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The ED90 of Prophylactic Oxytocin Administration in Low vs. High-Risk Parturients in Terms of Post-Parturition Uterine Tonicity: An Up-Down Sequential Allocation Dose-Response Study

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ABSTRACT

Background & Objective: This study was performed to determine and compare the ED90 of prophylactic oxytocin (OX) infusion after delivery of the placenta during cesarean section (CS) in low- and high-risk parturients for uterine atony.

Materials & Methods: This experimental study was a single-blind and dose-response study using a 9:1 biased-coin sequential allocation method to estimate the ED90 of prophylactic infusion of OX in women with high and low risk for uterine atony who underwent CS. The total administrated OX dose of each patient was determined in the two study groups. The primary outcome was the ED90 for desirable uterine tone based on the opinion of the in-charge obstetrician. The number of subjects receiving supplemental uterotonics was compared.

Results: In the low-risk group, three (3.7%), out of the 41 parturients, did not achieve a satisfactory suitable response to OX dose of 9; on the other hand, 24 high-risk parturients (58%) did not achieve a satisfactory and reasonable response to OX dose of 9. The OX ED90 was significantly greater for the high risk-group (11.55 units, 10.39-14.86) than the low-risk group (8.13 units, 8.31-9.56). Fisher's exact probability test showed a significant difference in ED90 of OX between the two groups (*P*=0.02).

Conclusion: The present study results showed that the mean ED90 of OX in low-risk parturients was significantly lower than that of high-risk ones. We suggest differentiation between low-risk and high-risk parturients in the guidelines of OX administration.

Keywords: Cesarean Section, Dose-Response Relationship, Drug, Oxytocin, Drug Dosage Calculations, Postpartum Hemorrhage, Uterine Inertia

Introduction

Cesarean section (CS) is the most commonly performed surgical operation to save pregnant women's lives and overcome childbirth-related complications worldwide **(1)**. In developed and developing countries, the rate of CS has been rapidly increasing over the past four decades and has reached 27%, with rates varying from 12% to 39% between hospitals within countries and 19% to 35% between countries **(2)**. Postpartum hemorrhage (PPH) is one of the most critical complications and the leading cause of maternal death following CS, which may occur in the post-operative phase and is predominantly caused by uterine atony **(3, 4)**. Uterine atony refers to the failure of the uterus to contract in response to endogenous oxytocin (OX) following delivery. Active management of the third stage of labor with prophylactic administration of OX has been demonstrated to decrease uterine atony and PPH risk. It is reported that the drug can reduce PPH by up to 40% **(5, 6)**. Although a slow intravenous (IV) bolus dose of 5 units of OX after delivery of the infant or placenta has been recommended by the Royal College of Obstetricians and Gynecologists (Grade of

recommendation: B), several studies have investigated the dose-response of IV OX administration in this regard **(7)**. Critical adverse effects, such as myocardial ischemia, hypotension, tachycardia, vomiting, and nausea, can be minimized with the administration of low-dose OX regimens **(8-10)**.

On the other hand, maximizing adequate uterine contractility in addition to minimizing OX-related side effects is critical. Still, the administration of uterotonic agents such as OX during CS is highly variable. A consensus has not been reached regarding the optimal dose for third-stage OX administration over the recent years. Determination of estimated effective dose (ED90) of prophylactic OX infusion was first and only performed by Lavoie *et al.* **(11)**. Still, to the best of our knowledge, there is no proper evidence in available literature regarding the minimum effective dose of OX to prevent uterine atony during CS in parturients with high and low risk of uterine atony, and this topic still needs to be investigated. Therefore, this study was performed to determine and compare the ED90 of prophylactic OX infusion after delivery of the placenta during CS in low- and high-risk parturients for uterine atony.

Methods

Study Design and Setting

This experimental study was conducted from October 1st 2017 until September 30th 2019, in Imam Hosein Hospital, Tehran, Iran. The authors adhered to principles introduced in the declaration of Helsinki throughout the study. The participants were enrolled in case of signing the prepared, informed consent. This study was approved by the institutional ethical committee of the Faculty of Medical School, Shahid Beheshti University of Medical Sciences, Tehran, Iran (approval code: IR.SBMU.MSP.REC.1397.710), and registered on www.irct.ir (IRCT20120430009593N11).

Study Participants

The parturients who were a candidate for performing CS under spinal anesthesia, aged between 18 and 35 years, in physical status I and II based on American Society of Anesthesiologists (ASA) classification, without any known cardiac disease or coagulopathy or pre-operation hemodynamic disorders were eligible. Exclusion criteria were general anesthesia and known placenta or uterine abnormalities. Based on the findings reported by Anne Lavoie *et al.* **(11)**, with a 95% confidence interval, the minimum required sample size was calculated to be 80.

All the parturients were subjected to complete clinical examination before surgery. A set of routine paraclinical tests including a complete blood count (CBC), a complete coagulation profile [prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), clotting time (CT), and bleeding time (BT)], and urine analysis was performed for all cases. Common monitoring modalities, including continuous electrocardiography (ECG), pulse oximetry, blood pressure (BP), and heart rate (HR), were used during the CS and the whole process of OX administration. Twenty-four hours after CS, another CBC test was performed, so the hematocrit and hemoglobin levels were measured and compared in each parturient after versus before CS.

Definitions

Parturients were categorized as high-risk for uterine atony if any risk factor was present. Risk factors for uterine atony include fibroid uterus, fetal macrosomia, high parity, chorioamnionitis, those with preeclampsia (PE) who received magnesium sulfate infusions, obesity or (BMI)>35, repeated CS, prolonged labor, uterine distension (multi-fetal gestation, polyhydramnios, fetal macrosomia), use of uterine-relaxing agents, and laboring women with exposure to OX. The other parturients who did not have any risk factor for uterine atony were categorized as low-risk parturients **(12-14)**.

Intervention

This single-blinded and dose-response study was designed using a 9:1 biased-coin sequential allocation method. All the parturients were spinally anesthetized and received a 1000 mL of IV ringer lactate, infused over 15 minutes before spinal anesthesia initiation. Surgery started when a bilateral T5 sensory block to pinprick test was confirmed. The CS was conducted by one team in all cases; the surgical incision was the Pfannenstiel incision in all cases.

In the present study, the “Rule of three” protocol was implemented with an up-down sequential allocation dose-response method. This method was introduced by Kovacheva *et al.* **(15)**. The total amount of OX administered to each parturient in each group and how she responded to it determined the dose of OX for the next parturient in the same group (Figure 1). As a general rule, all 3 units of OX were injected within 30 seconds. But if the parturient did not respond well to the first 3 units after 3 minutes, the other 3 units of OX were injected within 30 seconds. If there was no response again after 6 minutes, another 3 units were injected within 30 seconds. In this study, each group administered the initial 3 units’ dose of OX for the first parturient. It was reduced to 2 units in 10 percent of the next parturients when the proceeding parturient had been satisfactorily (uterine tone > 2) responding to OX infusion; If the uterine tone was reported as unsatisfactory at 3 minutes, the case was categorized as a failure, and the infusion was repeated with 3 units/3 min. The other 90 percent received the same 3 doses of OX.

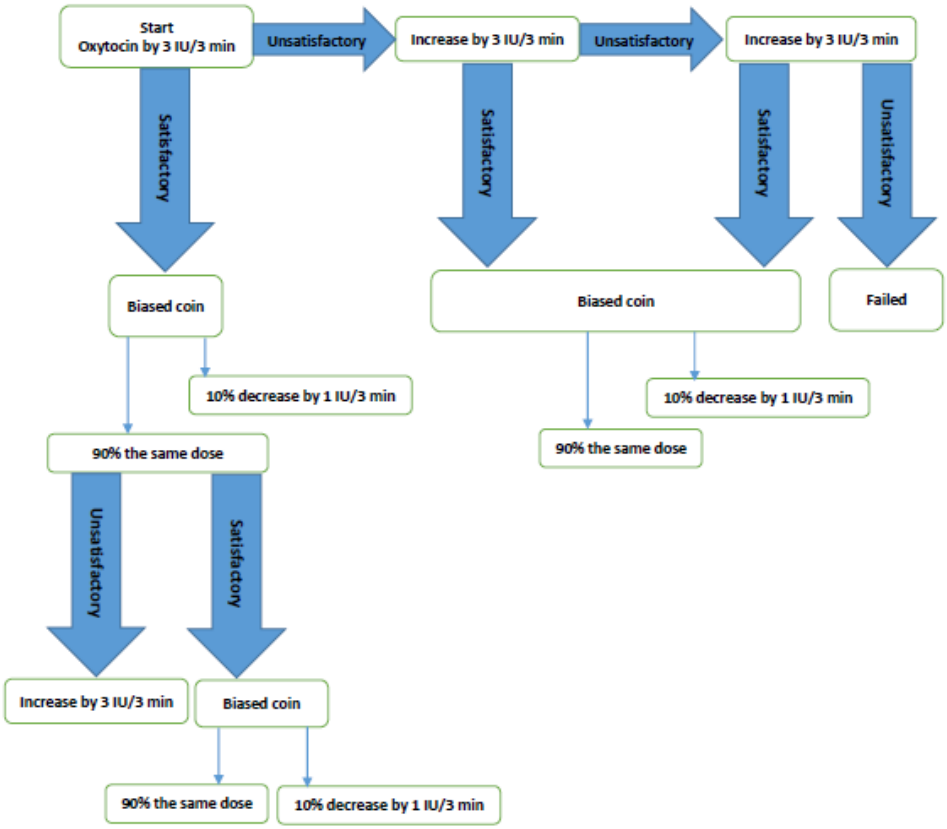

Figure 1. **Flowchart of the study protocol for oxytocin administration**

Outcome Assessment

Following the delivery of the placenta, an infusion of OX was started. Immediately after CS, the same obstetrician assessed uterine tone using manual palpation every 3 min for 30 minutes based on a five-point scale (1=atonic, 2=partial but inadequate contraction, 3=adequate contraction, 4=well contracted, and 5=very well contracted). The uterine tonicity of both groups was investigated at 3, 6, 9, 15, 30 minutes, and the end of surgery in the recovery room. The amount of bleeding was also assessed by the surgeon in all patients. The primary outcome was determining the minimum effective dose of OX infusion for each group, which led to a uterine tone score of 3 or above. Any adverse effect such as tachycardia, vomiting, flushing, bleeding, and a headache was recorded.

Rescue Medicine

If the parturient did not respond well 9 minutes after the last injection dose, the second line of treatment was used to achieve proper contraction. In parturients who did not respond to a total of 9 units, intramuscular injection of methylergonovine (0.2 mg /mL) at the 9th minute, repeated methylergonovine (0.2 mg /mL) at the 12th minute, and misoprostol 600 µg buccal at the 15th minute was administered as second and third lines of treatment.

Statistical Analysis

The statistical analysis was conducted using SPSS 22 (IBM Corp. IBM SPSS IBM Corp., Armonk, NY., USA). All data are expressed as mean ±standard deviation (SD). After testing for normality of pairwise differences with the Shapiro-Wilk normality test, the differences of OX dose and hemoglobin value between the two groups were analyzed using one-way ANOVA at various times and followed by post-hoc Tukey test. A P-value < 0.05 was considered statistically significant. The Chi-square test was used for the comparison of qualitative data. The dose of OX at which 90% of all the parturients had satisfactory uterine tone, determined using Probit regression. The ED90 values of both groups were compared using Fisher's exact test.

Results

Demographic Findings

Forty-one parturients in each group (a total of 82 parturients) completed the study. Their mean ages were 30.10±6.58 and 29.22±5.22 years for high and low-risk parturients, respectively. There was no significant difference between the two groups regarding demographic data such as age, gestational age, systolic and diastolic

BP at various times (Table 1). However, mean hemoglobin was significantly lower in the high-risk group compared with the low-risk group at 24 h post-surgery.

The high-risk group had one or more risk factors, the frequencies of which are presented in Table 2.

Table 1. Baseline information of the parturients in the two study groups

Variable	Low-risk	High-risk	P-value
	Mean ± SD		
Age	29.22±5.29	30.10±6.58	0.508
Gestational age	37.73±1.89	37.24±1.89	0.248
Pre-operative			
SBP	105.98±14.79	109.88±14.93	0.238
DBP	60.27±11.75	61.39±15.60	0.714
HR	87.80±15.45	87.02±17.54	0.780
Start of surgery			
SBP	122.02±10.84	127.93±15.98	0.504
DBP	73.39±9.71	77.39±11.19	0.243
HR	90.15±11.76	91.37±14.30	0.674
During surgery			
SBP 3min	109.17±11.93	109.27±15.15	0.974
DBP 3min	58.02±11.27	61.02±13.38	0.276
HR 3 min	89.61±15.05	91.10±16.53	0.671
SBP 6min	109±10.47	107.83±15.72	0.693
DBP 6min	57.54±10.65	57.88±13.52	0.891
HR 6 min	89.56±14.24	89.56±16.19	1.000
SBP 9min	109.56±9.71	107.20±14.87	0.396
DBP 9min	59.02±10.56	57.66±13.43	0.610
HR 9 min	87.27±18.43	87.59±16.15	0.934
SBP 15min	109.44±8.14	108.34±12.72	0.643
DBP 15min	59.49±10.66	59.66±14.08	0.951
HR 15 min	87.34±11.85	86.07±13.76	0.581
At the end of surgery			
SBP	110.73±8.58	112.05±12.58	0.581
DBP	61.41±10.47	62.32±12.15	0.720
HR	84.32±11.17	83.88±13.73	0.874
During recovery			
SBP	112.15±8.24	113.80±11.49	0.455
DBP	62.10±10.83	64.98±13.12	0.282
HR	86.34±10.29	85.63±13.20	0.787
Hemoglobin			
Pre-operative	12.36±1.13	12.02±0.91	0.874
24 h post-surgery	10.96±1.06*	10.46±0.98*	0.035
Decrement (Δ)	2.21±0.15	1.56±25	0.041

SBP: systolic blood pressure; DPB: diastolic blood pressure; HR: heart rate.

Table 2. Frequency of various risk factors among high-risk parturients studied

Variable	Number (%)
Preeclampsia	4 (9.75)
Body mass index	7 (17.07)
Chorioamnionitis	1 (2.44)
Prolonged labor	6 (14.65)
Repeated cesarean	14 (34.15)
Repeated cesarean+ Body mass index	7 (17.07)
Repeated cesarean + Body mass index +Preeclampsia	2 (4.87)

Uterine Tonicity

The frequency of adequate and inadequate uterine tonicity of both high and low-risk groups at different interval times is presented in Table 3. There was a significant difference between the two groups in terms of adequacy of uterine tonicity at 9, 15, and 30 min after placenta delivery.

Table 3. Number of subjects with adequate and inadequate uterine tonicity in the two groups at various times during surgery

	Uterine tonicity		
Group	**Inadequate**	**Adequate**	**P value***
	At 3 min		
Low risk	38	3	0.294
High risk	40	1	
	At 6 min		
Low risk	14	27	0.247
High risk	20	21	
	At 9 min		
Low risk	1	40	0.001
High risk	11	30	
	At 15 min		
Low risk	2	39	<0.001
High risk	17	24	
	Tonicity at 30 min		
Low risk	0	41	0.043
High risk	3	38	

*Pearson Chi-square

Oxytocin Consumption

The data obtained from the mean OX consumption showed that mean OX consumption was significantly higher in the high-risk group compared to the low-risk parturients 6 min after placenta delivery (Table 4). There was no significant difference between the two study groups in terms of mean OX consumption at other time intervals as well as total OX consumption.

ED90

Out of the 41 parturients in the low-risk group, adequate uterine tonicity was not achieved in three parturients (3.7%) after administering a total dose of 9 units OX. In these parturients, the second-line treatment administration of methylergonovine and misoprostol, resulted in adequate uterine tonicity. Whereas 24 high-risk parturients (58%) did not achieve

adequate uterine tonicity with a total dose of 9 units OX, 4 of them didn't respond to second-line treatment either. Data analysis showed that the ED90 of low and high-risk parturients were 8.81 (CI 95%: 8.31-9.56) and 11.55 (CI 95%: 10.39-14.86) units, respectively. Fisher's exact probability test showed a significant difference in ED90 of OX between the two groups (P=0.02). The results of second-line treatment (administration of methylergonovine and misoprostol alone or together at 15 to 30-minute post-placenta delivery); also showed a significant difference between the two groups (P<0.001).

Adverse Effects

There were no significant differences in the incidence of adverse effects such as nausea, flushing, chest pain, and ECG changes between the two groups. The surgeon assessed the amount of bleeding in all patients and was not more than 1000 cc in any of the parturients.

Table 4. The mean dose of oxytocin (OX) administered at various times during the study

Time	Group	Dose (Mean±SD)	P-value
Start	Low risk	3.00 ±0.00	1.00
	High risk	3.00 ±0.00	
3 min	Low risk	2.85 ±0.65	0.562
	High risk	2.93 ±0.46	
6 min	Low risk	2.56 ±0.92	0.029
	High risk	2.90 ±0.30	
9 min	Low risk	0.07±0.26	1.00
	High risk	0.07 ±0.26	
15 min	Low risk	0.10 ±0.49	0.365
	High risk	0.02 ±0.15	
30 min	Low risk	0.00±0.00	-
	High risk	0.00±0.00	
End of surgery	Low risk	0.00±0.00	-
	High risk	0.00±0.00	
Total dose OX	Low risk	8.59±1.20	0.094
	High risk	8.93±0.46	

Discussion

The primary aim of this study was to determine and compare the ED90 of prophylactic OX intravenous infusion after delivery of the placenta during CS in low and high-risk parturients for uterine atony. The primary finding of this biased-coin sequential allocation study was that the ED90 of the OX infusion rate administered for CS was significantly greater in high-risk parturients compared to low-risk subjects. In this study, we found that 8.81 units (8.31-9.56) and 11.55 units (10.39-14.86) are the ED90 of OX required for preventing uterine atony after an elective CS in low and high-risk parturients, respectively. Several studies have estimated ED90 of OX during CS **(11, 16)**. As far as we know, this is the first study that has compared the ED90 of OX in parturients with high and low risk of uterine atony. It has been shown that the ED90 of OX in laboring women with prior exogenous OX exposure is significantly greater than women undergoing scheduled CS without previous labor **(16)**. The minimum effective dose of OX infusion during CS in parturients with a high risk of uterine atony has been recently determined. The researchers have discovered that higher doses of OX do not further improve uterine tone **(17)**. Balki *et al.* (2006) have estimated the minimum effective dose of OX required for adequate uterine contraction after CS for labor arrest in 30 parturients using a biased-coin method and calculated ED90 of OX bolus to be 2.99 units, which was higher in parturients after elective CS compared to non-laboring women at term **(18)**. Over the past decade, there has been considerable discussion about the optimal dose and mode of administration for third-stage OX administration **(10, 19)**.

The high-risk group of parturients had one or more risk factors such as PE, obesity or BMI>35, repeated CS, prolonged labor> 3 hours, and chorioamnionitis. Some uterine atony risk factors such as repeated cesarean and prolonged labor may result in

desensitization of the uterus and make it less responsive or even not responsive to OX during CS **(18)**. Obesity is another risk factor for uterine atony. The multiple effects of OX signaling on improving pancreatic function, insulin sensitivity, and lipid homeostasis strongly suggest a role for OX signaling in obesity management **(20)**. Placental vascular tone is essential to maintain adequate placental blood flow (PBF). OX level of the placental system increases in the late stages of pregnancy. PE is associated with inadequate PBF. It has also been shown that DNA methylation-reprogrammed OX receptor leads to insensitivity to OX in PE placental vasculature **(21)**. Also, an increase in the risk of uterine atony in parturients with chorioamnionitis has been recently demonstrated **(22)**. This may explain the higher ED90 of OX in high-risk parturients than low-risk ones. The biased-coin design used in our study allows the researchers to set the quantile effect dose of interest, i.e., 90% and 95%. Despite the clinical relevance of ED95, it may sacrifice the precision of the estimate **(18)**.

The secondary outcome of this study was the determination of OX consumption over various time intervals during operation. There was no significant difference between high and low-risk parturients in OX consumption at various times, except at 6 min post-CS. The data obtained from the administration of alternative uterotonic agents showed that low-risk parturients require significantly less medicine for additional uterotonics agents than the high-risk parturients. This may explain why OX consumption at various time intervals during CS was not significantly different between the high and low-risk parturients. Based on our knowledge, the comparison of OX consumption between high and low-risk parturients has yet to be investigated.

The demographical data obtained showed that despite the lower ED90 of OX in the low-risk group when compared to the high-risk group, there were no differences in systolic or diastolic BP, HR, age, weight, week of laboring, and adverse effects; however, hemoglobin level at 24 hours post-operation was different between the two groups. The mean hemoglobin level in high-risk parturients was significantly lower than that of low-risk individuals indicating that the blood loss in high-risk parturients was more than that of the low-risk group.

The obtained data from ED90, OX consumption, side effects, second-line treatment, and demographic data of various risk factors subtypes showed no significant difference in these intra-group variables in the high-risk group.

Limitations

Due to the limited number of studied parturients, we could not assess the possible role of each risk factor on the study findings. Therefore, we highly recommend performing such a trial with a larger sample size to evaluate the potential role of the possible risk factors.

Conclusion

The ED90 of prophylactic OX infusion, blood loss, and administration of uterotonics agents during CD is significantly lower in low-risk parturients compared with high-risk parturients. A lower dose of OX is required to improve the uterine tone in low-risk parturients compared to the high-risk parturients.

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Author's Contributions

The conception and design of the work by EM, MF, AM, and SA. Data acquisition EM, DA, AT, SA, SS, and ShS; Analysis and interpretation of data by EM, MF and AM; Drafting the work by EM, AT and SA; Revising it critically for important intellectual content by MF, DA, SS, AM and ShS; All the authors approved the final version to be published; And agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

Conflict of Interest

The authors declared no conflict of interest.

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