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Original Article

Evaluation of *in vivo* effects of Oxytocin on coagulation of parturient during cesarean delivery by thromboelastography

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ABSTRACT

Objective: Oxytocin routinely used as an uterotonic drug in cesarean delivery. Clothing problems, adverse effects on fibrinogen and bleeding were presented as side effects of oxytocin. In *in vivo* investigation, modest hypercoagulable state was suggested as a side effect for infusion of oxytocin in parturients. In this study, effects of two different infusion rates of oxytocin on coagulation of parturient were evaluated during cesarean delivery.

Methods: In a randomized double-blinded clinical trial, 84 healthy parturient in two equal groups took oxytocin infusion with the rate of 15 IU/h (Group A) or 30 IU/h (Group B), after the umbilical cord clamping. Coagulation status measured 30 min after beginning of infusion by thromboelastography. Data were analyzed by χ^2, paired sample test and ANOVA considering as significant at $P < 0.05$.

Findings: The mean (standard deviation) of variables in Groups A and B were 2.4024 (0.86) and 2.0429 (0.68) for K (kinetics of clot development), 55.4429 (11.30) and 60.7595 (10.41) for α (speed of clot strengthening) and 59.779 (19.15) and 70.61 (11.30) for maximum amplitude (maximum clot strength), respectively. The *P* values for these variables were 0.036, 0.028 and <0.001, respectively; these changes are consistent with increasing coagulability. Other measures did not have significant differences.

Conclusion: This *in vivo* investigation clarified that increasing infusion rate of oxytocin to 30 IU/h can augment coagulability in term parturients.

Keywords: Cesarean delivery; coagulation; Oxytocin; thromboelastography

INTRODUCTION

The rate of delivery by cesarean section has increased dramatically in developed[1-3] and developing[4,5] countries since four decades ago and now it is one of the most commonly performed major operations in women throughout the world.[6] Postpartum hemorrhage can follow vaginal delivery or cesarean section and it is a major cause of maternal morbidity and mortality[7-9] in most cases which relates to uterine atony.[10-12]

In the management protocol of treatment of uterine atony or hypotony, administration of oxytocin is in early steps,[13-15] in addition, oxytocin is routinely used as an uterotonic for prophylaxis.[16-18]

The guidelines of the Royal College of Obstetricians and Gynecologists on cesarean section recommend a slow intravenous bolus dose of 5 IU of oxytocin after delivery of the infant.[19]

In settings where an oxytocin bolus is used routinely, an additional infusion of oxytocin may be required if hemorrhage occurs.[20] An alternative practice in the United States recommends the use of an oxytocin infusion instead of a bolus dose.[21]

Clothing problems, adverse effects on fibrinogen and bleeding were presented as side-effects of oxytocin.[22-24] The frequency and mechanism of these side-effects is poorly understood.[25]

In an *in vitro* study, Butwick studied the effects of two different infusion rates of oxytocin on clot formation in whole blood of healthy term parturients by thromboelastography and concluded that exogenous

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oxytocin is associated with modest hypercoagulable effects in the maternal blood.[26]

Butwick finding is in contrast to the known side-effects and adverse reactions of oxytocin on coagulation[22-24] and was based on an *in vitro* investigation, so this clinical trial designed to evaluate the effects of two different infusion rates of oxytocin on coagulation and clot formation of healthy parturients in an *in vivo* study by thrombolelastography.

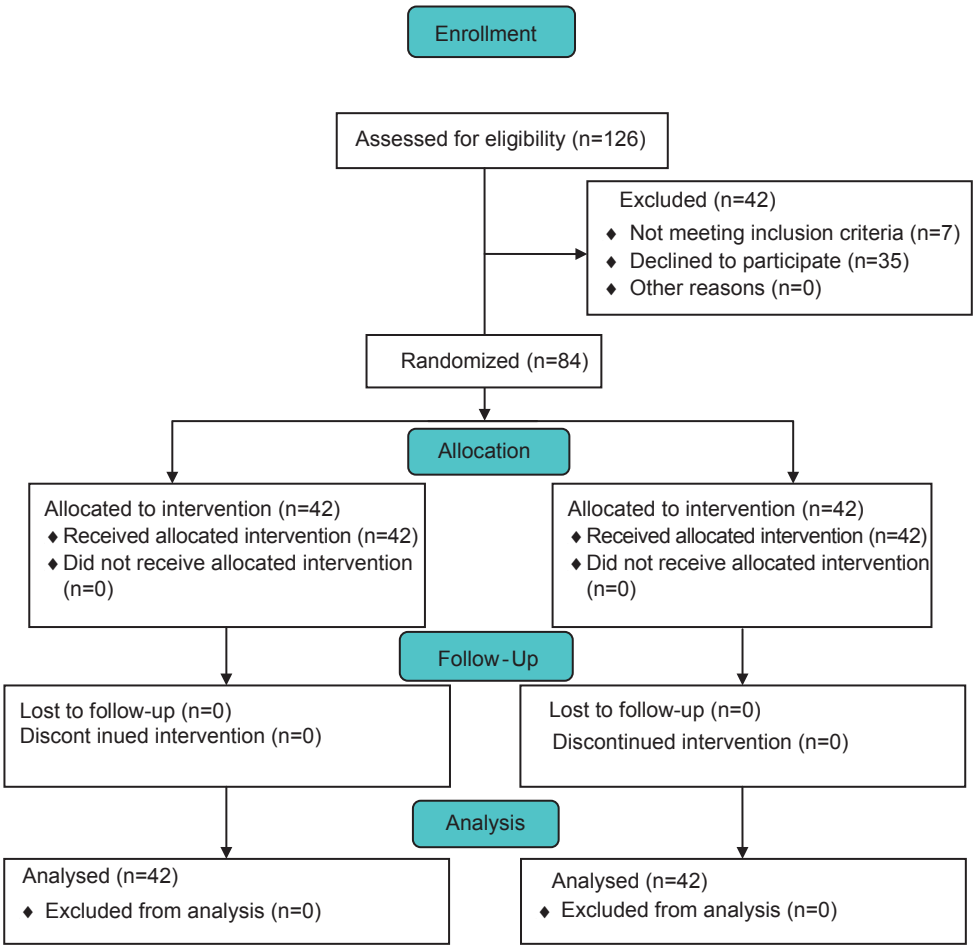
METHODS

After approval by the ethical committee and obtaining informed concept, 126 parturient who were a candidate for elective cesarean section were assessed for eligibility to be included in the study. A total of 35 patients did not accept spinal anesthesia for their delivery, one of them had anatomical abnormality in her spine and 6 parturients were suffering from diabetes and hypertension, so finally 84 of assessed patients entered to this prospective randomized double blinded clinical trial in a simple sampling method.

Participants had American society of anesthesiologists health status classification 1 and 2 and gestational age between 36 and 40 weeks without sign, symptoms and history of coagulation abnormality; also patients who took magnesium sulfate or non-steroidal anti-inflammation drugs in recent week or spinal column abnormality did not match the inclusion criteria of the study. Need to more doses of oxytocin or other drugs for enhancing uterus contraction, transfusion of blood products and administration of magnesium sulfate or calcium gluconate (or chloride) during section were excluding criteria of the study.

All participants were fasted for 8 h before section and took 2 mL/kg fluids (1/3 dextrose, 2/3 saline) during this period. After positioning of participant on the operating table (in 15° leftward tilt), standard monitoring was applied to all participants including electrocardiography, blood pressure, temperature and saturation of hemoglobin by oxygen (SpO_2) and basal vital signs measured, then 10 mL/kg ringer's lactate solution infused before spinal anesthesia.

Spinal anesthesia was performed in a sitting position by injection of 12.5 mg of bupivacaine (without barbotage) at the L2-L3 or L3-L4 interspace through midline approach with a 25-gauge Quincke needle. Patients were placed in the supine position (in 15° leftward



Flow Chart 1: CONSORT diagram of the study

tilt) after spinal anesthesia. Supplemental oxygen was administered (5-8 L/min) through a face mask.

Patients randomly divided in two groups according to the random list generated by randomized allocation software[27] to take their special coded drug. After delivery and clamping of umbilical cord, 2 μg/kg fentanyl and 1-2 mg midazolam prescribed intravenously as sedative. Infusion of oxytocin (Oxytip®, Caspaitamin, Tehran, Iran) begun by infusing coded syringe through infusion pump in a similar rate of 60 mL/h in all participants. Oxytocin were prepared in similar 60 mL infusion pump syringes by a coworker of study in two concentrations (0.25 IU/mL for Group A and 0.5 IU/mL for Group B) and coded according to cods created by randomized allocation software. All codes remained unclear for other co-workers of the study until the end of collecting data period.

At 30 min after beginning of infusion of oxytocin, 2 mL of participant blood were taken in atraumatized manner from the antecubital vein and immediately tested by thromboelastography in the operating room lab. Systolic, diastolic and mean blood pressure, respiratory rate (breaths per minute), temperature (measured by coated probe from axillary fossa) and SpO_2 were measured and recorded every 5 min during surgery.

Uterus contraction scored by a surgeon as relax, semi-contract, contract and full contract after delivery of the placenta and before returning of the uterus to the abdominal cavity. Hypotension (systolic blood pressure <90 mmHg) was treated with a rapid infusion of crystalloid solution and if unresolved in 5 min, it was treated with ephedrine (5 mg-venous bolus); also, heart rate under 50 beat/min without hypotension was treated by intravenous administration of 1 mg bolus dose of atropine. All these interventions were recorded in dose and times of prescription. The maximum level of sensory block was evaluated 20 min after the end of bupivacaine injection.

At the end of collecting data (in all participants), codes of randomization opened and data analyzed by Chi-square, paired sample test and repeated measured ANOVA in the Statistical Package for the Social Sciences (SPSS) for windows (SPSS, Chicago, IL, USA) version 20. Differences considered significant at level of 0.05.

RESULTS

This study evaluated coagulation status in 84 parturients during cesarean section. The mean standard deviation (SD) of parturient age, parity and gestational ages of all participants were 28.5 (4.63) years, 2.29 (0.86) and 37.45 (0.55) weeks, respectively. Two groups of the study didn't show significant differences in comparison of means of age (P = 0.963) and frequency distribution of parity (P = 0.079) and gestational ages (P = 0.111) [Table 1].

The results of this study demonstrated that infusion of oxytocin 15 unit/h and 30 unit/h have different effects on measures of thromboelastography regarding the mean of K (the time between initiation of clot formation to 20 mm widening of two branches of thromboelastorgraphy curve) the mean of α (the angle between two branches of thromboelastorgraphy curve) and the mean of maximal amplitude (MA) (the MA of thromboelastorgraphy curve) in two groups [Table 2]. Other measures of thromboelastography didn't show significant differences in two groups.

Participants in two groups did not have significant differences in temperature, respiratory rate, heart rate,

Table 1: Frequency distribution of participants regarding parity and gestational ages

Characteristics	Group A	Group B	*P* value
	(*N*=42)		
Parity age			0.079
1	6	6	
2	28	18	
3	6	10	
4	2	8	
Gestational age (weeks)			0.111
37	20	28	
38	20	14	
39	2	0	

Data presented as number of participants. Group A=Receiving oxytocin 15 units/h, Group B=Receiving oxytocin 30 units/h

Table 2: Mean of thromboelastographic parameters in two study groups

Parameter (unit)	Group	Mean (SD)	*P* value
R (min)	A	7.0524 (3.58)	0.434
	B	7.5857 (2.55)	
K (min)	A	2.4024 (0.86)	0.036
	B	2.0429 (0.68)	
α (°)	A	55.4429 (11.30)	0.028
	B	60.7595 (10.41)	
MA (mm)	A	59.7762 (19.15)	0.001
	B	70.6190 (7.72)	
Ly30 (%)	A	0.0048 (0.216)	0.068
	B	0.0381 (0.115)	
Ly60 (%)	A	0.2286 (0.3752)	0.150
	B	0.4095 (0.110)	

Group A=Receiving oxytocin 15 units/h, Group B=Receiving oxytocin 30 units/h, R or reaction time=The time between beginnings of process of coagulation to initiation of clot formation, K or kinetic time=The time between initiation of clot formation to time of 20 mm widening of two branches of thromboelastography curve, α or α angle=The angle between two branches of thromboelastography curve, MA or maximum amplitude=The maximum distance between two branches of thromboelastography curve, LY30 or lysis at 30=The presence of clot distraction 30 min after maximum amplitude, LY60 or lysis at 60=The presence of clot distraction 60 min after maximum amplitude, SD=Standard deviation

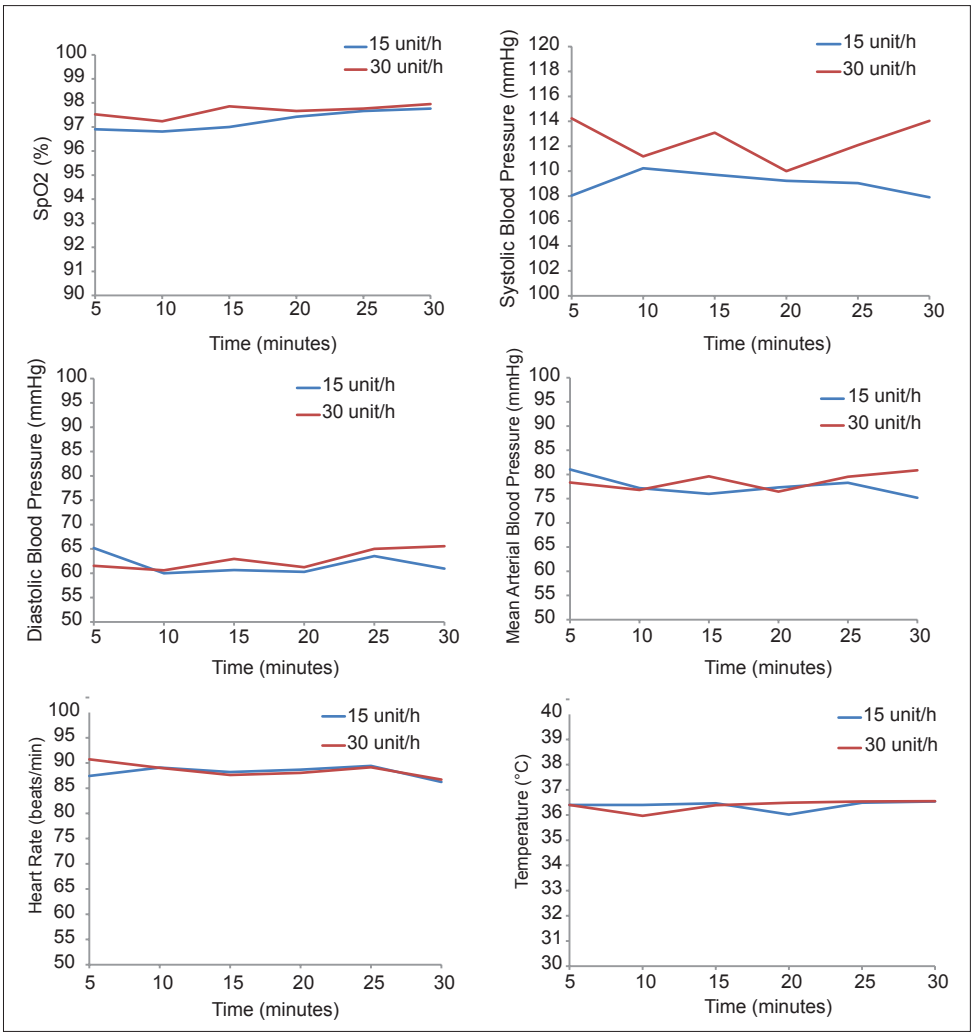


Figure 1: Mean of SpO_2 (saturation of hemoglobin by oxygen), Blood pressures (systolic, diastolic and mean), heart rate and temperature during cesarean section in two study groups (Group A = Receiving oxytocin 15 units/h, Group B = Receiving oxytocin 30 units/h)

SpO_2, systolic, diastolic and mean blood pressures before induction of anesthesia and during the surgery [Figure 1].

The mean dose of ephedrine for treating hypotension was similar in both groups; also the mean dose of midazolam and fentanyl did not have any significant differences between two groups [Table 3].

Table 3: Mean doses of ephedrine, midazolam and fentanyl used in two study groups

Medication (unit)	Group	Mean (SD)	*P* value
Ephedrine (mg)	A	1.79 (3.46)	0.135
	B	0.83 (2.19)	
Midazolam (mg)	A	1.33 (0.48)	0.187
	B	1.48 (0.51)	
Fentanyl (μg)	A	76.19 (25.27)	0.388
	B	71.43 (25.04)	

Group A=Receiving oxytocin 15 units/h, Group B=Receiving oxytocin 30 units/h, SD=Standard deviation

DISCUSSION

The purpose of this study was to evaluate *in vivo* effects of two different infusion rates of oxytocin on parturient coagulation by thromboelastography; in this double blinded clinical trial, we found that oxytocin infusion at a rate of 30 IU/h in comparison to 15 IU/h causes a significant decrease in K and increase in α and MA variables of thromboelastography. These changes are according to increase in coagulability. In fact, in thromboelastography, K represents the kinetics of clot development, α reflects the speed of clot strengthening, mostly affected by fibrinogen levels and in a lesser degree by platelet function and MA represents the maximum clot strength, mainly affected by platelet function and to a lesser extent by fibrin.[28] Therefore, probably the mechanisms of effects of oxytocin on coagulation are through affecting platelet function (such as increasing aggregation) and enhancing degradation of fibrinogen to fibrin.

Our results in major parts are in line with Butwick findings.[26] Their study showed a decrease of R and K and increase in α and MA, but in the present study, R did not have significant differences in two groups. Differences in R changes between Butwick and the present study can be related to differences in the kind of these two studies, whereas Butwick study was an *in vitro* research but we did our study *in vivo*.

In several drug information resources, adverse effects on hemostasis such as afibrinogenemia, hematoma formation and bleeding are mentioned for oxytocin;[22-25] while in this study these kinds of complications have not been evaluated, but our findings (decreasing of K and increasing of α and MA in increased oxytocin infusion rate group) can be translated to augmentation of coagulation by higher levels of oxytocin which may not support the mentioned side-effects for oxytocin.

This *in vivo* investigation clarified that increasing infusion rate of oxytocin to 30 IU/h can augment coagulability in term parturients. We did not study the effects of bolus doses of oxytocin (a more common approach for prescribing oxytocin in cesarean section) on coagulation and did not follow patients for evaluating postpartum bleeding or hematoma formation, which can be the subject for future studies in this field.

AUTHOR'S CONTRIBUTION

Golparvar M. MD: Data base search, Idea of study, Proposal preparation, Manuscript writing, Revisions correction and writing. Esterabi M. MD: Proposal preparation, Data collection, Manuscript writing. Talakoub R. MD: Data base search, Data collection, Manuscript writing. Saryazdi H. H. MD: Idea of study, Data collection, Manuscript writing.

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