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ORIGINAL ARTICLE

High dose versus low dose oxytocin for induction of labor of nulliparous Robson group II women at term

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ABSTRACT

Objective: Induction of labor refers to stimulation of uterine contractions before the beginning of the labor spontaneously. Labor induction procedure using oxytocin is increasing over the years. Herein, we aimed to compare the cesarean section (CS) rates in Robson Group II women by administering either high-dose or low-dose oxytocin induction protocols and to evaluate the duration of labor, fetal and maternal outcomes, and complications.

Material and Methods: In total of 150 nulliparas between 37and 42 weeks of gestation with singleton, viable, vertex presented and without uterine surgery, uterine anomaly history, and congenital anomalies were included to our study. The participants were divided into two groups regarding initial dose and dosing increments of oxytocin. Sixty-four patients were included in high dose group and 86 patients were included in low-dose group. Oxytocin was started at a dose of 4 miliunit (mU/min) and was increased 4 miliunit (mU/min) per 15 min until effective contractions were obtained in the high dose of oxytocin group. Oxytocin was started at a dose of 2 miliunit (mU/min) and was increased 2 miliunit (mU/min) per 15 min until effective contractions were obtained in the low dose of oxytocin group. Effective contractions are defined as over 200 montevideo unit in 10 min.

Results: High-dose induction protocol did not indicate a difference in the duration of the first stage of active labor but shortened the second stage significantly (p=0.015). There was no significant difference in the CS rates, maternal, and fetal complications of two groups. High-dose induction protocol may have induced an increase in thick meconium-stained births (p=0.044), however did not promote fetal distress rates determined with cord blood gas or reduce Apgar scores.

Conclusion: There was no difference between high- and low-dose induction protocols in terms of CS rates, maternal, and fetal complications. Both protocols seem safe to use in nulliparous term pregnant women.

Keywords: Cesarean section, high-dose oxytocin, labor induction, low-dose oxytocin, maternal and fetal complications.

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INTRODUCTION

Rising cesarean section (CS) is a major public health concern in Türkiye due to maternal and perinatal consequences. While CS has been reported to be 53.2% in year 2017, Robson classification for analysing the drivers of the increase in CS to propose and implement effective measures has revealed that the CS rate is higher in Robson group II (46.3%) compared to Robson I (19.4%) in 168.268 deliveries occurring at Ministry of Health hospitals, emphasizing the incremental effect of induction to CS in nullipar, single, and cephalic presentation group with gestational age >37 weeks.[1]

Induction of labor is one of the most common procedure in obstetric practice performed on thereabout 20% of the patients.[2] Worldwide, the most favourite agent to induce labor is oxytocin.[3] For induction of labor, various oxytocin protocols are used according to starting doses, dosing intervals, dosing increments, and maximum dose. It has not been clarified, in which protocol is the most appropriate for the achievement of vaginal delivery as minimizing perinatal and maternal complications.

The aim of this study is to compare the CS rates in Robson Group II women by administering either high-dose or low-dose oxytocin induction protocols and to evaluate the duration of labor, fetal and maternal outcomes, and complications.

MATERIAL AND METHODS

Study was designed as randomised prospective trial. All of nulliparas presented to Zekai Tahir Burak training and research hospital between January 2014 and April 2014-at 37–41 gestational weeks with positive fetal cardiac activity, bishop score >6, vertex presentation, and not in active phase of labor yet were included in this study. Patients with the following characteristics were not included: Patients in active phase of labor (regular contractions with ≥4 cm cervical dilatation), previously uterin operation, cephalopelvic disproportion, fetal malpresentation, fetal anomalies, multiparas, and regular uterin contractions on cardiotocograph. Indications of oxytocin induction were encompassing of patients diagnosed with postterm pregnancy, rupture of membranes, and oligohydramnios. None of the patients received cervical ripening agent before oxytocin induction. Data collection started after the Local Ethics Committee approval (Decision no:16, date 07/12/2012).

Gestational week was appointed, medical history was interrogated, and physical and obstetric examination was performed. Routine blood tests and ultrasonographic findings were recorded. All patients were informed about study and their consent was received.

Patients were divided into two groups in our study:

Low-dose oxytocin protocol group low-dose group (LDG): Low-dose oxytocin protocol was carried to this group out according to the recommendations of American congress of obstetricians and gynecologists (ACOG)).[4] Five units of synthetic oxytocin (Synpitanc amp. Deva, İstanbul) in 500 cc 5% dextrose solution was infused intravenously at 2 mU/min and increased by 2 mU/min every 15 min until effective contractions achieved. Oxytocin infusion was not increased unless the frequency of contractions was reduced. Effective contractions were defined as over 200 montevideo units in 10 min. Maximum allowed dose of oxytocin was 40 mU/min. Patients were followed with vaginal examination and cardiotocograph.

High-dose oxytocin protocol group high-dose group (HDG): High-dose oxytocin protocol was carried to this group out also according to the recommendations of ACOG.[4] Five units of synthetic oxytocin (Synpitan® amp. Deva, İstanbul) in 500 cc 5% dextrose solution were infused intravenously at 4 mU/min and increased by 4 mU/min every 15 min until effective contractions achieved. Similarly, maximum allowed dose of oxytocin was 40 mU/min. Patients were followed with vaginal examination and cardiotocograph.

In both groups, oxytocin infusion rate was decreased or stopped in case of hyperstimulation without fetal heart rate abnormalities and the patient was supported with nasal oxygen and bolus 5% dextrose solution. In severe cases of fetal heart abnormalities, oxytocin induction was stopped. Contractions that occurred more frequently than 2 min or lasting longer than 90 s were evaluated as hyperstimulation.

Groups were assigned in simple randomisation. In total of 200 closed opaque, envelopes containing equal number of high-dose and low-dose cards were chosen by patients after admission to the hospital. In planned period of study, we reached 86 low dose and 64 high dose patients in groups.

Vaginal examination was performed hourly. Fetuses were closely monitored by cardiotocograph. Duration of the first stage was determined by marking the points when cervical dilatation is 4 cm to complete dilatation and efacement. Duration from complete dilatation and efacement to delivery was defined as second stage and duration from delivery to plasental expulsion as third stage. The time point when the membrane rupture was also recorded. Failed induction was considered if there was no progress in labor despite 12 h of induction.[5]

Umblical artery blood samples were drawn from double-side clamped 20 cm cord part to blood gas injectors pre-washed with heparin and analyzed within 30 min. Perinatal asphyxia was considered in neonates who have metabolic acidosis with pH <7.0, base deficit-12, APGAR score=5 in 10 min, and presence of multiple organ-system failures.[6] Placenta weight also was recorded. 6 h after delivery also a control complete blood count was analyzed. Postpartum hemorrhage was defined as 1000 mL or more blood loss within 24 h after delivery regardless of mode of delivery.[7]

Patients were followed for complications through intrapartum and postpartum period. The newborn was also evaluated in terms of height, weight, apgar scores, and complications.

Statistical analysis of the results of this study was performed with Microsoft® Excel® for Mac 2011 (Microsoft Corp., SantaRosa. California, USA) with IBM® SPSS® Statistics 20 for Mac. Mean±-standard deviation and standard error values were used in data definition. Mean±standard deviation and standard error values were used to define the data. t-test for independent groups; if it is not homogeneously distributed, the Mann–Whitney U-test was used. Dependent Groups T-test and Wilcoxon Test were used to evaluate repeated measures. Frequency comparisons between groups were made using the Chi-square test. The relationship between continuous data was made using Pearson and Spearman correlation tests. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

Table 1: Demographic and baseline characteristics

	Low-dose group	High-dose group	p
Maternal age (years)	24.33	24.83	0.459
Maternal height	161.85	161.64	0.843
BMI at first antenatal visit	24.03	23.43	0.248
BMI at delivery	29.7	29.01	0.974
Gestational age (days)	277.45	279.03	0.303
Max dose used (mU/min)	4.8372	8.1875	0.037
Mean cervical dilatation (cm)	2.13	2.26	0.634

BMI: Body mass index.

Table 2: Mode of delivery and distribution of cesarean indications

	Low-dose group		High-dose group		p
	n	%	n	%	
Cesarean section	14	16.3	7	10.9	0.632
Spontaneous vaginal delivery	72	83.7	57	89.1	0.341
Indications for cesarean section					0.632
Fetal distress	6	7.0	2	3.1	
Failed induction	1	1.1	0	0	
Failed labor progress	7	8.1	5	7.8	

Table 3: Duration of stages of active labor, meconium stained amniotic fluid status, fetal and maternal outcomes

	Low-dose group	High-dose group	p
Duration of labor (min)			
First stage	247.42	280.51	0.272
Second stage	27.88	19.21	0.015
Third stage	10.04	11.18	0.247
Meconium stained amniotic fluid, n (%)			
Thin	8 (9.3)	3 (4.7)	0.087
Thick	0 (0)	3 (4.7)	0.044
Vaginal and periurethral lacerations	11 (12.9)	5 (7.9)	0.599
Maternal complications, n (%)			0.521
>500 mL hemorrhage	3 (3.5)	3 (4.8)	
Transfusion	1 (1.2)	0 (0)	
Other	0 (0)	1 (1.6)	
Fetal outcomes			
Birth weight (g)	3304.13	3191.8	0.072
Umbilical cord pH	7.28	7.26	0.261
Umbilical cord $cHCO_3$	20.72	20.98	0.562
Fetal complications, n (%)			0.864
Metabolic acidosis	1 (1.2)	0 (0)	
Hyperbilirubinemia	3 (3.5)	3 (4.7)	
Infection	3 (3.5)	2 (3.1)	
Cephal hematoma	1 (1.2)	0 (0)	
Asphyxia	1(1.2)	0 (0)	

RESULTS

Demographic features of each groups were comparable. Age (LDG 24.33±3.88; HDG 24.83±4.39), height (LDG 161.85±6.17; HDG 161.64±6.62), gestational age (p=0.303), body mass index (BMI) at delivery time (p=0.974), and education levels (p=0.323) were similar in two groups (Table 1).

Cesarean rate was higher in LDG with 16.3% versus 10.9% compared to HDG, but it was not statistically significant (p=0.341) (Table 2). There was no difference between groups according to cesarean indications (p=0.632) (Table 2).

Duration of stages in active labor is summarized in Table 3. Duration of second stage significantly decreased in HDG compared to LDG (27.88 min vs 19.21 min p=0.015). There was no difference in the first and third stage between the groups (p=0.272 and 0.247).

BMIs of two groups were not significantly different. Both in low dose and HDGs, there was a weak positive correlation between BMI and total labor time (stage1+2+3) in r=0.023 and r=0.185, respectively, but not statistically significant (p=0.845; p=0.169). When the stages are compared one by one; there was a very weak relationship between BMI and stage 2 with a positive correlation of r=0.183 with regardless of high- or low-dose oxytocin and this relationship was found statistically significant (p=0.038).

In both groups, there was a weak positive correlation between hemoglobin change (before and 6 h after delivery) and total labor time (stage1+2+3) in r=0.083, but not found statistically significant.

Data about the distribution of meconium stained amnion according to the groups is summarized in the Table 3. With reference to this, in high-dose oxytocin group, thick meconium stained amnion incidence increased compared to LDG (p=0.044).

Labor – trauma-related periurethral and vaginal laceration rates were similar in both groups (p=0.599). All lacerations were repaired with local anesthetics which were not as severe as requiring general anesthesia. 3rd and 4th degree perineal lacerations were not observed.

Postpartum maternal complications are summarized in Table 3. Accordingly, no significant difference was observed between two groups. As three patients in both groups followed up due to >500 mL bleeding, only one patient in LDG needed transfusion of two units of eritrocyte suspension. Maternal fever was observed in one patient in HDG.

The comparison of fetal data according to groups is given in Table 3. Umblical artery blood pH and $cHCO_3$ mean values were similar after delivery and no significant difference was observed between two groups (p=0.261; p=0.562). Although there was no difference between groups in umblical cord blood pH, only three neonates, one in the low-dose group and two in the high-dose group, had pH <7.1 and only one of them was evaluated as true metabolic acidosis. Neonatal asphyxia related death occurred in one newborn in low-dose group. Although Apgar score of newborns was similar, none of the patients had a 5 min Apgar score <7. Complications in neonatal follow-up are summarized in Table 3. No trauma (clavicle fracture etc.) due to delivery in any newborn had been followed. There was no significant difference in terms of hyperbilirubinemia and infection in newborns. Metabolic asidosis was observed in one neonate in LDG and also one death occured in LDG due to asphyxia but afterward, it was confirmed that asphyxia was not related to intrapartum events. Except those cases not any neonates needed intensive care unit.

DISCUSSION

In our study, we evaluated whether there is difference at CS rates, labor durations, postpartum, and perinatal outcomes between low-dose and high-dose oxytocin protocols on nulliparous women undergoing labor induction with <4 cm cervical dilatation.

In a randomized controlled study conducted by Zhang et al.,[8] in nulliparous women who were started with 2 mU/min and 4 mU/min oxytocin dose had a significant shortening of first stage of labor when compared to who were started 1 mU/ min oxytocin, but there was no significant change in the duration of the second stage. In a study of Kenyon et al.,[9] it was reported that the total oxytocin volume used in the high-dose induction group was less, but the first stage was significantly shorter. Jamal et al.,[10] in a study of 200 nulliparous women, showed that duration of oxytocin start to delivery is shorter in high-dose oxytocin group compared to LDG. The only double-blind randomized study conducted until now showed that labor times in high-dose group were shorter.[11] Although there is a difference between the dosages and dosage intervals used in these studies, similar results are observed. In our study, lower doses were used in both low and HDGs compared to many of these studies. However, in our study, as a difference from literature, it was observed that there was no difference in the duration of the first stage, but the duration of the second stage was significantly shortened in HDG (low dose-27.88 min vs. high dose-19.21 min) (p=0.015).

In the same study by Zhang et al.,[8] it was reported that the increase in the risk of CS was equal in all three dose groups. Recent studies by Selin et al.,[12] and Prichard et al.,[13] also revealed that there was no significant difference in terms of CS rates between high- and low-dose oxytocin protocols. Various large scale studies also reported similar results.[14–16] However, in studies conducted by Xenakis et al.,[17] and Lopez-Zeno et al.,[18] they stated that cesarean rates were higher in the LDG due to dystocia. In the present study, although the cesarean rate in the HDG (10.9%) was lower than the LDG (16.3%), similar to most of the studies, the cesarean rates and cesarean indications were not significantly different between two groups.

The study of Lopez-Zeno et al.,[18] showed that there was no difference in maternal complications between high-dose and LDGs and even infectious morbidities such as chorioamnionitis and endometritis were decreased with high-dose protocol. In another study, it was determined that there was no difference between two protocols in terms of postpartum hemorrhage, atonia, and transfusion necessity.[17] Both intrapartum and postpartum examinations were performed for maternal complications in our study. The results of postpartum hemorrhage, birth trauma (vaginal and perineal lacerations), and transfusion necessity are similar in low and HDGs.

In Zhang's study, decreasing rate of meconium stained amniotic fluid was detected with 2 mU/min and 4 mU/min oxytocin infusion when compared to 1 mU/min oxytocin infusion.[8] In our study, the rate of thick meconium was significantly higher in high dose protocol compared to low dose protocol. Although the rate of thin meconium was lower in the low-dose group, it was not statistically significant. However, not any complication due to meconium stained amniotic fluid was observed and it is difficult to say whether meconium stained amnion fluid that detected in intrapartum period is related to oxytocin induction.

In the present study, fetal cord blood gas was analyzed for perinatal outcomes and newborns were followed for possible metabolic acidosis, hyperbilirubinemia, birth trauma, and infection. Although there was no difference in umblical cord pH results between two groups, in three neonates-one in LDG and two in HDG – umblical cord pH was <7.1 and only one which was in LDG evaluated as true metabolic acidosis. One death occured in LDG due to neonatal asphyxia. Not any birth injury was detected. There was also no significant difference in hyperbilirubinemia and infection in neonates. Frigoletto et al. and Rogers et al.[14,16] reported no difference on perinatal outcomes. Zhang et al.[8] reported decreased risk of meconium staining and newborn fever in high-dose protocol.

It is important to determine an optimal oxytocin protocol to avoid problems in labor induction by the use of very low doses or very high doses of oxytocin.

Almost all of the studies on this subject use different oxytocin protocols. Even though the results are similar, it is still a matter of discussion as to which of these protocols is more practical and efficient. Many more studies will probably produce new protocols and give new ideas.

Although the number of patients is limited, the results of the present study are supported by the literature. We use low-dose oxytocin induction routinely in clinical practice in our hospital, but the high-dose oxytocin protocol has proved itself both in our study and in the literature. High-dose induction protocol may be preferred for appropriate patients due to shortening second stage of labor and reducing cesarean rates even not significant in our study.

However, this issue needs further scrutiny. Large scale randomized and double-blind studies will improve our understanding. Increasing the number of patients will give more accurate incidence of complications, and double blindness will eliminate practitioner-patient bias.

CONCLUSION

There was no difference between high- and low-dose induction protocols in terms of CS rates, maternal, and fetal complications. Both protocols seem safe to use in nulliparous term pregnant women and shortening the second stage of labor alone may not be sufficient as a reason to prefer high-dose protocol.

Statement

Ethics Committee Approval: The Zeki Tahir Burak Women's Health Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 07.12.2012, number: 16).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ÜT, EGYE; Design – ÜT, EGYE; Supervision – ÜT, EGYE; Resource – ÜT, EGYE; Materials – ÜT, EGYE; Data Collection and/or Processing – ÜT; Analysis and/or Interpretation – ÜT; Literature Search – ÜT; Writing – ÜT; Critical Reviews – ÜT.

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REFERENCES

1. Eyi EGY, Mollamahmutoglu L. An analysis of the high cesarean section rates in Turkey by Robson classification. J Matern Fetal Neonatal Med 2021;34:2682–92.
2. Zhao Y, Flatley C, Kumar S. Intrapartum intervention rates and perinatal outcomes following induction of labour compared to expectant management at term from an Australian perinatal centre. Aust N Z J Obstet Gynaecol 2017;57:40–8.
3. Diven LC, Rochon ML, Gogle J, Eid S, Smulian JC, Quiñones JN. Oxytocin discontinuation during active labor in women who undergo labor induction. Am J Obstet Gynecol 2012;207:471.e1–8.
4. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol 2009;114:386–97.
5. Oğlak SC, Bademkıran MH, Obut M. Predictor variables in the success of slow-release dinoprostone used for cervical ripening in intrauterine growth restriction pregnancies. J Gynecol Obstet Hum Reprod 2020;49:101739.
6. Gillam-Krakauer M, Gowen Jr CW. Birth asphyxia. StatPearls [Internet] 2017.
7. Oglak SC, Obut M, Tahaoglu AE, Demirel NU, Kahveci B, Bagli I. A prospective cohort study of shock index as a reliable marker to predict the patient's need for blood transfusion due to postpartum hemorrhage. Pak J Med Sci 2021;37:863–8.
8. Zhang J, Branch DW, Ramirez MM, Laughon SK, Reddy U, Hoffman M, et al. Oxytocin regimen for labor augmentation, labor progression, and perinatal outcomes. Obstet Gynecol 2011;118:249–56.
9. Kenyon S, Armstrong N, Johnston T, Walkinshaw S, Petrou S, Howman A, et al. Standard- or high-dose oxytocin for nulliparous women with confirmed delay in labour: Quantitative and qualitative results from a pilot randomised controlled trial. BJOG 2013;120:1403–12.
10. Jamal A, Kalantari R. High and low dose oxytocin in augmentation of labor. Int J Gynaecol Obstet 2004;87:6–8.
11. Merrill DC, Zlatnik FJ. Randomized, double-masked comparison of oxytocin dosage in induction and augmentation of labor. Obstet Gynecol 1999;94:455–63.
12. Selin L, Wennerholm UB, Jonsson M, Dencker A, Wallin G, Wiberg-Itzel E, et al. High-dose versus low-dose of oxytocin for labour augmentation: A randomised controlled trial. Women Birth 2019;32:356–63.
13. Prichard N, Lindquist A, Hiscock R, Ruff S, Tong S, Brownfoot FC. High-dose compared with low-dose oxytocin for induction of labour of nulliparous women at term. J Matern Fetal Neonatal Med 2019;32:362–8.
14. Frigoletto FD Jr, Lieberman E, Lang JM, Cohen A, Barss V, Ringer S, et al. A clinical trial of active management of labor. N Engl J Med 1995;333:745–50.
15. Sadler LC, Davison T, McCowan LM. A randomised controlled trial and meta-analysis of active management of labour. BJOG 2000;107:909–15.
16. Rogers R, Gilson GJ, Miller AC, Izquierdo LE, Curet LB, Qualls CR. Active management of labor: Does it make a difference? Am J Obstet Gynecol 1997;177:599–605.
17. Xenakis EM, Langer O, Piper JM, Conway D, Berkus MD. Low-dose versus high-dose oxytocin augmentation of labor--a randomized trial. Am J Obstet Gynecol 1995;173:1874–8.
18. López-Zeno JA, Peaceman AM, Adashek JA, Socol ML. A controlled trial of a program for the active management of labor. N Engl J Med 1992;326:450–4.