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# Induction of Labour by Oxytocin: A Randomized Clinical Trial at Al-Sabeen Maternal Hospital, Sana'a city

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## Abstract

*Background: There is no enough data to know whether induction or augmentation of labour with oxytocin should be continued or stopped after the onset of active labour.*
*Aim: To answer the question of whether oxytocin induction of labour should be continued beyond the active phase or not?*
*Methods: A Clinical Randomized Trial for patients admitted for medical induction of labour with oxytocin .Exclusion criteria for induction of labour included non-vertex presentation, multiple pregnancies, non-reassuring fetal heart rate, past history of more than one caesarean delivery and estimated fetal weight of more than 4250 g . The study was conducted in the Department of Obstetrics and Gynecology at Al-Sabeen Maternal Hospital, Sana'a, Yemen. Patients who were admitted for induction of labour in Al-Sabeen Hospital from 1st march 2012 to 30th march 2013. By randomization, patients were divided into two groups. In the first group(1) ,Infusion of oxytocin was incremental until 5cm dilation and continued at the same level throughout the labour. In the second group (2) , infusion of oxytocin was incremental but discontinued when cervical dilatation reached 5cm. Main Outcome Measures: The first outcome variable was duration from induction to delivery. The secondary outcome variables included: maximal dosage and total amount of oxytocin used, duration of labour stage, fetal heart rate abnormalities and episodes of uterine hyper stimulation, mode of delivery, maternal and neonatal outcome.*
*Results: One hundred and six patients participated in this study. The active phase of labour was shorter in group2compared with group I , but this difference was not statistically significant ( 2.5 ± 2 vs. 3.2 ± 2.8 , P= 0.07 ). In group I, there were ten caesarean deliveries and in group 2 only seven. No significant differences were found when the other outcome parameters were compared.*
*Conclusion: There is no benefit in continuing oxytocin infusion after the onset of active phase of labour.*
*Keywords: Oxytocin, induction of labour, Yemen.*

## Introduction:

Oxytocin and its derivatives are drugs of varying chemical nature that have the power to excite contractions of the uterine muscles[1]. In 1950 de Vigneaud and coworkers did the noble prize winning work on structure of oxytocin[1]. It is synthesized in the supra optic and Para ventricular nuclei of the hypo – thalamus[1]. By nerve axons it is transported from the hypothalamus to the posterior pituitary where it is stored and released [1]. Oxytocin has a half-life of 3-4 minutes and duration of action of approximately 20 minutes. Myometrial (myometrium) oxytocin receptor concentration increases to maximum (100 – 200 fold) during labour [1] Oxytocin is the primary and the most widely used agent for induction of labour [2].

Induction of labour is intended in conditions that include ruptured membranes for more than 24 hours, postdate pregnancy (over 42 weeks), oligohydramnios (amniotic fluid index<5cm), intrauterine growth restriction, diabetic and non- reassuring fetal heart rate pattern. Whereas, it is not intended in certain conditions which include more than one caesarean section, non-vertex presentation, persistent

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non-reassuring fetal heart rate before induction of labour, multiple pregnancies and son graphically estimated fetal weight of more than 4250 gram [2].

Despite its extensive use, there is no consensus regarding initial dose, dosage increments and or the maximal dose [3-13]. In addition, there is not enough data to know whether induction or augmentation of labour with oxytocin should be continued or stopped after the onset of active labour. This is an important issue considering that the main adverse effect of oxytocin is uterine hyper-stimulation (six or more contractions in 10 minutes) [1]. This led to unnecessary fetal compromise, dysfunctional labour and uterine rupture [1].

In an attempt to address the issue of oxytocin infusion after the onset of active labour, this randomized clinical trial was carried out, by comparing the course and outcome of labour between two groups of patients admitted for induction or augmentation.

## Subjects and Methods

To answer the question of whether oxytocin induction of labour should be continued beyond the active phase or not?, a randomized clinical trial was carried out, for 106 pregnant women who were admitted for induction of labour in Al-Sabeen maternal hospital in Sana'a city during 1st march 2012 and 30th march 2013. The study sample size was calculated by Epi-info software using formula for comparing two-population proportion at confidence level 95%. Thus the sample size estimated was 106 pregnant women which were selected by convenient sample, according to inclusion criteria included postdate pregnancy (over42 weeks), ruptured membranes for more than 24 hours, oligohydramnios (amniotic fluid index<5cm), intrauterine growth restriction, diabetes and a sporadic non-reassuring fetal heart rate pottern. and exclusion criteria for induction of labour included non-vertex presention, more than one caesarean section, multiple pregnancies, persistent non-reassuring fetal heart rate before induction of labour and sonographially estimated fetal weight of more than4250g. All patients gave signed consent. By randomization, the selected pregnant (106 pregnant) were divided into two equals groups.

Patients were randomized using a computer_ generated random number sequence. The sealed opaque envelopes were opened before dividing the patients in two groups

In Group (1), infusion of oxytocin was incremental until 5cm dilatation, and was maintained at the same level until delivery. in group (2), infusion of oxytocin was discontinued when cervical dilatation reached 5cm. at the beginning of the active phase of labour (which defined as 5cm dilatation). Patients were recruited when cervical dilatation was less than 3cm and there were fewer than two contractions in 10 minutes, as recorded by electronic fetal monitoring, before the beginning of the active phase of labour.

Induction of labour was started by oxytocin infusion of 1 mIU/minute (5iu of oxytocin was diluted in 500mL of 0.9 Na saline). The dose was increased every 20 minutes 1mLu/minute until regular contractions at a rate of 3-5/10 minutes were reached. The maximal allowed dose of oxytocin was 20 m1u/minute. Uterine contractions were recorded during labour in all patients using electronic fetal Monitoring.

During carrying of the study, Oxytocin was discontinued in 5 patients of group (1) because of non-reassuring fetal heart rate, and similarly, Oxytocin was restarted in 5 patients of group (2) due to arrest of labour.

The data collection technique is an observation by record checklist, which contains recorded data that includes: duration from induction to delivery and the duration of stages of labour, maximal dose and total amount of oxytocin used, the used of analgesia and abnormalities in fetal heart rate, episodes of uterine hyper stimulation (>5 contractions in 10minutes), mode of delivery and maternal and neonatal outcome. Forty-six patients in each group were sufficient for the detection of 1.5 hours prolongation of labour. A well- trained female technical data collector

carried the clinical trial under the supervision of the principal investigator.

Study data were analyzed by SPSS (version 24). The qualitative variables were described by the calculation of frequency, while the quantitative variables were described by the calculation of mean and standard deviation. Power analysis was performed under the assumption of type 1 error of 6 % and a power of 81%. The estimation of the active phase of labour (primary outcome) was 4 hours. Chi- square was used for significance and odds ratio, for estimation of effect and was collected with 95% confidence interval. P<0.05 was considered significant. Comparison between categorical variables was performed using 2x2 cross tables.

## Results

Table (1), (2) and (3) summarizes the characteristics of the two study groups. No significant differences were found comparing the various parameters between the two groups. The two main indications for induction of labour were rupture of membranes and postdate in both groups.

**Table1 : Characteristics of labour among the study sample**

| Clinical data | Group 1(Oxytocin continued) | Group 2(Oxytocin discontinued) | p-value |
|---|---|---|---|
| Maternal age (years) Mean± SD | 25.5 (6.1) | 27.1(6.1) | 0.0569 |
| Parity Mean ± SD | 1.5 (1.8) | 1.6(1.6) | 0.7742 |
| Gestational (weeks) Mean ± SD | 40.0(1.5) | 40.0(1.5) | 0.9999 |
| Maternal weight (kg) Mean ± SD | 55.9(11.4) | 55.3(12.8) | 0.8089 |
| Weight gain | 10.5(5.6) | 10.9(5.6) | 0.7272 |
| Previous caesarean section (%) | 70% | 5% | 0.000 |

**Table 2: Indication for induction among the study groups**

| Variables | Group 1(Oxytocin continued) | Group 2(Oxytocin discontinued) |
|---|---|---|
| Postdate pregnancy | 26 | 22 |
| Rupture membrane 24 hours | 26 | 43 |
| Oligohydroaminios | 1 | 11 |
| Intrauterine growth retardation | 8 | 8 |
| Hypertensive disorders | 9 | 5 |
| Diabetes | 6 | 4 |
| Non-reassuring f6atal heart rate pattern | 9 | 9 |
| Other | 5 | 6 |

**Table 3: Cervical condition before induction among study groups**

| Cervical condition | Group 1 | Group 2 |
|---|---|---|
| Dilation (cm) Mean + -SD | 2.1 (0.5) | 2 (0.7) |
| Effacement (%) | 65 (12.4) | 60(15.3) |
| Station of the head(s) | 2.1(0.6) | 2(0.7) |

**Table 4. The course and outcome of labour in the study groups in mean (SD)**

| Time interval (hours) | Oxytocin Continued (N=53) | Oxytocin Discontinued (N=53) |
|---|---|---|
| From induction until active phase of labour. | 4(3.1) | 4.1(3.2) |
| Active phase | 3.3(2.9) | 2.6(2) |
| Second stage of labour | 0.5(0.6) | 0.53(0.6) |
| Maximal dose of oxytocin (mu/minute) | 6.7(2.9) | 6.9(3.5) |
| Uterine contractions before active labour (no. per 10 minutes) | 3.6(0.9) | 3.7(0.8) |
| Non-reassuring fetal heart rate during labour (%) | 9 | 9 |
| Uterine hyper stimulation (%) | 17 | 11 |
| Mode of delivery (no.) Caesarean section | 10 | 7 |
| Birth weight (g) | 3298(525) | 3391(513) |

Table(4) presents the course and outcome of labour in both groups. No significant differences were found when comparing the condition of the cervix before induction and the characteristics of labour.

Active phase of labour was shorter in group 2 compared with group 1, but this difference was not significant (OR = 1.48, 95% CI =0.56- 3.8). Oxytocin was discontinued in five women in group 1 because of a non-reassuring fetal heart rate.

Oxytocin was restarted in five women in group 2 because of insufficient uterine activity resulting in arrest of labour . In group I there were 10 caesarean deliveries and in group 2 there were seven (OR=2.13 , 96% CI =0.43-13.8). The indications for caesarean delivery in group 1 were: non-progressive labour (n=3), non-reassuring fetal heart rate (n=3). The indications for caesarean delivery in group 2 were also non-progressive labour (n=2) and non-reassuring fetal heart rate (n=1). No maternal or neonatal complications were recorded.

## Discussion

Oxytocin stimulates uterine contractions by mechanisms involving activation of receptor-operated calcium channels and release of calcium from the sarcoplasmic reticulum [6].

The level of oxytocin receptor transcripts increases according to the course of pregnancy. The receptor messenger RNA level increases over 300 fold at parturition compared with the non-pregnant myometrium [14]. Moreover, the receptor protein is also augmented at term and after the onset of labour . The myometrial sensitivity to oxytocin is governed by the concentration and binding kinetics of its available receptor [6]. It has been proposed that the effect of oxytocin on the conductivity of the uterus depends also on the gap junctions between myometrial cells and their expression during labour [15].

According to prior studies, we know that G-protein coupled receptors, such as the oxytocin receptor, undergo desensitization after prolonged and repeated stimulation[16,17 ] .

Indeed, exposure of cultured myometrial cells to oxytocin for a prolonged period causes desensitization, and the oxytocin receptor mRNA is reduced to a new low steady state concentration[18] . Phaneuf etal. described the changes of oxytocin receptors during the process of labour [16] .

After 12 hours of labour the concentration of oxytocin receptor mRNA in myometrial biopsies was approximately 50 times lower compared with the concentration of oxytocin receptor mRNA in biopsies obtained from patient in labour for less than 12 hours[16]. Adachi and Oku reported that the concentration of oxytocin receptors at cultured myometrial cells depended on the concentration of the oxytocin added and the time after addition of oxytocin to the culture[19]. These studies provide the background to our clinical experience. We frequently start oxytocin infusion during active labour in order to increase the frequency and the intensity of uterine contractions. This is probably due to changes in the concentration of oxytocin receptors during labour. However, once we start oxytocin induction of labour, the duration and concentration of the drug administered may have an opposite effect on the course of labour by desensitizing of uterine receptors to exogenous and endogenous oxytocin [20] . Therefore, it is reasonable to discontinue oxytocin infusion at the beginning of active labour because the process of labour is self-sustaining and continuing Oxytocin induction may only interfere with labour at this point [6]. Intravenous administration of a very dilute solution of oxytocin is the most effective medical means of inducing labour. Oxytocin exaggerates the inherent rhythmic pattern of uterine motility, which often becomes clinically evident during the last trimester and increases as term is approached[21]. The dosage must be individualized. The administration of oxytocin is determined with a biologic assay : the smallest possible effective dose must be determined for each patient[21].

Constant observation by qualified attendants is required[21].

Oxytocin is a powerful drug, and it has killed and maimed mothers through rupture of the uterus and even more babies through hypoxia from markedly hypertonic uterine contractions [22].

## Conclusion

There are a variety of different dosing protocols and dosing intervals for the administration of oxytocin for labour induction and augmentation. In general, higher doses are associated with shorter times to delivery but more uterine hyper-stimulation than are lower doses. Lower doses of oxytocin do not increase operative delivery rates or prolong delivery intervals. Complications of oxytocin administration include water intoxication, uterine hyper-stimulation and uterine rupture. Theses complications are most commonly seen with high-dose ,prolonged infusions.

So Infusion of oxytocin for induction of labour can be stopped at the beginning of the active phase, without prolongation of labour.

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