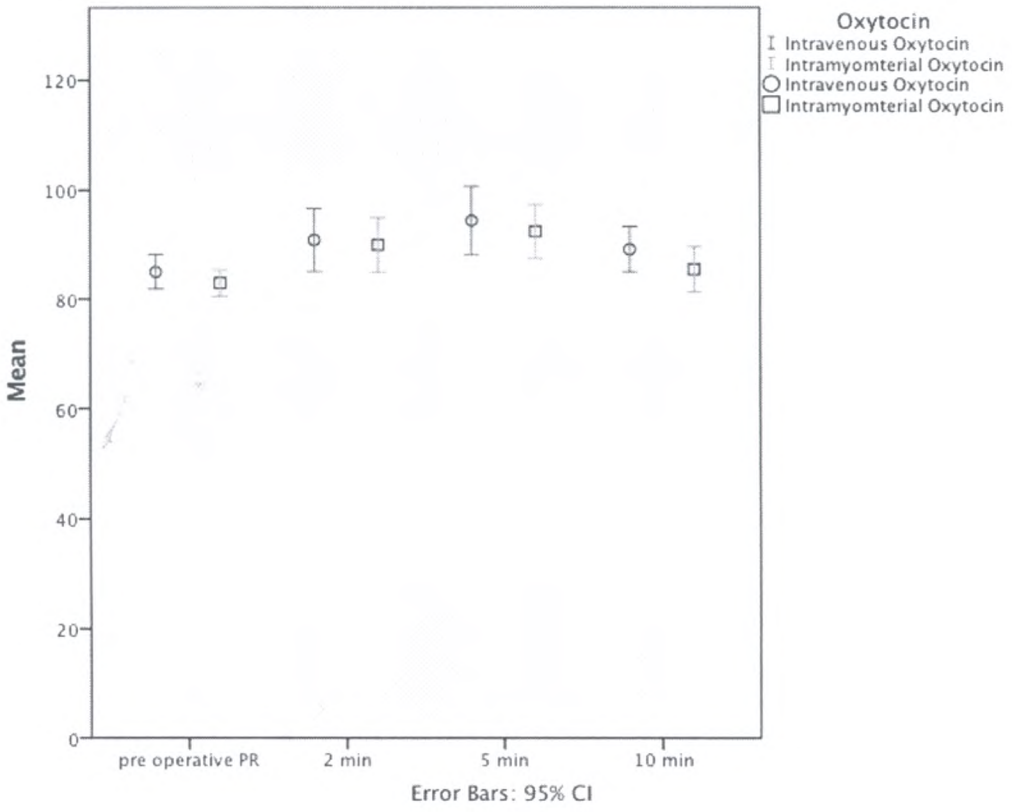
Table 4 : Side effects following oxytocin administration by either route.

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%)

There was a increase in the heart rate in both IVO and IMO groups at 2 minutes and 5 minutes, 10 minutes following drug administration. The heart rate was highest at 5 minutes in both groups, with a mean increase of 9.36 (±15.30) beats per minute (bpm) in the IVO group and an increase of 9.46 (±13.06)bpm in the IMO group. Overall there was no difference between the two groups in the increase in heart rate at 2, 5 and 10 minutes (p= 0.40, 0.67, 0.65)

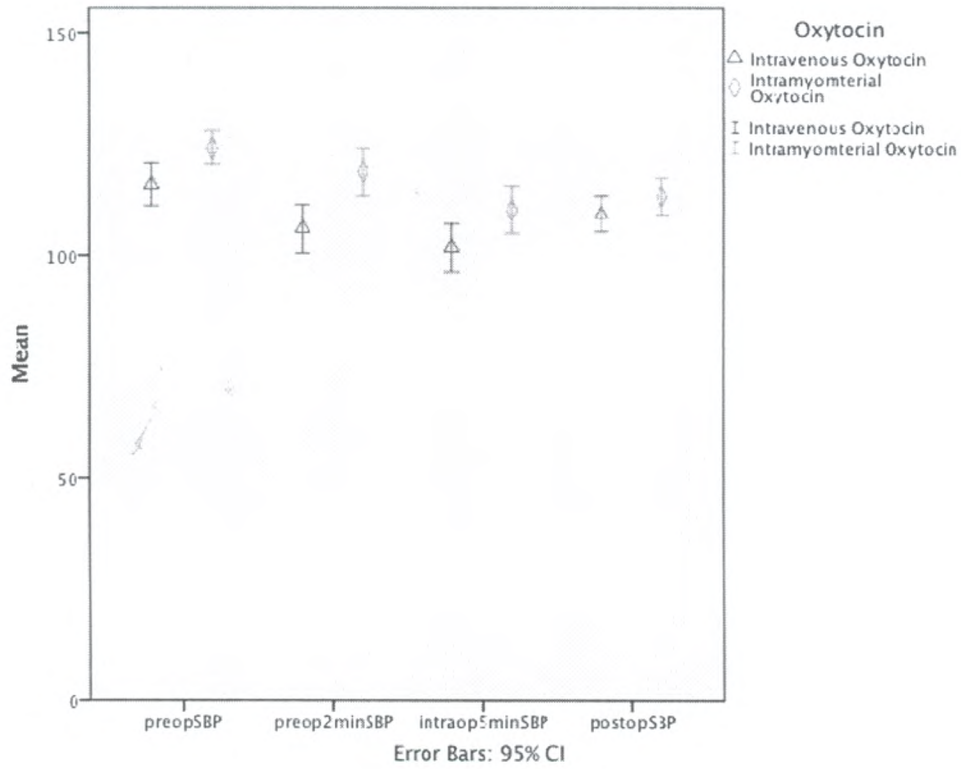
Figure 3: Mean heart rate with time following oxytocin administration in IVO and IMO groups



The systolic blood pressure decreased in both groups following oxytocin administration. In the IVO group the decrease was highest at 5 minutes, with a decrease of 14.03 (±19.74)mmHg. Only a mean decrease of 9.81(±18.51)mmHg and 6.48(±15.74)mmHg of systolic blood pressure occurred at 2 minutes and 10 minute in the IVO group. In the IMO group the decrease in systolic blood pressure was highest at 5 minutes with a mean

decrease of 13.9 (±17.12)mmHg, while at 2 minutes and 10 minutes it was 5.40 (±14.88)mmHg and 10.84 (±16.23)mmHg. There was no difference in the systolic blood pressures between the two groups at 2 minutes (p=0.15), 5minutes (p=0.53) or 10 minutes (p=0.64).

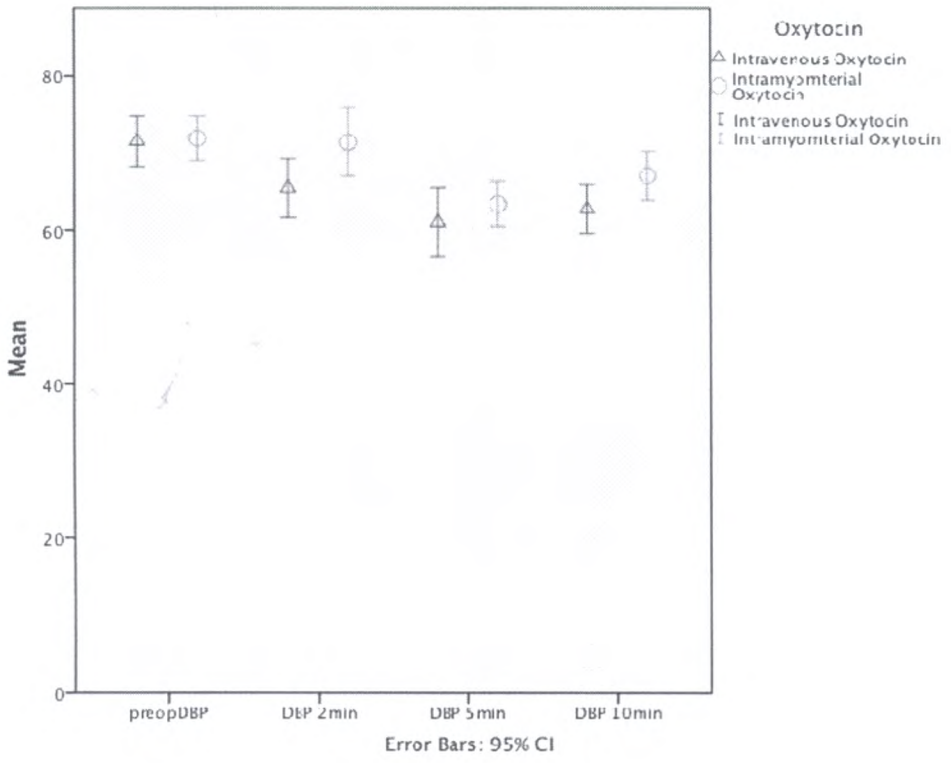
Figure 4 : Mean systolic blood pressure changes with time following oxytocin administration in IVO and IMO groups



The diastolic pressures too decreased following oxytocin administration in both groups. In the IVO group the highest mean decrease occurred at 5 minutes which was 10.54 (±18.03)mmHg. At 2minutes and 10 minutes the mean decrease was 6.63 (±14.41)mmHg and 9.33 (±13.01)mmHg respectively. Although the decrease in diastolic blood pressures in the IMO group was highest at 5 minutes as well with a mean decrease of 8.56

(±11.35)mmHg, it was significantly less than the decrease observed in the IVO group (p=0.01). At 2 minutes and 10 minutes the mean decrease in diastolic blood pressures were 0.53 (±11.33) mmHg and 4.87 (±11.35)mmHg in the IMO group and similar to IVO group at these intervals (p = 0.06, p= 0.75).

Figure 4 : Mean diastolic blood pressure changes with time following oxytocin administration in IVO and IMO groups



SECTION-6

Discussion

Considering the effectiveness of intramyometrial oxytocin and intravenous oxytocin during elective Caesarean section, this study does not show any statistically significant difference in either route of administration in terms of blood loss or side effect profile.However, intramyometrial oxytocin was more effective than intravenous oxytocin in regards to uterine contractility, at 10 and 15 minutes following administration. Intramyometrial oxytocin use resulted in more stable post operative haemoglobin levels compared to intravenous route. Despite similar decreases in blood pressures and increases in heart rate, IMO had more stable diastolic blood pressures at 5 minutes.

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. Further more, due to minimal systemic availability of Oxytocin with intramyometrial administration it was expected that IMO would cause less side effects including hameodynamic disturbance, compared to IVO. Yet the findings from this study indicate that such localized effects are not apparent in the doses of Oxytocin studied, particularly in relation to blood loss.

At Caesarean section Oxytocin is administered as part of active management to ensure adequate uterine contraction following delivery and to minimize blood loss due to reduced uterine contractility. The two groups had similar blood loss, assessed by both gravimetric and allowable blood loss calculation methods. This finding was similar to a double blind randomized control trial conducted by Akinaga et al who, compared IMO and IVO at a dose of 0.07IU/kg during Caesarean section measuring blood loss as a secondary outcome. Their study demonstrated similar blood loss between the two groups as well. 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. Further more in their study in regards to uterine contractility, IMO resulted in a delay in causing effective uterine contractions of 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 group(15). In our study too althougha similar delayed contractility was observed in the IMO group it was overall more effective than the IVO. Yet this increased contractility did not translate into a resultant decrease in blood loss in the IMO group. Akinaga et al in their study, used a continuous low dose oxytocin infusion routinely, in both groups in addition to the initial bolus dose. This might have contributed to additional effect in the intravenous group. This limits the comparability of Akinaga et al results with the current study which only used the initial bolus dose of oxytocin and subsequent doses used if clinically indicated only as second line.

Conversely a prospective randomized control study conducted by DivyaMangala et al demonstrated IMO 5IU given prior to placental separation was significantly effective, in regards to blood loss than intravenous 20 IU Oxytocin infusion as well as IMO 5IU administered after separation of the placenta. Although similar intra myometrial dose was used in the current study, the intra venous group differed from DivyaMangala et al as a bolus dose was used rather than an infusion.

Hameodynamic parameters are of importance in administering Oxytocin as it is associated with significant haemodyanmic effects which may increase morbidity in Caesarean section especially in already haemodynamically unstable patients. Dennehy et al observed more severe hypotension with 20IU of IMO compared to 5IU of IVO with comparable contractibility in both groups. The resulting increase in heart rate and decrease in SBP was highest at 1minute following administration and was considered to be due to an immediate absorption of Oxytocin into the systemic circulation. The IMO group in their study received a relatively large dose compared to intravenous Oxytocin

which may be the cause for the significant severe side effects. Akinaga et al in their study demonstrated a 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 may be due to low blood concentrations of Oxytocin after intra myometrial injection, though blood concentrations were not assessed in the study. In contrast DivyaMangala et al observed a significant lesser decrease in blood pressure in IMO group compared to IVO infusion. In our studytoo the decrease in systolic and diastolic blood pressures were highest at 5 minutes in IMO group which may further strengthen the argument of delayed effect on hameodynamic parameters with IMO proposed by Akinaga et al. However, in our study this delayed effect did not appear to have an impact on contractility which may make IMO a more favourable option.IMO was administered to each cornu in our study, while Akinaga et al injected only to the fundus of the uterus. The technique adopted in this study which was similar to DivyaMangala et al may result in a quicker and even spread of oxytocin through out the myometrium potentiating its effect.

In our study although statistically significant decrease in DBP at 5 minutes were observed in the IVO group it may not be clinically significant, considering 10mmHg drop as clinically significant. (95% CI -9.48 to 5.15). Further more the decease in post operative haemoglobin in the IVO group compared to IMO group may not be clinically significant as well. (95% CI -0.80 to 0.07)

SECTION-7

Limitations

There werefew limitations in this study which need to be considered.The estimation of blood loss using gravimetric methods and calculation methods may not be accurate. In spite of measures taken to minimize admixture of amniotic fluid, it could not be completely prevented. Immediate measurement of soaked swabs and towels to minimize the effect of evaporation and using separate canisters to drain the amniotic fluid were used to improve accuracy. Furthermore the measuring staff were blind to the treatment received to minimize bias in measurements. Use of photometric methods were not freely available, but in future studies use of spectrophotometry of alkaline haematin may improve accuracy in blood loss estimation.

Assessment of uterine tone and contractility was subjective. A scoring system was used to add objectivity in assessment. A single surgeon was used to minimize variability. An intrauterine pressure gauge would accurately determine the strength of the contraction and uterine tone objectively.

The oxytocin concentration in the blood was not calculated which would allow to identify the oxytocin available in the systemic circulation after administration by either route. Furthermore in few cases the use of additional uterotonic agents would have influenced the final contractility, blood loss values and have confounded the observations.

In considering the difference in haemoglobin values observed this study did not consider the volume of intravenous fluid infused at the time of surgery which may have a confounding effect on the haemodynamic parameters and the difference in haemoglobin values observed.

The strengths of the study lie in its double blinded nature and randomization.Both groups had similar characteristics pre operatively and therefor can be assumed to be matched for confounding variables which may influence interpretation of the results.

SECTION-8

Conclusions and Recommendations

In conclusion this study assessed the effectiveness of intramyometrial oxytocin against intravenous oxytocin at the time of Caesarean section in terms of blood loss, uterine contractility, side effects and haemodynamic changes. There was no difference in blood loss between the either route although IMO achieved higher contraction scores with a slight delay in effect. Although IVO may be associated with more side effects such as chest pain both routes of administration in the given dose have similar effects on hameodynamic parameters. Oxytocin should be continued to be administered intravenously at the time of Caesarean section, as evidence is insufficient to recommend any change of current practice. Further research on the effectiveness of IMO including the optimum technique of administration, with more accurate blood loss assessment is recommended. A multi center trial with a larger sample size is recommended which will be more sensitive in detecting differences in effectiveness between the two groups.

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5. **Signature of trainee**