Pre-incisional Oxytocin infusion in elective cesarean section delivery, maternal and neonatal outcome

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Abstract

Background: Best timing for giving prophylactic oxytocin during cesarean section (CS) to prevent post-partum hemorrhage (PPH) is still a debatable issue.

Objectives: Assess maternal and neonatal effects of starting prophylactic oxytocin infusion just before uterine incision during CS.

Methods: This study is a randomized controlled trial, evaluating best timing of oxytocin administration in cesarean deliveries as regard amount of intraoperative and postoperative estimated maternal blood loss, also evaluated change of pre-operative to post-operative hemoglobin levels, intraoperative maternal nausea and vomiting and immediate postpartum neonatal condition. One hundred and fifty patients had done pre-labor cesarean section, half of participants received oxytocin immediately before uterine incision and the other half received oxytocin in the third stage of labor. The study hypothesized that administering oxytocin immediately before uterine incision, resulted in less overall maternal blood loss, better maternal and neonatal outcome.

Results: Results were pooled, mean, standard deviation, P value and 95% confidence intervals (CI) were calculated. There was a significant reduction in the need for additional uterotonics and also reduced intra-operative and postoperative blood loss and need for blood transfusion, when oxytocin was given immediately before uterine incision versus after fetal delivery.

Conclusion: Immediately pre-incisional oxytocin infusion was superior to post-placental delivery oxytocin infusion as regard additional use of ecbolics in elective cesarean sections, further studies with large sample sizes are needed for further evaluation of other maternal and neonatal parameters.

Keywords: Oxytocin, cesarean section, postpartum hemorrhage, maternal outcome, neonatal outcome.

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Introduction

Inability to have an efficient uterine contractions post-delivery, accounts for 1 every 40 deliveries and accounts for approximately seventy-five percent of postpartum hemorrhage

(PPH) [1]. This is one of the uppermost five reasons for maternal mortality [2].

In the developing countries, around 1.2% of births are complicated by PPH and around three percent of these ladies died [3]. Worldwide, PPH happens 8.7 million times and causes death in 44,000 to 86,000 yearly [3][4][5].

Blood loss and blood transfusion are major problems of CS [2, 6]. The huge hyper-perfusion of uterus (750 mL/min) in third trimester of gestation which is around (10–12% of cardiac output) [1] clarifies the high blood loss during CS (500–750 mL) [7].

In developing countries the rate of CS is high, and Females who deliver by CS are at a greater possibility for postpartum hemorrhage than those who deliver by vaginal delivery [8, 9] [10,11].

The surgeons often undervalued the amount of blood lost during CS [12]. Undervaluing blood loss during CS make ladies at danger of uncorrected blood loss and uncorrected anemia, poor wound healing, surgical site infection (SSI), fatigue, and physical debility [13, 14].

PPH is considered when the amount of blood loss is ≥500 mL after vaginal birth or ≥1000 mL after cesarean delivery [15]. Oxytocin is routinely given in cesarean and vaginal deliveries during the third stage of labor in the United States [15].

The current WHO recommendations, published in 2018, for prevention PPH is 10 IU of intravenous or intramuscular oxytocin for preventing PPH for all deliveries [16].

As the evidence is still lacking, as regards the best timing of oxytocin infusion in cesarean section, this raised the need to perform this randomized controlled study.

Patients and methods

Ethical committee approval of Al Gazeerh hospital was obtained before the study start (Ethical committee approval number 0024886 NTR), also obtaining an informed consent before enrollment of each woman accepting to participate in the study was done, after complete explanation of the procedure to the participant woman.

This randomized controlled trial included one hundred and fifty patients, who were planned to deliver by elective cesarean section in Al Gazeerh hospital, Giza, Egypt. The study started in December 2017 and ends in January 2022. Patients were assigned to one of 2 groups; group A (study group), 75 patients were infused by oxytocin immediately before uterine incision and group B (control group), 75 patients were infused by oxytocin in the third stage of labor.

Pregnant women age 20 years or older, with average BMI (not including those with morbid obesity) and undergoing elective cesarean section at gestational age 37-41 weeks were included in the study. Women with anemia (hemoglobin < 10 gms%), coagulopathies, gestational or chronic medical disorders, anticoagulant therapy, risks of thrombo-embolism, and/or post-partum hemorrhage, uterine over distension (fetal macrosomia, multiple pregnancy, polyhydramnios), history of antepartum hemorrhage, placental abnormalities as previa or accrete were excluded from the study.

All patients underwent full history taking, thorough clinical examination, obstetric ultrasound and routine preoperative laboratory investigations. Neonatal evaluation after delivery included recording APGAR score, neonatal weight, incidence of transient tachypnea of newborn (TTN), respiratory distress syndrome (RDS), neonatal hypoglycemia and NICU admission.

Randomization and blinding was done through a computer generated model, and a closed-envelope system was implemented where subjects were divided into 2 groups; Group A and B as the ward nurse opened the envelope after the women were enrolled,

while the participant and outcome assessor were blind.

This study evaluated best timing of oxytocin administration in cesarean deliveries as regard amount of intraoperative and postoperative estimated and quantitative maternal blood loss, also evaluated change of pre-operative to post-operative hemoglobin levels, intraoperative maternal nausea and vomiting and neonatal immediate postpartum condition.

Uncomplicated CS was defined when the duration of the CS was < 45 min with < 750 mL intra-operative blood loss, no bladder, ureteral, intestinal, or uterine artery injuries, and no uterine atony [17].

Intervention

All patients received regional spinal anesthesia. One bag of 500 ml 0.9% NaCl (normal saline) with 10 units of Oxytocin (Syntocinon, NOVARTIS Pharmaceutical, Egypt) (Oxytocin solution) was hung by the anesthetist at an infusion rate 10 ml/min immediately before uterine incision in group A, this amount of fluid is part of standard of this group of patients care.

A transverse uterine incision was done in LUS, then the amniotic fluid (AF) was drained by suction to minimize soaking of the towels and gauzes by the AF as possible. After draining of the AF and delivery of the fetus, the umbilical cord was clamped and placenta was delivered. Group B patients were infused by One bag of 500 ml 0.9% NaCl (normal saline) with 10 units of Oxytocin (Syntocinon, NOVARTIS Pharmaceutical, Egypt) (Oxytocin solution) at an infusion rate 10 ml/min, this amount of fluid is part of standard of this group of patients care as an active management of the third stage of labor to avoid uterine atony [18-20].

After delivery of the placenta, the uterus was exteriorized and the uterine incision was repaired in 2 layers using no. 1 absorbable polyglycolic sutures (Vicryl-Ethicon, NJ, USA) [17].

After excluding any adnexal abnormalities, the uterus was entered back to the abdominal cavity, peritoneal toilet was done and rectus sheath was repaired after making sure that the uterine tone was retained, (considering it to be of delayed tone if not retained at start of rectus sheath repair). Additional uterotonics, ergometrin (Methergin 0.2 mg ampules, NOVARTIS Pharmaceutical, Egypt) intramuscular injection and/or misoprostol (Misotac 200mcg tablets, SIGMA Pharmaceutical, Egypt) given intrauterine, were used if retaining uterine tone was delayed, most of these cases needed continuing postpartum uterotonics.

Postoperative blood samples were taken from participants 6 hours after delivery and or before discharge (48 hours after delivery) to measure hemoglobin and hematocrit values.

Intraoperative blood loss was obtained through measuring the volume of blood in the suction machine reservoir and weighing the swabs (surgical towels) as soon as possible. The weights of dry swabs were subtracted from the weights of swabs used during the operation. The weight of swabs found in grams was translated to ml by using blood density (1.050 g/ml) [21].

Postoperative blood loss in the first and after 24 hours was measured by subtracting intraoperative blood loss from total blood loss. Total blood loss was measured using pre and postoperative hematocrit values, by multiplying the calculated pregnancy blood volume by percentage of blood volume lost.

- Pregnancy blood volume = (0.75 × {[maternal height (inches) × 50] + [maternal weight in pounds × 25]})
- Percent of blood volume lost = ({predelivery HCT − postdelivery HCT}/ predelivery HCT)
- Total blood loss = pregnancy blood volume × percent of blood volume lost [22].

Outcomes

The primary outcome measures were total blood loss (both estimated blood loss and quantitative blood loss) after completing the surgery and incidence of intraoperative or postoperative nausea and or vomiting (that could occur from early use or excessive uterotonic drugs). The secondary maternal outcome measures included incidence of primary postpartum hemorrhage (women who lose 1000 milliliters or more blood from cesarean delivery), need for blood transfusion (if hemoglobin level is below 7 g/dl or there is acute blood loss), unacceptable change in pre-operative to post-operative hemoglobin levels in the immediate 24 hours post-surgery (average post-cesarean drop in hemoglobin was 1.52±1.27 gm/dl and drop in hematocrit was 5.49±4.1% [23]) and neonatal condition (incidence of transient tachypnea or respiratory distress of newborn and neonatal Intensive care unit admission).

Sample size justification

Sample size calculation was done using the comparison of total intraoperative blood loss between women undergoing elective Cesarean delivery treated with prophylactic oxytocin infusion before uterine incision and treated with conventional oxytocin infusion. Accordingly, we calculated that the minimum proper sample size was 66 mothers in each group to be able to reject the null hypothesis with 80% power at $\alpha = 0.05$ level using Student's t test for independent samples. Sample size calculation was done using PS Power and Sample Size Calculations Software, version 3.1.2 for MS Windows [24]. Accounting for possible withdrawal after randomization, we increased each group to 75 women in each group (Figure I).

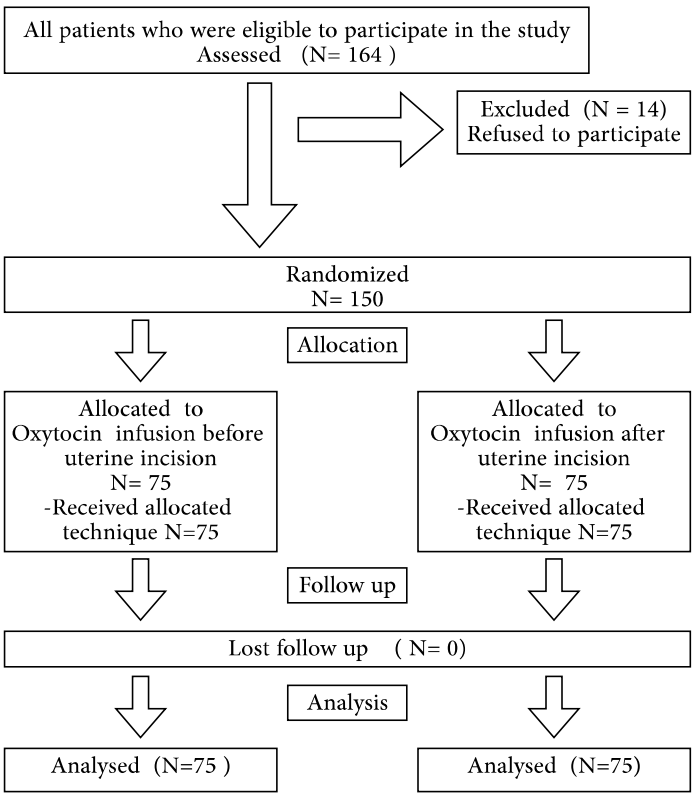

Figure I: Consort flow diagram

Statistical analysis

Data was coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test (Chan, 2003a). For comparing categorical data, Chi square (c2) test was performed. Exact test was used instead when the expected frequency is less than 5 (Chan, 2003b). P-values less than 0.05 were considered as statistically significant [25] [26].

Results

One hundred and fifty pregnant females, planned to terminate their pregnancy by elective cesarean section, participated in the study and were divided into two equal groups. Table I and II show the baseline characteristics of the studied groups, there were no significant difference in the baseline terms as regard age, education, profession, residence and gravidity (p-value > 0.05). Indications of cesarean section showed no significant differences between both groups, with repeat lower segment cesarean section being the commonest indication in both groups.

As regard intraoperative findings, figure II shows incidence of intraoperative nausea and vomiting in both groups, being more in group A (cases), but with no significant statistical difference between both groups (p-value; 0.24) (Table III).

Additional uterotonics (ergometrin and prostaglandins) were used if retaining uterine tone was delayed till starting rectus sheath repair, only 8 cases of group A showed delayed retaining uterine tone, while 15 cases of group B showed delayed retaining of uterine tone (Figure IV). This was reflected on use of additional intraoperative and postoperative uterotonics, in both groups, where only 12 cases in group A while 18 cases in group B need intraoperative additional uterotonics (Figure V) and 15 cases in group A while 28 cases in group B need postoperative uterotonics (Figure VI) with a statistical significant difference between both groups (p-value; 0.019) (Table III and Table IV).

As regard intraoperative blood loss, 14 cases in group A while 18 cases in group B showed excess intraoperative blood loss, this was reflected objectively by measuring postoperative hemoglobin and comparing it to preoperative measurements (Figure III). 2 cases in group A showed signs of postpartum hemorrhage, while 5 cases in group B showed signs of postpartum hemorrhage (blood loss more than 1000 cc) (Figure VII). Unacceptable drop in pre-operative to post-operative hemoglobin levels in the immediate 24 hours post-surgery being more than 1.52±1.27 gm/dl [24] was observed in 8 cases of group A while being observed in 12 cases of group B (Figure VIII) (Table III and Table IV).

2 cases in group A need blood transfusion, while 3 cases in group B need blood transfusion. Only one case in the study, being in the control group (group B) necessitated doing cesarean hysterectomy as the patient was 40 years old, multigravida, with history of repeat LSCS, showed delayed retaining uterine tone and excess intraoperative blood loss and had been counseled preoperatively for doing hysterectomy if there is surgical risk on maintaining the uterus (Table III).

Table V showed data of neonatal outcome in both groups, with no statistically significant difference between both groups as regard neonatal APGAR scores and incidence of TTN or RDS. 5 cases in group A need NICU admission while 7 cases in group B need NICU admission (Figure IX).

Table I: Base line terms between both groups (cases and control)

	Cases		Control		
	Mean	Standard Deviation	Mean	Standard Deviation	P value
Age	30.81	5.69	30.12	5.23	0.439
Termin Gest age	38.25	1.07	38.12	0.84	0.396

Table II: Base line terms between both groups (cases and control)

		Cases		Control		P value
		Count	%	Count	%	
Educ.	**Illiterate**	18	24.0%	10	13.3%	0.299
	Educated	19	25.3%	17	22.7%	
	Graduate	36	48.0%	45	60.0%	
	Postgraduate	2	2.7%	3	4.0%	
Occup	**Occupied**	25	33.3%	32	42.7%	0.239
	Unoccupied	50	66.7%	43	57.3%	
	Rural	18	24.0%	20	26.7%	0.707
	Urban	57	76.0%	55	73.3%	
Gravidity	**Multipara**	55	73.3%	45	60.0%	0.083
	Primigravida	20	26.7%	30	40.0%	
Indication for CS	**Breech**	6	8.0%	9	12.0%	0.779
	contracted pelvis	7	9.3%	3	4.0%	
	delayed conception	7	9.3%	6	8.0%	
	failed vaginal delivery	4	5.3%	4	5.3%	
	Low liquor	5	6.7%	8	10.7%	
	Macrosomia	1	1.3%	4	5.3%	
	on demand	7	9.3%	7	9.3%	
	previous cs	35	46.7%	31	41.3%	
	small for gestational age	3	4.0%	3	4.0%	

Table I: Base line terms between both groups (cases and control)

		Cases		Control		P value
		Count	%	Count	%	
intra operative nausea and vomit	**Yes**	32	42.7%	25	33.3%	0.239
	No	43	57.3%	50	66.7%	
Intraoperative adhesions	**Yes**	9	12.0%	13	17.3%	0.356
	No	66	88.0%	62	82.7%	
Retain uterine tone	**Immediate**	67	89.3%	60	80.0%	0.113
	Delay	8	10.7%	15	20.0%	
use of other intraop uterotonics	**Yes**	12	16.0%	18	24.0%	0.221
	No	63	84.0%	57	76.0%	
Intraop blood loss	**Accepted**	61	81.3%	57	76.0%	0.425
	Excess	14	18.7%	18	24.0%	
Blood transfusion	**Yes**	2	2.7%	3	4.0%	1
	No	73	97.3%	72	96.0%	
Hystrectomy	**Yes**	0	0.0%	1	1.3%	1
	No	75	100.0%	74	98.7%	

Table I: Base line terms between both groups (cases and control)

use of other post op uterotonics	**Yes**	**15**	**20.0%**	**28**	**37.3%**	**0.019**
	No	60	80.0%	47	62.7%	
unacceptable	**Accepted**	67	89.3%	63	84.0%	0.337
	Excess	8	10.7%	12	16.0%	
change of pre-post op hb	**Yes**	2	2.7%	5	6.7%	0.442
	No	73	97.3%	70	93.3%	

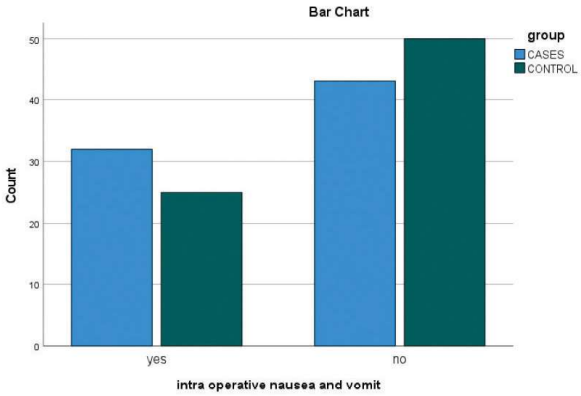

Figure II: Intra operative nausea and vomiting in the study groups

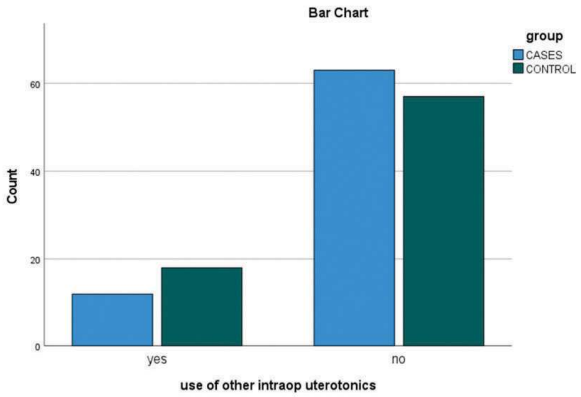

Figure V: Use of intra operative additional uterotonics in study groups

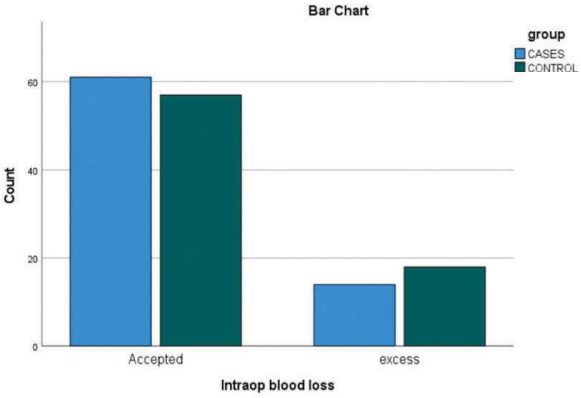

Figure III: Intra operative blood loss in the study groups

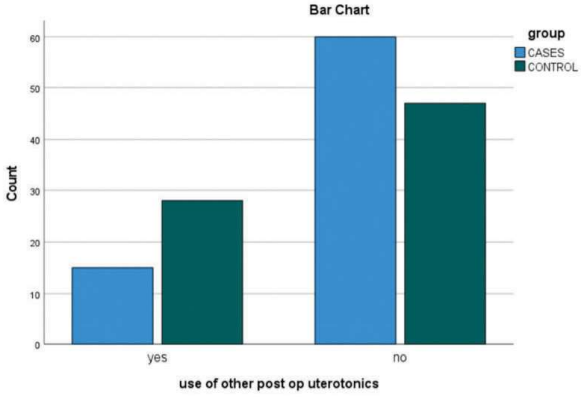

Figure VI: Use of postoperative additional uterotonics in study groups

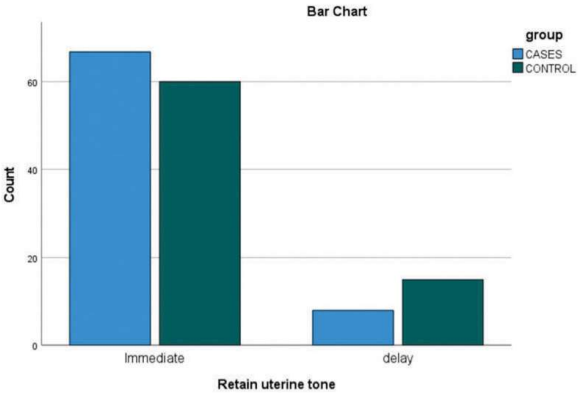

Figure IV: Retaining uterine tone in the study groups

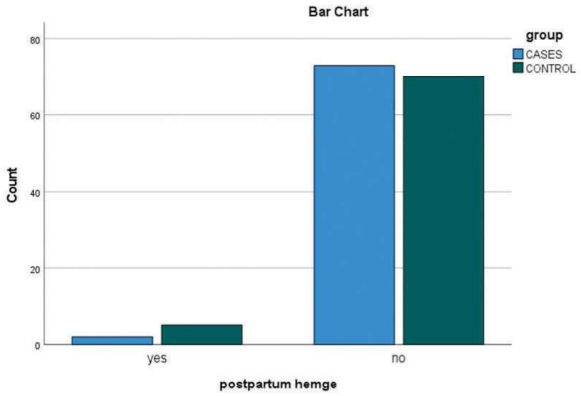

Figure VII: Postpartum hemorrhage in the study groups

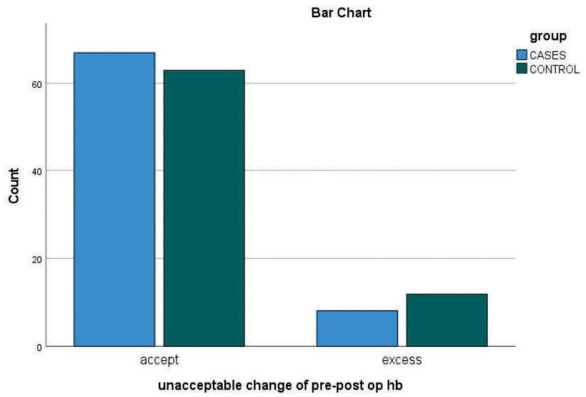

Figure VIII: Preoperative to postoperative change in hemoglobin in the study groups

Table V: Neonatal outcome

		Cases		Control		P value
		Count	%	Count	%	
TTN	**Yes**	2	2.7%	3	4.0%	1
	Absent	73	97.3%	72	96.0%	
RDS	**Yes**	3	4.0%	5	6.7%	0.719
	No	72	96.0%	70	93.3%	
ICU ADMIT >24 HRS	**Yes**	5	6.7%	7	9.3%	
	No	70	93.3%	68	90.7%	0.547

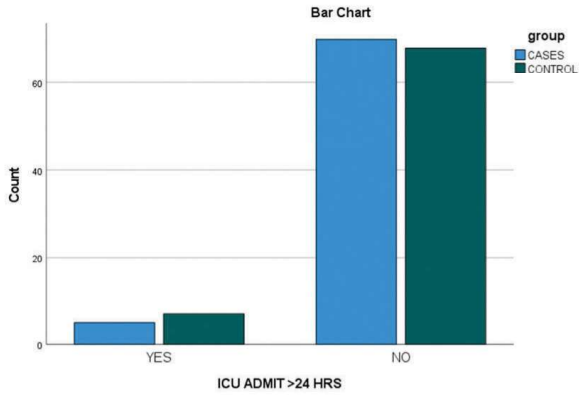

Figure IX: NICU admission in the study groups

Discussion

Prophylactic oxytocin at any dose with different regimens decreases both postpartum hemorrhage (PPH) and need for therapeutic uterotonics. Active management of the third stage of labor has been shown to reduce the risk of postpartum hemorrhage (PPH) greater than 1000 ML. Prophylactic uterotonics, as regard dose, timing and route of administration vary across the globe and may have an impact on maternal and neonatal outcomes.

Oxytocin is the routinely used and effective uterotonic drug, but still regimens of prophylactic oxytocin infusion to avoid peripartum hemorrhage in elective pre-labor cesarean section (CS) differ in various guidelines. Randomized controlled double-blind trials supported by expert opinions mainly and studies with low evidence rates are still the main source of evidence in this issue. Extra use of Oxytocin must be taken into consideration, especially among female patients with any pre-existing heart conditions. One of the important research priorities is the identification of the optimal regimen of intravenous oxytocin at caesarean section, as still there is no consensus on the best timing for prophylactic oxytocin administration during CS to prevent post-partum hemorrhage.

ACOG indorses postponing elective CS at spontaneous labor pains to let oxytocin secretion, and its helpful action on epithelial sodium channels (ENaC), which prepares the lung for gas exchange, and decreases the neonatal respiratory morbidity [27]. In addition, Abdelazim et al. reported significant decrease in neonatal respiratory morbidity when the elective CS is made at ≥ 39 weeks of gestation [27]. Blood loss > 750 mL is reflected as Class-I hemorrhage, in which minimal physiological changes happen [17, 28].

In a study done by Maria Torloni et al. 2021, nine databases were searched to identify relevant randomized controlled trials (RCT). They found no statistically significant differences between oxytocin given before versus after fetal delivery were found. There was a significant decrease in using additional uterotonics when oxytocin was administered immediately before uterine incision versus after fetal delivery.

Oxytocin given before fetal delivery significantly reduced intra-operative blood loss but did not change the incidence of blood transfusion. One trial (N = 100) compared prophylactic oxytocin before versus after placental separation and found no significant differences on PPH, additional uterotonics, or nausea/vomiting. There is very limited evidence suggesting no significant differences between prophylactic oxytocin given before versus after placental separation on PPH, need for additional uterotonic, or nausea/vomiting. The overall certainty of the evidence was mostly low or very low due to imprecision [29].

Future studies on larger sample of patients are still needed to expand our understanding and establish long-term safety regarding the pregnancy outcome in using prophylactic oxytocin starting just before fetal delivery. This may have an important impact on lowering hospital stay and a lot of maternal and fetal complications especially in countries with limited economic resources in which cesarean section rates are increasing. The strength point in this study, the consort statement of randomized study was followed. The limitation is the lack of settled data and evidence in the topic of our study.

Conclusions

In women having pre-labor CS, no significant statistical differences between prophylactic oxytocin given before versus after fetal delivery were found as regard the mother nausea/vomiting, incidence of intra-partum or postpartum hemorrhage or blood transfusion, or hysterectomy. Earlier oxytocin administration significantly reduces need for additional uterotonics and may reduce intra-partum and postpartum blood loss.

Acknowledgement

The author is grateful to the women who participated in this study.

Conflict of interest

The author declares no conflict of interest.

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