Induction of Labor Using Native (OXYTIP) in Comparison to Foreign Oxytocin (SYNTOCINON)

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Abstract

Objective: This study was conducted with the aim to investigate and compare Iranian produced and foreign oxytocin for use in induction of labor.

Materials and methods: This random clinical trial was conducted on a population of 198 pregnant women with live fetus and cephalic presentation and conditions conducive to induction of labor, monitored by obstetricians and gynecologists .They were randomly divided into group A (n=99) received 10 units of Syntocinon (Novartis Pharma Canada) in 500 cc Ringer lactate, and group B (n=99) received 10 units of Oxytip (Caspian Tamin Company Iran) in 500 cc serum, who entered the study to commence induction, by signing written consent. Study variables such as induction indications (post-term, ruptured membranes, diabetes, and ..), induction duration, duration of the 1st and the 2nd stages of labor, and delivery method; as well as labor outcomes like hyper-stimulation of uterine, postpartum bleeding, 5-minute Apgar score, and infant's birth weight; and neonatal outcomes (admission to NICU, oxygen and intubation) were assessed for the two groups by a trained midwife and registered in the patient's questionnaire. Data were analyzed in SPSS software using statistical tests: t-test, Chi-square, and Mann-Whitney.

Results: Two groups were similar in demographic variables such as; age, BMI, parity, education. There was no significant difference regarding to obstetric and gynecologic characteristics such as: gestational age, dilatation, effacement, and fetal positioning, as well as the indication for labor induction when the study began. After intervention, variables including: induction duration, duration of the 1st and the 2nd stages of labor, delivery method; and labor outcomes such as: hyper-stimulation of uterine, postpartum bleeding, 5-minute Apgar score, and infant's birth weight; and neonatal outcomes (admission to NICU, oxygen and intubation), in the two groups, were found to be the same ($P<0.05$). Mean oxytip dosage needed was less than that of oxytocin to reach for appropriate pain ($P=0.042$).

Conclusion: The two drugs in terms of labor induction and neonatal complications had similar outcomes and the locally made drug with a lower dosage appears to produce the desired outcome.

Keywords: Induction, Oxytocin, Labor Induction, Oxitip

Introduction

Labor induction is a common intervention technique in childbirth, which is performed in 1 out of every 4 pregnant women in cases as: pre-eclampsia, diabetes, prolonged pregnancy, when cervix is ready or membranes are ruptured. It is administered intravenously as a labor induction strategy in term

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pregnancies (1). Shortening duration of labor by induction, especially when prolonging pregnancy, for whatever reason, poses a serious risk to mother and/or fetus, is a valuable successes in obstetrics (1). In addition to increased rate of maternal and fetal infections, prolonged labor has other consequences such as: increased hospitalization costs, increasing need for cesarean section. It is also an important factor in lowering Apgar score and infant's need for NICU (1, 2). Among standard indications for labor induction, gestational hypertension, and prolonged pregnancy are the most common criteria. In the U.S., labor induction from 9.5% in 1990 reached 22.1% by 2004 (2).

Various labor induction methods including use of oxytocin, prostaglandins, and amniotomy are available. In the Parkland Hospital, oxytocin was used to induce labor in 30% of deliveries. At Alabama University, Birmingham Hospital, oxytocin was used in 20% of deliveries between 1996 and 1999 (3).

Oxytocin is the most common medication used to induce labor in viable pregnancies, and it is the first synthetic polypeptide hormone made, which brought its creators the Noble Prize (1). This octa-peptide is secreted in pulse form and has a half-life of 10-12 minutes (4, 5).

The level of oxytocin that causes effective uterine contractions varies in different people, mostly due to the difference in clearance speed and number of oxytocin receptors in the uterus (6). Its success in induction of labor depends on condition of cervix at the onset of induction. To stimulate the pregnant uterus, this drug is administered intravenously because it is possible to measure dosage of administered drug, and in case of a complication, it can quickly be discontinued. The initial dose of this drug varies from 0.5 ml/min to 2 ml/min, and the interval between increased dosage also varies from 15 to 40 minutes (low dosage regimen) (7).

According to the new pharmacokinetics data, most obstetricians use a regimen in which oxytocin dosage is increased by 1-2 ml/min every 40 minutes (8, 9).

Considering the importance of labor induction and the drugs used, and given the circumstances in the country, the global sanctions, and the rising cost of medication, an important and valuable strategy for social empowerment is to turn to, and support national products. Also, in the particular economic circumstance of the country, it is important to try and locally produce medications that require valuable foreign currency to import. Thus, considering local production of these drugs and implementation of different approval stages, this study was conducted to compare the effects of foreign (Novartis Pharma Canada) and Iranian-produced oxytocin (Oxitip, Caspian Tamin Company) in labor induction in term and post-term deliveries. If the Iranian drug is efficient, it will help self-sufficiency of the country in pharmaceutical production. Through comparison of the locally-produced and foreign produced oxytocin, we can determine its particular side-effects and report them to the manufacturer in order to improve this drug. With its improved quality, or similarity of studied effects, this drug can be marketed globally, thereby reducing unwanted import costs of the drug.

Materials and methods

This study was a randomized double-blind clinical trial that was performed from 2012 till September 2013 in the Academic Medical Centre, the Vali-e-Asr Hospital, Tehran, Iran, with a target population of 220 pregnant women with live fetus and cephalic presentation and more than 37th week of gestational age (Fig 1). According to gynecologists' and obstetricians' opinions, induction of labor was indicated for these women because their cervix did not conform to medical parameters and was not appropriate for childbirth without intervention. Study inclusion criteria were singleton, cephalic presentation, healthy fetal membranes, Bishop score less than 4, reactive NST, or BPS8/10 and uterine contractions less than 3 in every 10 minutes.

Regular uterine contractions (more than 6 contractions per hour), fetal death, contraindication for amniotomy (like HIV positive), mother's age less than 18 years, history of cesarean section, multi-parity (>3), chorio-amniotitis, history of asthma, multiple pregnancy, placenta previa, non-cephalic presentation, glaucoma, vaginal bleeding, history of allergy to prostaglandins or beta-adrenergics, abnormal fetal heart rate, were exclusion criteria. 198 women was randomly and equally divided into group A and group B. Patient follow-up, in terms of delivery process to the end was carried out by obstetricians other than research team.

Before performing induction protocol, Bishop score was calculated for each pregnant woman by a qualified person and dilatation less than 3 cm and effacement of 10-30% were considered. To that end, all patients were first examined for uterine contractions by the researcher patients with Bishop

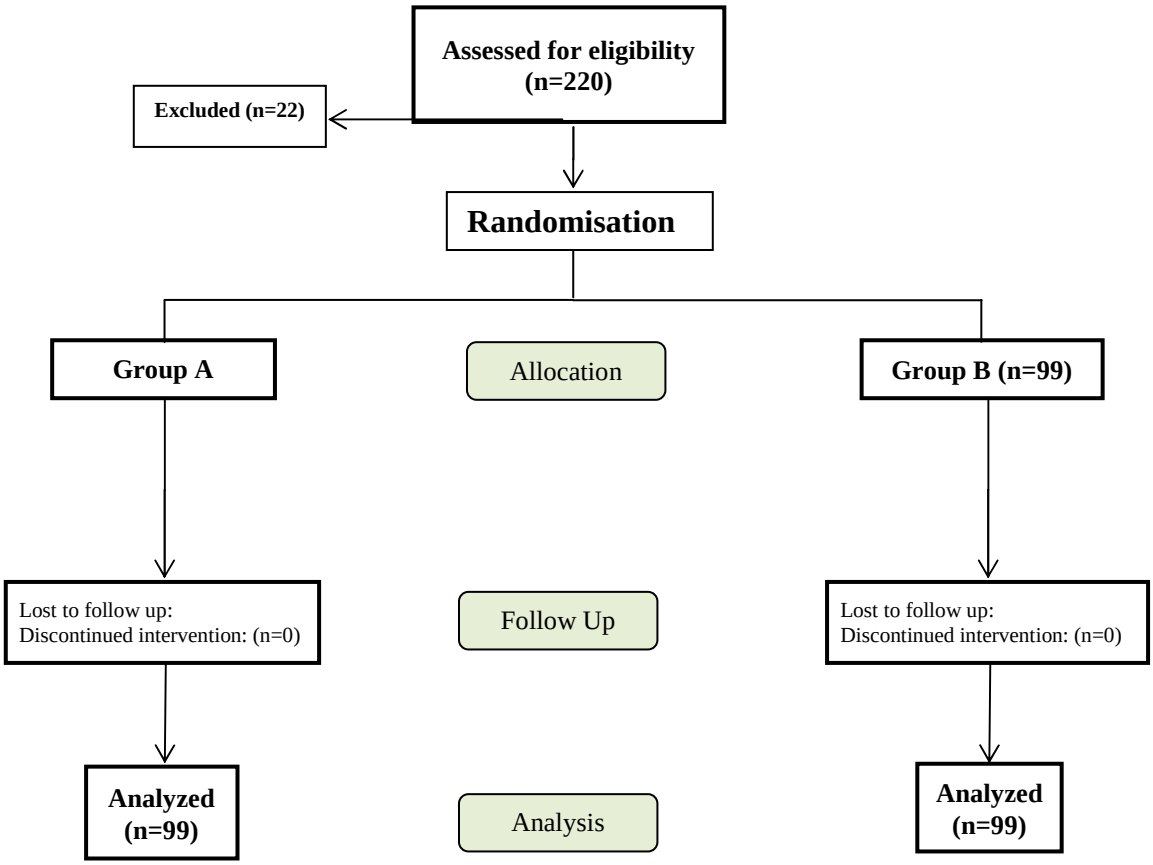

Figure 1: The consort flowchart

score of 4 or less and absence of uterine contractions were entered the treatment and intervention phase of the study. Before initiating induction, all patients underwent NST, and fetal heart rate was monitored. Patients that showed signs of fetal distress were excluded from the study. Written consent for participation in the study was obtained from all patients. This project was approved by the ethics committee of Tehran University of Medical Sciences, and was registered in the clinical trials site IRCT 201011275181N3.

Induction of labor initially began with 10 unit oxytocin in 1000 cc Ringer solution (2.5 mu/min), then increased every 15 minutes at infusion rate of 4 drops of 2.5Cc per minute, to reach a maximum of 40 mu/min, and continued at this rate, or until number of drops reached a maximum of 64 drops/min. With the right rate of contractions (3 contractions in every 10 minutes, each lasting more than 40 seconds and maximum of 60 seconds) there was no need to increase dosage and injection was maintained at the same rate. Obviously, healthcare providers in the delivery ward were blinded to the nature of the intervention.

With the onset of good contractions, vaginal examination was performed every hour with intact membranes, and every 2 hours with ruptured membranes, and uterine contractions were monitored every half hour. Before oxytocin injection, maternal vital signs were controlled, and then monitored every hour. Oxytocin was discontinued when fetal distress or uterine hyper-stimulation signs were observed. When uterine hyper-stimulation and fetal distress were improved, infusion re-started at half the previous dose, and continued as before. It was decided that, if within 6 hours of induction no change was observed, the patient was considered as an induction failure, and induction was discontinued. However, with change in status of cervix, induction continued. With non-spontaneous rupture of membranes, amniotomy was performed at dilatation of 5 cm. Furthermore, during induction, fetal heart rate was controlled every 15 minutes, and with any change in fetal heart rate, induction was stopped and permanent monitoring was performed. Also, during induction, uterine contractions were controlled, and with more than 4 contractions in every 10 minutes, or

with each contraction lasting more than 90 seconds and contraction intervals less than 60-90 seconds, uterine hyper-stimulation was assumed and induction was discontinued. Also, to assess progress of labor, cervical dilatation and effacement were controlled every 30 minutes during the 1st active stage of labor, and every 15 minutes during the 2nd stage of labor.

Data such as age, gestational age, number of pregnancies, induction indications, type of delivery, 5-minute Apgar score, birth weight, and primary and secondary outcomes were completed in the questionnaire. Data were analyzed with SPSS software using statistical tests: t-test, Chi-square, and Mann-Whitney.

Primary outcomes such as induction interval and labor duration, and secondary outcomes like duration of the second stage, and abnormal fetal heart rate pattern forceps delivery rate, cesarean rate, 5-minute Apgar score, number of indications for neonatal counseling cases, NICU cases were measured and compared in two groups.

Results

Mean age of the foreign oxytocin (group A) was 25.7 years and mean age in the locally produced oxytocin (group B) was 26.3 years. Mean BMI was 28.55 kg/m^{2}in group A, and 28.7 kg/m^{2}in group B. There was no difference between the two groups in terms of age (P=0.633), weight (P=0.678), height (P=0.257), or BMI (P=0.846) (Table 1).

No significant difference was found between the two groups in the reasons of labor induction like post-term, maternal diabetes, membrane rupture, or pre-eclampsia (p= 0.239); uterine hyper-stimulation was not reported in either of the group.

Mean drug dose was 28.98 drops in group A, and 24.29 drops in group B, and the difference between the two groups was statistically significant (p= 0.042). Also, duration of contractions was 42.96 seconds in the oxytocin group and 40.25 seconds in oxytocip group, which was less than that in foreign-made drug (P=0.016) (Table 1).

Study variables such as labor induction interval and onset of the first pain, duration of labor induction, duration of 1st and 2nd stages of labor and frequency of natural childbirth were the same in both oxytocin and oxytocip groups (Table 2).

Neonatal outcomes (admission to NICU, receiving oxygen, and intubation) were also the same in both oxytocin and oxytocip using pregnant women groups.

Postpartum hemorrhage was slightly more in group B compared to group A; however, the difference was insignificant (P=0.59). Hyper-stimulation did not occur in any of the two groups.

Table 1: Pre-intervention qualitative and quantitative variables in two groups

	Oxytocin (A) n= 98	Oxitip (B) n= 98	p value
Age (year) (mean± SD)	25.7± 4.56	26.30± 5.23	0.633
Weight (kg) (mean± SD)	75.92± 11.56	75.17± 14.30	0.687
BMI (kg/m2) (mean± SD)	28.55± 4.40	28.70± 5.91	0.846
Number of pregnancies (mean± SD)	1.71± 0.92	1.66± 0.96	0.706
Gestation age (weeks) (mean± SD)	39.10± 1.47	38.75± 1.33	0.080
Mean prenatal cervical dilatation (fingers) (mean± SD)	1.44± 0.63	1.46± 0.63	0.821
Education			
Illiterate-primary school (n, %)	6 (6.1)	9 (9.2)	0.821
Junior-high school	33 (33.3)	35 (35.7)	
High school Diploma (n, %)	57 (57.6)	51 (52.0)	
Bachelor's degree (n, %)	3 (3.0)	3 (3.0)	
Labor induction reasons			
Post-term fetus (n, %)	10 (10.1)	8 (8.1)	0.239
Intensifying labor pains (n, %)	39 (39.4)	40 (40.4)	
Maternal diabetes (n, %)	1 (1.0)	3 (3.0)	
Membrane rupture (n, %)	18 (18.2)	29 (29.3)	
Pre-eclampsia (n , %)	3 (3.0)	4 (4.0)	
Others (n,%)	27 (27.3)	16 (16.2)	

Table 2: Post-intervention childbirth variables in two groups

Variables	Cyntocinon (A) n= 98	Oxytip (B) n= 98	p value
Drug dosage at onset of pain (drops) (mean ±SD)	11.27± 9.11	7.45± 3.38	0.003
Interval between labor induction and onset of first pain (min) (mean ±SD)	41.9± 49	32± 54.9	0.067
Interval between labor induction and main pains (min) (mean ±SD)	198.96± 279.50	160.95± 182.95	0.245
Duration of labor induction (hr) (mean ±SD)	11.59± 7.92	9.74± 6.06	0.067
Duration of 1st phase of labor (hr) (mean ±SD)	2.62	4.75	0.158
Duration of 2nd phase of labor (hr) (mean ±SD)	31.96± 17.21	37.77± 24.06	0.695
Drug dose at onset of proper contractions (drops) (mean ±SD)	28.98± 15.84	24.29± 15.83	0.042
Duration of contractions (seconds) (mean ±SD)	42.96± 10.28	40.25± 4	0.016
Interval between contractions (min) (mean ±SD)	2.34± 1.43	2.52± 1.87	0.454
Cesarean (n, %)	47 (48%)	41 (41.4%)	0.454
Postnatal hemorrhage	0	4 (4.1%)	0.059
Neonatal complications			
5-minute Apgar score(mean	9.80± 0.51	9.84±0.40	0.261
Admission to NICU (n, %)	3 (3%)	6 (6.1%)	0.306
Nasal oxygen (n, %)	4 (4%)	5 (5.1%)	0.733
Oxygen mask (n, %)	3 (3%)	4 (4%)	0.700
Intubation (n, %)	1 (1%)	0	0.999

Discussion

Use of oxytocin in labor induction or augmentation is common in childbirth and delivery (10). Oxytocin is a potent drug, and its improper and prolonged use at high doses can cause complications such as cardiovascular effects, hypotension, uterine over-stimulation, fetal distress, uterine rupture, and water intoxication (11, 12). Considering that an important and valuable strategy for social empowerment is to turn to and support national produce, the present study was conducted to examine and compare the effects of Iranian produced with foreign produced oxytocin, and to determine the specific side-effects of the drug to report to the producing company, so that steps could be taken to improve the drug. Through enhanced quality and similarity of effects studied, the company could then market the drug globally.

In the present study, mean induction duration (induction onset to full opening of cervix) in the oxytocin group was 11.59± 7.92 and in the oxytocip group was 9.74±6.06 hours, which was nearly the same as the study conducted in the U.S. on 816 patients that used low dose of oxytocin, in which induction duration was 9.7 hours (13). Also, in a study by Aram in Isfahan, induction duration until completion of labor was nearly 771 minutes (12.5 hours) (14).

In a study by Sohrabi et al., in which a low dose of oxytocin was administered, duration of induction until labor was 14.5 hours (412.8 minutes) (15). Another study by T Tam in 2013 conducted on 625 patients from population of women undergoing induction with oxytocin, duration of induction until labor was 11.917 hours, and cesarean rate of 16% and natural birth of 74% were also reported (16).

It seems duration of induction until onset of labor in this study was almost similar to those of other studies, and within the normal range.

Given that type of delivery, duration of induction, and duration of effective pains were the same in both groups, the main cause of cesarean and lack of progress of labor was CPD (Cephalo-Plevic Disproportion). In a study by Charoenboon, cesarean rate caused by CPD increased from 3.2% in 1992 to 7.8% in 2011, which was more common than other indication like breech presentation, fetal distress, and multiple pregnancy [13]. As for Vali-e-Asr Hospital is a referral and teaching hospital, perhaps reports of high number of cesarean cases may be due to reasons other than oxytocin use. Selection of subjects with no particular risk factors largely reduced this limitation.

Conclusion

Both drugs had similar labor induction properties, and also similar effects on neonatal complications. However, the locally-made drug achieves the same results at low dosage.

Considering the results obtained and lack of specific complications, the Iranian oxytocin (Oxytip, Caspian Company) produces similar labor induction results to its foreign counterpart and it can be used as

an Iranian-made drug in current circumstances, benefiting from resistive economy in production and distribution of drugs, which will reduce current costs in the country.

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