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Early versus Delayed Oxytocin Administration during Caesarean Section: A Randomized Controlled Clinical Trial

Heba Mohamed Hamdy*, Hend AbdElrahman Shalaby,
Yasser Mohamed Mosbah, Mohamed Elsayed Taman
Departments of Obstetrics and Gynecology, Faculty of Medicine, Mansoura University, Egypt
***Corresponding author:** Heba Mohamed Hamdy**, Mobile:** (+20) 01099761801, **E-Mail:** hebahamdy1481992@gmail.com

ABSTRACT

Background: Cesarean delivery (CD) is commonly performed operation in modern obstetrics. The risks of cesarean section (CS) include maternal mortality, hemorrhage, venous thrombosis, infections, and anesthetic complications. Oxytocin is the most commonly used ecbolic agent during management of atonic postpartum hemorrhage. The aim of the current study was to compare between the influence of early IV oxytocin infusion early and the standard administration on intraoperative blood loss during caesarean section.

Patients and methods: A randomized controlled clinical trial was conducted at Obstetrics and Gynecology Department of Mansoura University Hospitals. This clinical trial included women aged between 18 and 40 years old admitted for elective CS (low risk). The study population consisted of 80 women who were randomly divided into 2 groups. Intervention group included 40 women who received oxytocin infusion immediately after incision of pelvic peritoneum. Control group included 40 cases who received oxytocin after clamping the umbilical cord.

Results: There was no significant difference between both groups in terms of primary post-partum hemorrhage or the need for blood transfusion. However, the mean intraoperative blood loss was significantly lower among females who received early oxytocin prior to uterine incision as compared to the control group who received oxytocin after fetal delivery.

Conclusion: Early administration of oxytocin (before uterine incision) compared to late oxytocin (after clamping of umbilical cord) is associated with significantly lower mean intra-operative blood loss.

Keywords: Caesarean section, Placenta accreta, Primary postpartum hemorrhage, Oxytocin.

INTRODUCTION

The rate of caesarean deliveries increased from 5.5% in 1970 to 16.5% in 1980, and continued to rise till appearing to have steadied around 31-32% in the US in 2019 [(1)].

Caesarean section (CS) is considered the most common major surgical procedure in Egypt with a rate of 51.8%, making Egypt graded the third top country with the supreme CS rate worldwide [(2,3)].

CS is considered one of the major abdominal surgeries that caries medical hazards to woman's health including; hemorrhage, need for transfusion, injury to other organs, and infections [(4)].

Despite considerable improvements of modern obstetrics care, hemorrhage remains the most important cause of maternal mortality, specifically in developing countries [(5)]. Though post-partum hemorrhage itself might not be preventable, early recognition of blood loss, and enlistment of resources might prevent poor outcome. Multidisciplinary planning at the system level, confirming that hemorrhage protocols are available, as well as for management of high-risk women is significant to improve the outcome [(6)].

Approaches decreasing the intra-operative blood loss are necessary for reducing the risks of blood transfusion and the post-operative complications [(7)]. Primary postpartum hemorrhage (PPH) related to CS (incidence 3-15%) is demarcated as vaginal bleeding ≥500mL within 24 hours after CS in mild cases and ≥1000 ml in severe cases [(8)]. Most of complications of CD could be prevented. The prophylactic use of ecbolics as oxytocin, methylergonovine, prostaglandin E1, and prostaglandin F2-alpha in the third stage of labor diminishes the risk of PPH by nearly 60% [(9)].

Oxytocin is considered as the first-line agent for PPH prevention. Some treatment protocols of oxytocin have been measured during CS, however its ideal dose and infusion rate have not yet to recognized in the literature [(10)].

Notably, this wide use of oxytocin is due to its lesser cost and rapid onset of action. The advantage of oxytocin infusion is in maintaining uterine contraction during CS and immediate post-partum period, and thus decreases the incidence and amount of intra-operative bleeding and PPH [(11)].

The aim of this work was to compare between the influence of early IV oxytocin infusion early (just prior to uterine incision) and the standard administration (following clamping the umbilical cord) on intraoperative blood loss during elective CS.

PATIENTS AND METHODS

Study design

A randomized controlled clinical trial was conducted at Obstetrics and Gynecology Department of Mansoura University Hospitals. This study included women aged between 18 and 40 years old admitted for elective CS (low risk) during the study period 2021/2022.

We excluded patients who refused to be included in the study, patients with uterine overdistension,

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history of medical diseases (such as DM or uncontrolled hypertension or thrombophilia or other blood disorders), on anticoagulant therapy, with placenta accrete spectrum or placental abruption and with previous difficult or complicated delivery.

Study Population

The study population consisted of 80 women who were randomly divided into 2 groups. Intervention group included 40 women who received oxytocin infusion immediately after incision of pelvic peritoneum and just prior to incision of the lower uterine segment. Control group included 40 cases who received oxytocin following umbilical cord clamping.

Studied groups were matched for confounding variables (age, sex, socioeconomic level). Intervention group (*Group A*) received Oxytocin infusion immediately following the incision of visceral peritoneum and just prior to the uterine incision, while control group (*Group B*) received Oxytocin Infusion after clamping of umbilical cord.

Technique

After taking a thorough history from all patients including age, parity and gestational age, the surgery was performed by experienced assistant lecturers and residents under spinal anesthesia.

Oxytocin was administrated either immediately following incision of pelvic peritoneum and just prior to incision of the lower uterine segment (Study group) or following umbilical cord clamping (Control group). The dose given was 20 IU oxytocin (2 ampoules of syntocinon® Novartis, 10 IU/ml, concentrate for infusion), dissolved in 500 ml normal saline 0.9% and infused at a rate of 125 ml/hour.

Evaluation of uterine tone was performed by palpation of its fundus and anterior wall. Uterine suturing was done by continuous unlocked. Packed RBC transfusion and peritoneal closure were done if indicated. Blood loss underwent estimation by towels weighting (dry and socked) and volume of blood in suction apparatus. Blood loss underwent estimation following exclusion of amniotic fluid volume in the suction bottle in each case. The total blood loss was calculated by adding the amount of blood in suction container and blood-soaked towels. Any additional post-operative uterotonic or blood transfusions were recorded. Preoperative and 24h postoperative HB and HCT levels were measured.

Outcomes

The primary outcome was to estimate the difference of intraoperative blood loss between 2 groups. The secondary outcomes were to determine if a significant difference would be detected in the following items; mean amount of post-operative blood loss, mean drop of hemoglobin values, mean difference of Hematocrit values, necessity for blood transfusion and additional uterotonics.

Ethical consideration:

Study protocol was approved by IRB committee in the Faculty of Medicine, Mansoura University. The procedure was explained to each of patients. Informed written consent was obtained from participants with respect to confidentiality and privacy during the study. Data was not utilized for any purpose rather than the current study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were analyzed by utilizing IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, v 22.0. Armonk, NY: IBM Corp. Qualitative data were defined by utilizing number and percent. Quantitative data were defined by utilizing medians and means, SD for parametric data following testing normality by utilizing Kolmogrov-Smirnov test. Qualitative data were utilized and involved Chi-Square test and Monte Carlo test for comparison between at least 2 groups. Independent samples Student's t-test was used to compare between two independent groups of normally distributed variables and Mann-Whitney U test for non-parametric data. P-value was set at ≤ 0.05 for significant results.

RESULTS

There were no statically significant differences between both groups base line data including' age, occupation, or number of previous deliveries. Also, neither method of induction of abortion, nor number of previous abortions, could lead to a significant difference between both groups. As included subjects were medically and surgically free, this rendered these two parameters insignificant between the two groups (**Table 1**).

Table (1): Sociodemographic and clinical data in the study groups.

Variable	Intervention Group (n= 40)	Control Group (n= 40)	P-value (NS: Non-significant)
Age (Years)	25.05 ± 4.47	25.70 ± 5.36	0.55 (NS)
Primigravida	17 (42.5%)	10 (25%)	0.09 (NS)
Multigravida	23 (57.5%)	30 (75%)	
Previous abortion			
Once	7 (17.5%)	6 (15%)	0.72 (NS)
Twice	1 (2.5%)	0 (0%)	
Method of induction of abortion			
Medical	1 (2.5%)	1 (2.5%)	0.76 (NS)
MVA	4 (10%)	1 (2.5%)	
Spontaneous	3 (7.5%)	4 (10%)	
Medical history			
Free	40 (100%)	40 (100%)	1 (NS)
Surgical history			
Free	24 (60%)	29 (72.5%)	0.36 (NS)
Positive	1 (2.5%)	1 (2.5%)	

No statistically significant difference was detected between the two groups in terms of the number of previous CS, duration since last CS, or place of delivery. Also, different forms of outcome from previous deliveries yielded insignificant difference between both groups (**Table 2**). A non- significant difference was detected between both groups when the indication for CS was statistically assessed (**Table 3**).

Table (2): Data analysis of previous cesarean deliveries.

Variable	Group 1 (n= 40) [Early oxytocin]	Group 2 (n= 40) [Delayed oxytocin]	P-value (NS: Non-significant)
Number of previous CS	23 (57.5%)	30 (75%)	0.09 (NS)
Duration since last CS (years)	3.48 ± 0.59	4.13 ± 0.84	0.32 (NS)
Place of previous CS			
MUH	19 (47.5%)	21 (52.5%)	0.13 (NS)
Other governmental hospitals	4 (10%)	9 (22.5%)	
Outcomes of previous deliveries			
Living male	13 (32.5%)	9 (22.5%)	0.2 (NS)
Living female	9 (22.5%)	17 (42.5%)	
Twin	0 (0%)	1 (2.5%)	
IUFD	0 (0%)	1 (2.5%)	

Table (3): Indications of CS in the current pregnancy in the study groups.

Variable	Group 1 (n= 40) [Early oxytocin]	Group 2 (n= 40) [Delayed oxytocin]	Test of significance
Breech presentation	3 (7.5%)	2 (5%)	0.26 (NS)
Contracted pelvis	7 (17.5%)	3 (7.5%)	
Failure to progress in labor	3 (7.5%)	2 (5%)	
Flat CTG	0 (0%)	1 (2.5%)	
Maternal request	1 (2.5%)	1 (2.5%)	
Postdate	3 (7.5%)	1 (2.5%)	
Previous scar	23 (57.5%)	30 (75%)	

*NS: Non-significant

The intra-operative blood loss, was statistically significant lower in the study group (early oxytocin) as compared to control group (late oxytocin) (418 ml vs 511 ml, respectively). A non- significant difference existed between both groups regarding the average post-operative blood loss or the need for blood transfusion.

No cases of blood loss > 1000 ml were reported in the study groups. No sepsis or PPH was detected in both groups. No women in both groups needed administration of additional uterotonics. A significant difference existed between pre- and post-operative HB values in the same group.

A significant difference existed between pre- and post-operative HCT values in the same group. A non-significant difference existed between early and late oxytocin regarding the percentage of postoperative drop in HB and HCT values (**Tables 4 and 5**).

Table (4): operative and postoperative data of the study groups.

Variable	Early oxytocin Group (n= 40)	Delayed oxytocin Group (n= 40)	Test of significance
Intraoperative blood loss (ml)	418.50 ± 42.03	511.50 ± 35.34	< 0.001 (HS)
Postoperative blood loss (ml)	15.25 ± 3.73	15.13 ± 3.30	0.88 (NS)
Units of transferred packed RBCs units			
1 Unit	2 (5%)	5 (12.5%)	0.28 (NS)
2 Units	0 (0%)	1 (2.5%)	
Incision to delivery time (min)	4.90 ± 1.17	4.95 ± 1.01	0.83 (NS)

Table (5): Hemoglobin and hematocrit levels before and after delivery.

Variable	Early oxytocin Group (n= 40)	Delayed oxytocin Group (n= 40)	Test of significance
Hemoglobin			
Pre-operative haemoglobin (gm/dl)	11.46 ± 0.73	11.13 ± 0.73	
Post-operative haemoglobin (gm/dl)	10.83 ± 0.78	10.43 ± 0.75	
P1	< 0.001 (HS)	< 0.001 (HS)	
Percentage of change in hemoglobin			
Mean ± SD	-5.53 ± 1.98	-6.17 ± 5.86	0.51 (NS)
Range	-8.33: 0.86	-10: 34.75	
Haematocrit			
Preoperative hematocrit (%)	35.58 ± 2.28	34.30 ± 2.19	
Postoperative hematocrit (%)	33.52 ± 2.43	32.22 ± 2.31	
P1	**< 0.001** (HS)	**< 0.001** (HS)	
Percentage of change in haematocrit			
Mean ± SD	-5.78 ± 2.51	-5.90 ± 6.69	0.91 (NS)
Range	-13.07: 0.52	-10.99: 30.36	

P1: Comparison between preoperative and postoperative value in each group. S: Significant. HS: Highly significant. NS: Non-Significant

DISCUSSION

Cesarean delivery is commonly practiced operation in modern obstetrics. Its rates are increasing not only in both the developed and developing countries [(12)]. However, CS is not without risks, which include maternal mortality, hemorrhage, venous thrombosis, infections, as well as anesthetic complications. Intra-operative complications include damage to neighboring organs, such as bladder, ureter or bowel, as well as inadvertent damage of uterus or cervix [(13)]. Oxytocin is highly effective agent in prevention and treatment of atonic postpartum hemorrhage and thus decreasing maternal mortality rate [(12)].

In this study, we included 80 pregnant women who met the inclusion criteria. All participants in our study were at term (>37 weeks) with low risk for PPH, and all CS were performed under spinal anesthesia. Every case received 20 IU of oxytocin (2 ampoules of syntocinon® Novartis, 10 IU/ml, concentrate for infusion), dissolved in 500 ml of normal saline 0.9% and infused at a rate of 125 ml/hour. This study was conducted to compare the effect of oxytocin administration at different times during CS.

The main result was the amount of intraoperative blood loss. Other results included drop of HB level and HCT values, and whether or not there was a necessity for additional uterotonics or blood transfusions. Comparison between both groups regarding the basic characteristics including age, gravidity, parity and associated medical diseases revealed no statistically significant differences (P >0.05). This was done to assure that both groups are well-matched regarding these data.

A randomized controlled clinical trial was conducted by **Abdelaleem *et al.*** [(14)] to study the effects of early and late oxytocin on the amount of intra-operative blood loss. A total of 200 pregnant women scheduled for CS at term gestation were subjected to either early IV oxytocin administration prior to uterine incision (Group I) or delayed administration after umbilical cord clamping (Group II). The drop of pre- and postpartum HB and hematocrit values were not statistically significant different in 2 groups. There was a significant decrease in intra-operative blood loss in group I in comparison to group II (432.7 ± 90.6 versus 588.9 ± 96.3 mL respectively, p= 0.001). Both groups showed non-significant differences in terms of the necessity for blood transfusions or other surgical interventions.

We used a different oxytocin dose in our study (20 IU). Our results matched with previous study as regard to the significant decrease in introperative blood loss in Group I (418 ml) in comparison to Group II (511 ml). We found a significant difference between pre- and post-operative HB and HCT, as both values dropped significantly in both groups, and no significant difference existed between early and late oxytocin groups as regards the change of HB level and HCT values.

Another study was conducted by **Ozcan *et al.*** [(10)] to evaluate efficacy of early IV oxytocin infusion prior to uterine incision on the volume of intra-operative blood loss in 101 females aged 18–40 years who had CS. Every participant received 20 IU dissolved in 500 mL of normal saline 0.9% and infused at 125 mL/h. The women were divided into 2 groups. In Group I (51 women), oxytocin infusion was initiated immediately following incision of visceral peritoneum and just prior to uterine incision. In Group II (50 women), infusion was initiated immediately following umbilical cord clamping. They concluded that early oxytocin was a better and more effective alternative to late oxytocin. This was in agreement with our results.

Rajan and Gopu [(15)] conducted a study on 200 patients scheduled for elective and emergency CS. Participants were allocated in 2 groups, one group received 100 ml normal saline (NS) without 2 U of syntocinon and other Group received 100 ml NS with 2 U of syntocinon. Infusion rate was 30-50 drops/ min, given directly after the subarachnoid block in both groups. The authors concluded that peri-operative syntocinon infusion before uterine incision is effective in maintaining vital signs, uterine contractility and decreasing blood loss, without change in APGAR scoring. Our study matched with the previous study as regard to the benefits of early oxytocin infusion in lowering intraoperative blood loss and PPH.

Tharwat *et al.* [(16)] study evaluated the effectiveness of early IV oxytocin infusion at induction of anaesthesia in reducing blood loss in 300 women planned for CS. Women in group A (150 women), are given IV oxytocin infusion (10 U) in 200 ml of lactated Ringer's over 15 min prior to skin incision during induction of anesthesia while in group B (150 women) oxytocin was initiated following fetus delivery. They found that women in group A had a lower blood loss and thus a less incidence of PPH with lower alterations in hemodynamic state and no adverse fetal outcomes.

In our study, we used 20 IU instead of the 10 IU used in the previous studies and oxytocin was administrated just before uterine incision instead of being applied during anesthesia administration. Our findings were in agreement the previous study regarding the beneficial effect of early oxytocin as compared to late oxytocin, in reducing intraoperative blood loss.

In conclusion, early administration of oxytocin (before uterine incision) compared to late oxytocin

(after clamping of umbilical cord) is associated with significantly lower mean intra-operative blood loss.

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