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Original Article

A Randomized Clinical Trial on the Need of Continuing Oxytocin Infusion in Active Phase of Induced Labour

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Abstract

Objective: To evaluate the effect of continuation and discontinuation of oxytocin infusion on maternal and neonatal outcome once the active phase of labour is established. **Methods:** This is a prospective randomized clinical trial on 100 pregnant women in whom labour was induced on obstetric ground in our institute. Patients were randomly divided in two groups. In the first group oxytocin infusion continued throughout labour and in the second group oxytocin infusion discontinued after establishment of active phase of labour. **Result:** Consumption of total oxytocin dose, induction-delivery interval, uterine hyperstimulation, caesarean section rate were significantly less in oxytocin discontinued group. Concurrently in oxytocin-continued group rate of *postpartum hemorrhage* (PPH), neonatal asphyxia, hyperbillirubinemia were higher in comparison to oxytocin-discontinued group. **Conclusion**: Continuous oxytocin infusion during active phase of labour increases chance of caesarean section, PPH and also of neonatal asphyxia, hyperbillirubenemia. Discontinuation of oxytocin infusion reduces labour risk and gives good neonatal outcome.

Key words: Oxytocin; Labour; Neonatal risk.

INTRODUCTION

Labour is a physiological process which may be defined as a coordinated effective sequence of involuntary uterine contraction that result in effacement and dilatation of the cervix and voluntary bearing down effort leading to the expulsion per vagina the product of conception.[1] It consists relatively long latent phase at the beginning and then a short and probably irreversible active phase follows.

Induction of labour is an integral part of modern obstetrics practice leading to progressive dilatation and effacement of cervix and delivery of baby. The safety and reliability of induction has greatly increased in recent years by applying different appropriate methods.

Oxytocics are the drugs of varying chemical nature that have the power to excite contraction of the uterine muscle.[5] Oxytocin, ergot derivatives dilates, and prostaglandins are extensively used in clinical practice.[5] Medical induction of labour is done by oxytocin and prostaglandins (PgE_2, PgE_1, $PgF_{2\alpha}$).[5] Oxytocin is an octapeptide hormone secreted mainly from posterior pituitary gland, is recognized as a potent stimulant that is thought to be essential for the contractile event of parturition.[7] The paracrine and autocrine mechanism regulating oxytocin and

its receptor within foetoplacental unit are central to the control of uterine contraction and parturition.[8]

The dose schedule of oxytocic drugs in induction and augmentation should aim to initiate effective contraction, leading to shorter induction-delivery interval and good obstetric outcome.[4] Thus, whereas, the need to use oxytocin may be considered pharmacologic, the regimen employed should be founded upon as understanding of the physiology and biochemistry of oxytocin during labour and human parturition.[6]

For an effective labour, strong and synchronous uterine contraction is required.[9] Oxytocin stimulate uterine contraction by activation of receptor-operated calcium channels and release of calcium from sarcoplasmic reticulum.[8] The effectivity of oxytocin depends on the expression of oxytocin receptor sensitivity.[10] Once myometrial oxytocin receptor concentration reaches a certain threshold level, effective uterine contraction are triggered.[11]

Induction of labour with oxytocin is successful only when oxytocin induces contractile activity results in prostaglandin $F_{2\alpha}$ production.[8] An interaction between oxytocin and prostaglandin thus seems to be essential for human parturition, at least when labour is induced with oxytocin.[11]

Oxytocin augmentation of labour is associated with uterine atony and long episode of labour induction may result in postpartum atony where bleeding cannot be stopped by intravenous oxytocin infusion.[14]

However, once we start oxytocin for induction of labour, the duration and concentration of drug administered may have an opposite effect on the course of labour by desensitizing oxytocin receptor to exogenous and endogenous oxytocin.[10] Therefore, it is reasonable to discontinue oxytocin infusion after establishment of active phase of labour, because the process of labour is self sustaining.[10]

There is also an important issue to consider. The main adverse effect of oxytocin for the mother include uterine hyperstimulation which may lead to unnecessary foetal compromise, and dysfunctional labour and also cause water intoxication and pulmonary oedema in the most extreme cases uterine rupture and postpartum atonic uterus, while the foetus may develop neonatal jaundice, transplacental hyponatremia, foetal circulatory collapse, foetal and neonatal bradycardia and elevated foetal scalp temperature.[6]

The purpose of this study is to support the hypothesis that discontinuation of oxytocin infusion after established active phase of induced labour give good obstetric outcome without any adverse maternal and neonatal effect.

MATERIALS AND METHODS

This was a prospective 6-month randomized clinical trial done from 01 June 2004 to 16 December 2004 on 100 pregnant women, conducted in the Department of Obstetrics and Gynaecology (Maternity Unit-I & II), Chittagong Medical College & Hospital, Chittagong, in whom labour was induced on obstetric ground.

The criteria of the patient's who were included in this study were as follows:

- Patients with ≥37 weeks to 40 weeks with singleton foetus in vertex presentation
- Post dated pregnancy (40–42 weeks)
- Term premature rupture of membrane
- Mild pre-eclampsia/hypertension at ≥39 weeks pregnancy

Following type of cases was excluded from this study:

- Non-vertex presentation
- Previous history of LSCS
- Multiple pregnancy/hydromnious
- Cervical dilatation of >3cm, on admission
- Congenital foetal anomaly
- Foetal distress on admission
- Foetal weight >4 kg
- Preterm labour
- Severe maternal disease/complication. For example, severe pre-eclampsia/eclampsia, APH, diabetes, and heart disease

Research Instrument

A pre-designed protocol was used as research instrument and its development based on specific objective of the study which included:

- History taking with particular aspect relevant to this study
- General examination
- Obstetrical examination
- Per abdominal examination
- Per vaginal examination
- Continuous monitoring of labour using a partograph (WHO recommended)
- Measurement of duration of different stages of labour
- Record of maximum dosage and total amount of oxytocin used
- Mode of delivery
- Record of foetal and neonatal outcome
- Maternal complication

PROCEDURE

Pregnant women who required induction of labour and who fulfilled the criteria of study population were included. Clinical assessment was performed with particular scrutiny of the menstrual and obstetrical history. Then after explaining the need for induction of labour and after taking signed consent, the patients were randomized using a computer-generated number sequence. The sealed opaque envelops were opened before dividing the patients in two groups. They were prepared and induction was initiated by starting synthetic oxytocin infusion.

Study Group (G-A): Infusion of oxytocin was started in incremental doses until 5 cm cervical dilatation and to be maintained at that level, throughout the labour.

Control Group (G-B): Infusion of oxytocin was started incrementally but discontinued when cervical dilatation reached 5 cm.

After admission following careful abdominal and vaginal examination, only those patients were recruited in whom cervical dilatation was less than 3 cm and there were fewer than two contraction in 10 minutes, before the beginning of active phase of labour.

Induction or augmentation of labour was done by starting oxytocin infusion either prior to or following rupture of the membrane depending mainly upon the state of the cervix. When the cervix was not ripened, per vaginal prostaglandin was given first followed by oxytocin infusion. The oxytocin used for this study was synthetic oxytocin, each ampoule (1 ml) contained 5 IU.

The concentration of oxytocin was 5 IU and 2.5 IU in 500 ml ringer lactate solution or 5% dextrose in normal saline in primi and multigravid patients, respectively. The infusion was started at a rate of 10 drops per minute. The drip rate was increased every half hourly until there was an effective uterine contraction (3/4 contraction per 10 minute) and reaching 5 cm cervical dilatation, provided the foetal heart rate was within normal range (120 to 160 beat per minute). In most of the cases patient responded by the time they were received 20–25 drop per minute. In some cases drop rate had to be increased up to 30 drop per minute where the maximum allowed dose was 20 mu/min.

The patient's sensitivity to the drugs was monitored by clinical observation. The duration and frequency of uterine contraction was determined by palpation rather than patient's statement and the intensity was estimated by the firmness with which the muscle contracted (when it could not be indented with firm finger pressure) and the contraction persisting for 40 sec were considered to be satisfactory. When effective uterine contraction was achieved, vaginal examination was done to assess the cervical dilatation. With cervical dilatation of 5 cm the oxytocin drip was continued in the existing dose in control group and discontinued in study group. But if after discontinuation of oxytocin drip effective contraction disappeared for 1 hour and then oxytocin drip was restarted. The foetal heart rate was heard with an ordinary stethoscope. All the cases were monitored by close and careful clinical observation and a partograph was maintained in each case to ensure correct supervision. The labour was managed according to the situation.

The recorded data included (a) duration from induction to delivery; (b) duration of the stages of labour; (c) maximal dose, total dose of oxytocin used; (d) the use of analgesia; (e) abnormality in foetal heart rate; (f) episode of uterine hyper stimulation (more than 6 contraction per 10 minute); (g) mode of delivery; and (h) maternal and neonatal outcome.

Data Collection and Data Analysis

All relevant information for each study subject was recorded on data collection sheets. Data compilation and relevant data analysis were done after thorough checking, editing, and also by using computer-based software, statistical package for social science (SPSS). Comparison between two group were made by using unpaired student's '*t*' test and 'chi-square' test as appropriate value <0.05 was taken as minimum level of significance.

RESULTS

This study was conducted in the Department of Obstetrics and Gynaecology in Chittagong Medical College & Hospital from 01 June 2004 to 16 December 2004. During this period a total number of 100 cases, requiring induction of labour and who fulfilled the study criteria were randomly selected. These 100 cases were divided into two groups for comparing course and outcome of labour. In Group-A, oxytocin was administered until delivery and in Group-B it was discontinued when active phase of labour was established. The observation and results of the study were shown in the form of table.

Table 1 shows that indications for induction or augmentation of labour in two groups were almost similar. The finding was found statistically, not significant. Highest percentage of women was induced for postdated pregnancy. Term pregnancy with PROM (premature rupture of membrane)

was the second most common indication for induction of labour.

Table 1: Indication for induction or augmentation of labour in the two groups

Indication	Group-A (n = 50) No (%)	Group-B (n = 50) No (%)	P value[a] χ^2
Postdated pregnancy	19 (38.0)	20 (40.0)	
Term pregnancy with PROM*	15 (30.0)	11 (22.0)	
Term pregnancy with labour pain	8 (16.0)	9 (18.0)	>0.50[ns]
Term pregnancy with mild hypertension	6 (12.0)	6 (12.0)	
Term pregnancy with labour pain with Rh negative blood group	2 (4.0)	4 (4.0)	

[a]Unpaired student's 't' test; *Premature rupture of membrane
Group-A: control group; Group-B: study group

Table 2 shows that mean Bishop's score on admission was nearly comparable in both group.

Table 2: Bishop's score on admission

Bishops score	Group-A (n = 50)	Group-B (n = 50)	P value a
Mean Range ± SE	6.50 ± 0.11	6.72 ± 0.11	>0.10

Table 3 shows that dose of oxytocin requirement was significantly less in study group, i.e., in Group-B (P < 0.001***).

Table 3: Total dose of oxytocin infused to patients of the study groups

Total dose of oxytocin (mu/min)	Group-A (n = 50) No (%)	Group-B (n = 50) No (%)	P value [a] χ^2
400–2000	6 (12.0)	27 (44.0)	
2100–4500	24 (48.0)	20 (40.0)	
4600–6500	6 (12.0)	7 (14.00	<0.001***
6600–8500	6 (12.0)	1 (2.0)	
8600–10,000	8 (16.0)	0	

Table 4 shows that the induction-delivery period in maximum number women in control group (54%) and in study group (56%) was within 4–11 hours. Some women in control group (16%) had delivery period >11 hours. The mean duration of delivery period was comparatively shorter in study group (2.5–10.5) than that of control group (3.5–13.0). The finding was found statistically significant (P < 0.01**).

Table 4: Induction-delivery interval in study population

Duration (hours)	Group-A (n = 50) N (%)	Group-B (n = 50) N (%)	P value[a] χ^2
4–6	15 (30.0)	22 (44.0)	
7–11	27 (54.0)	28 (56.0)	<0.01**
>11	8 (16.0)	0	

Table 5 shows maximum number of women had three to four uterine contraction per 10 minute in both control and study group (86% and 90%, respectively). But incidence of uterine hyperstimulation was 10% in control group whereas none in study group. This finding was found statistically significant (P < 0.05*).

Table 5: Uterine contraction during active phase of labour

Number of uterine contraction (per 10 min)	Group-A n = (50) N (%)	Group-B n = (50) N (%)	P value [a] χ^2
3–4	43 (86.00)	45 (90.0)	>0.10[ns]
>4–5	7 (14.0)	5 (10.0)	
>6	5 (10.0)	0	<0.05*

Table 6 shows that maximum number of women in Group-A (80%) and in Group-B (88%) delivered vaginally. Incidence of cesarean birth rate was higher in Group-A (16%) compared to Group-B (4%). The finding was statistically not significant (P > 0.10).

Table 6: Mode of delivery

Mode of delivery	Group-A (no = 50) No (%)	Group-B (no = 50) No (%)	P value[a] χ^2
Spontaneous vaginal delivery	40 (80.0)	44 (88.0)	
Vaccum extraction	2 (4.0)	4 (8.0)	> 0.10 [ns]
Cessarian delivery	8 (16.0)	2 (4.0)	

Table 7 shows that intrapartum foetal heart rate abnormality was observed in 8 (16%) of control group and in 5 (10%) of study group neonates. Within this two in control group and one in study group suffered from foetal distress. The finding was found statistically non-significant.

Table 7: Intra partum foetal outcome in study population

Parameter	Group-A (n=50) N(%)	Group-B (n=50) N(%)	*P* value[a] χ^2
Total	8 (16.0)	5 (10.0)	>0.10[ns]
Abnormality in intrapartum foetal heart rate	6 (75.0)	4 (80.0)	>0.05[ns]
Abnormal foetal heart rate with meconeum staining liquor	2 (25.00)	1 (20.0)	>0.05[ns]

Table 8 shows that there was no difference in both group in respect of neonatal resuscitation, admission to neonatal care unit, birth asphyxia. But neonatal jaundice was more common (14%) in control group. This is statistically significant ($P < 0.01$*). There was no difference between the two groups with regard to birth weight. Apgar score at 1 minute was significantly better in study group ($P < 0.01$*).

Table 8: Neonatal outcome in study population

Parameter	Group-A (*n* = 50) N(%)	Group-B (*n* = 50) N (%)	*P* value [a] χ^2
Resuscitation required	11 (22%)	6 (12.0)	>0.10[ns]
Admission to NCU	6 (12.0)	2 (4.0)	>0.10[ns]
Birth asphyxia	6 (12.0)	3 (6.0)	>0.10[ns]
Jaundice	7 (14.0)	0	<0.01**
Birth weight (kg) Mean range ± SE	3.40 ± 0.04 2.8 –3.9	3.34 ± 0.04 2.8–3.9	*P* value[b] >0.10 [ns]
Apgar score (1-min) Mean range ± SE	7.58±0.13 6–9	8.04±0.11 6–9	<0.01**

[b] unpaired student's '*t*' test

Table 9 shows that incidence of PPH was 12% women of control group whereas no incidence of PPH in study group and the finding was found statistically significant (*P* value[a] < 0.05*).

Table 9: Incidence of PPH in both groups

Complication	Group-A (*n* = 50) No (%)	Group-B (*n* = 50) No (%)	*P* value [a] χ^2
Postpartum haemorrhage	6 (12.0)	0	<0.05*

DISCUSSION

Oxytocin is a common drug used for induction or augmentation of labour. It is estimated that in most obstetric unit, 15–25% of women required oxytocin for either induction or augmentation of labour.[32]

Despite its common use, no unanimity exists as to the optimal dosage regimen. There is no consensus regarding the initial dose, dosage increment, and or the maximal dose. 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 established active phase of labour.

The purpose of this study is to find out whether there is any advantage in continuing oxytocin infusion after established active phase of labour and that stopping oxytocin at this stage can save the parturient from the hazard of excessive oxytocin use.

The study of Phaneuf et al.[15] demonstrated that during the progress of oxytocin-induced and, to a lesser extent, oxytocin-augmented labour, there is a significant reduction in both the concentration of myometrial oxytocin binding site and oxytocin receptor mRNA. These two parameters are integral part of myometrial oxytocin receptor desensitization in cultured cell in vitro.

Oxytocin stimulates uterine contraction by a mechanism involving activation of receptor operated calcium channels and release of calcium from the sarcoplasmic reticulum.[11] The level of oxytocin receptor messenger RNA increases over 300-fold at parturition compared with the non-pregnant myometrium.[12] The myometrial sensitivity to oxytocin is governed by the concentration and binding kinetics of its available receptor.[11]

According to prior studies we know that G-protein coupled receptors, such as the oxytocin receptors, undergo desensitization after prolonged and repeated stimulation.[13,15] Indeed, exposure of cultured myometrial cells to oxytocin for a prolonged period causes desensitization and the oxytocin receptor messenger RNA is reduced to a new low steady state concentration.[14]

Crall and Mattison study reported uterine response to fixed doses of oxytocin over long infusion time (up to 120 min) in 10 patients with secondary arrest of dilatation.[33]

Adachi and Oku[16] reported that the concentration of oxytocin receptor at cultured myometrial cell depended on the concentration of the oxytocin added and the time after addition of oxytocin to the culture. This study provides the background to our clinical experience. However, once active phase of labour is established, continuation of oxytocin may have an opposing effect on the course of labour by desensitizing of uterine receptor to exogenous and endogenous oxytocin. On the other hand, if misused or overused oxytocin leads to important complication such as uterine hyperstimulation, foetal distress, uterine rupture, postpartum uterine atony, rarely water intoxication, and neonatal hyperbilirubinemia.

In respect of age and gravidity difference in both groups were not significant. The indication for induction or augmentation of labour did not vary between the two groups significantly (Table 1) and this is correlated with previous study of Daniel-Spigel et al.[10] In the present study most of the women in both groups were induced for postdated pregnancy (Table 1). Term pregnancy with pre-labour rupture membrane, term pregnancy with labour pain were next most common cases.

There was no significant difference in mean Bishop's score before induction or augmentation of labour (Table 2) and this is correlated with the study by Daniel-Spigel et al.[10]

In the present study, oxytocin discontinuation group consumed significantly lower amount total dose of oxytocin than that of oxytocin continuation group (Table 3) and their success in achieving vaginal delivery is compelling.

In the present study, duration of active phase of labour was shorter in Group-B compared with that of Group-A. On the other hand, duration of second phase of labour was nearly similar in both the groups.

Oxytocin discontinued group was associated with significant shortening of induction-delivery interval of labour compared with that of oxytocin continued group (Table 4). Uterine contraction during active phase of labour did not differ significantly in both groups (3.77 ± 0.11 vs 3.53 ± 0.08). This finding is consistent with that of Daniel-Spigel study. In a study by Daniel-Spigel et al.[10] the incidence of uterine hyper stimulation in both groups were more or less similar, but the result of present study are particularly interesting in this regard. In present study, the incidence of uterine hyper stimulation was only in oxytocin continued group but none in oxytocin discontinued group (Table 5). Oxytocin was discontinued for uterine hyper stimulation in three women of control group but only in one women of study group for no reassuring foetal heart rate. In another study[10] oxytocin was discontinued in four women only in control group for non reassuring foetal heart rate.

In the present study, oxytocin was restarted in two women in Group-B for arrest of labour and two in Group-A for uterine inertia after discontinuation oxytocin causing uterine hyper stimulation, In the previous study, four women in similar group caused arrest of labour (done by Daniel-Spigel et al.[10]).

Regarding mode of delivery, there was no difference between the finding of present study and other previous studies[10] except in vacuum extraction (Table 6). In this study, vacuum extraction was higher in Group-B (8%) compared with that of Group-A (4%). But in the study by Daniel-Spigel et al.,[10] vacuum extraction was higher in Group-A (5%) compared with that of Group-B (3.8%).

Regarding intrapartum foetal monitoring, present study showed that 6 in control group and 4 in study group had abnormality in foetal heart rate. Two in control group and one in study group developed foetal distress (Table 7).

Neonatal outcome regarding birth weight shows no significant difference between present and Daniel-Spigel et al study[10]. There was some difference in other parameter between present and Daniel-Spigel et al study.[10] In the present study (Table 7) Apgar score is comparatively better in Group-B than that of Group-A. In this study, with respect to neonatal resuscitation, admission to NCU, there was no difference in both groups. Incidence of neonatal hyperbilirubinemia in oxytocin continued group was about 14%, whereas there was none in Group-B. An increased incidence of neonatal hyperbilirubinemia has been observed when the mother is given a total oxytocin dose more than 4500 mu.[34,35] On the other hand, a study by Daniel-Spigel et al.[10] showed no neonatal complication.

Though previous studies showed no maternal complication, in the present study 12% women in Group-A had PPH but women in Group-B had no complication (Table 9). According to Phaneuf et al.[13] study prolonged oxytocin infusion lead to desensitization of receptor which ultimately causes postpartum atony.

In present study it was observed that oxytocin discontinued regimen required less maximal dose of oxytocin, less amount of total dose of infused oxytocin, and had shorter labour, a statistically non-significant tendency for fewer

cesarean delivery, without any adverse maternal and neonatal effect. But there was some adverse maternal and neonatal outcome like uterine hyper stimulation, PPH, and neonatal jaundice in oxytocin continued group.

So the assumption that discontinuing oxytocin may prolong labour was not supported by present study or Daniel-Spigel study. The result of this study supports the hypothesis that continuing oxytocin infusion once, the active stage of labour is established may complicate labour and affect maternal and neonatal outcome.

Further investigations are needed to establish optimal protocol for the effective use of oxytocin. So we hope that larger and long-term well-designed clinical trial with a bigger sample size should be carried out to address the issue again.

Like all other studies this study has also some limitations. Such as it was based on small sample size, uterine activity (rate of contraction, tone, amplitude, etc.) was assessed only clinically, and intrapartum foetal monitoring was done only by clinical assessment. Besides that due to lack of facilities, the suspected intrapartum foetal distress could not be confirmed by intrapartum cardiotocography (CTG) or foetal scalp blood P^H estimation. In this study, foetal distress was diagnosed by auscultatory monitoring of foetal heart rate and presence of meconium in liquor.

CONCLUSION

It may be reasonable to discontinue oxytocin infusion after established active phase of labour.

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