Pulsatile Versus Continuous Oxytocin for the Augmentation of First Stage of Labour: Randomized Control Study

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Abstract
For the management of delay in the first stage of labour, oxytocin is usually administered as a continuous infusion. However, endogenous oxytocin from the posterior pituitary is not released continuously but as a pulse every three to five minutes. Numerous studies have reported that it is possible that pulsatile administration of oxytocin for dystocia may have advantages over continuous administration.

Aim: The current work aimed to study and compare the effects of pulsatile versus continuous intravenous oxytocin for the augmentation of delayed 1st stage of labor. Also, if there is an increase in the rate of vaginal delivery and reduction in fetal morbidity with the use of pulsatile versus continuous intravenous oxytocin.

Patients and Method: The current study is a randomized controlled study that was conducted in Ain Shams University Maternity Hospital in the prelabour ward at the period from May 2016 till Nov. 2016. 132 patients were studied and classified into 2 groups: Group (1) Pulsatile group: 66 patients were treated with the pulsatile regime in which a programmable syringe pump containing Syntocinon, stock solution: 10 iU/mL was administered for 10 seconds every 6 minutes and the dose (2mU/pulse). It was doubled every 30 minutes until uterine contractions are established (3/4 in 10). Group (2) control group: continuous oxytocin augmentation regimen). 66 patients were treated with oxytocin (Syntocinon, stock solution: 10 iU/mL) at starting dose (2mU/min) in a continuous manner doubled every 30 minutes until uterine contractions will be established (3/4 in 10).

Results: Showed that the mean time of augmentation of 1st stage of labor was in the study group (8.95 hours) and in the control group (7 hours) so that pulsatile oxytocin regimen wasn’t as effective as continuous oxytocin regimen in the augmentation of 1st stage of labor. The total dose of oxytocin was much lower in the study group (308.6 MIU) than in the control group (1368.8 MU).

The failure of vaginal delivery was in the study group 19 cases and in control group 16 cases with no statistically significant difference. As for maternal and neonatal outcomes there was no statistically significant difference as regards maternal admission to the ICU, postpartum hemorrhage, fetal apgar score or admission of neonates to the NICU.

Conclusion: The present study demonstrated that pulsatile oxytocin regimen was less effective than continuous oxytocin regimen in augmentation of the 1st stage of labour with lower total dose of oxytocin and mostly the same maternal and neonatal outcomes.

Key Words: Pulsatile oxytocin – Continuous oxytocin – Labour.

Introduction

OXYTOCIN, a neural hormone produced by the hypothalamus, is released by the posterior pituitary via the hypothalamohypophysial tract. A cyclic nanopeptide it is metabolised by the liver and kidneys. Oxytocin exerts its effect via a seven transmembrane G-protein coupled receptor, which is extensively expressed throughout the central nervous system and peripheral tissues. The action of oxytocin in the female reproductive tract is well recognized and the mechanisms underlying oxytocin stimulated myometrial contractions are increasingly understood [1,2].

Oxytocin is thought to contribute to the generation of the uterine contractions that occur during labour. Although basal plasma oxytocin levels may increase during the latter stages of pregnancy and the density of myometrial oxytocin receptors is increased in women in labour compared with those not in labour the role of oxytocin in the initiation of parturition has not been fully elucidated [2]. Syntocinon, commercially available as oxytocin, is produced by synthesis or extracted from the pituitary glands of mammals. This white or almost white powder is diluted in water to produce a colorless liquid with a pH of 4.5 that is buffered with dehydrated alcohol and acetic acid [3]. Syntocinon is administered for the induction of labour, management of delay in the first stage of labour and for the prevention and treatment of postpartum hemorrhage [4].
The main adverse event associated with intrapartum use of oxytocin is excessive uterine activity (hyperstimulation) which can lead to fetal compromise.

Oxytocin can be administered by intramuscular injection, slow intravenous injection or intravenous infusion. Many infusion regimes have been trialed for the management of delay in the first stage of labour.

A review comparing low- or high-dose oxytocin regimens for delay in labour concluded that the use of a high-dose oxytocin regimen was associated with an improvement in the number of vaginal deliveries achieved, but was unable to make any recommendations due to the quality of the evidence [5].

NICE currently recommends that the dose should not be increased quicker than every 30 minutes, with the aim of achieving four to five contractions in 10 minutes. Whether oxytocin should be administered as a continuous or pulsatile infusion is yet to be reviewed [4].

Delay in the first stage of labour is a common condition but there are limited management options available, with surgical intervention (caesarean section) being the last resort. The caesarean section rate has been steadily increasing since the 1980s. Previous reviews have reported that although oxytocin shortened the time to delivery, it did not affect the mode of delivery achieved but that high dose oxytocin may be more effective for the management of delay in labour [5].

A review of a different aspect of oxytocin administration may lead to further improvements in the management of delay in the first stage of labour increasing the vaginal delivery rate and reduce the caesarean section burden. Furthermore, pulsatile oxytocin administration may be less likely to cause uterine hyperstimulation, reducing the chances of fetal distress and improving neonatal outcome [6]. The aim of work of This study is to compare the efficacy of pulsatile oxytocin infusion with continuous oxytocin infusion for augmentation of the 1st stage of labour in women with delayed first stage of labour.

**Patients and Methods**

This study is a randomized controlled trial comparing continuous intravenous oxytocin infusion with the pulsatile administration of intravenous oxytocin for augmentation of the first stage of labour.

**Selection of subjects:**

The study population comprises 132 cases with spontaneous onset of labor who are admitted to the pre labor ward at causalities of Ain Shams University Maternity Hospital 2016.

Subjects who were included in this study should satisfy these inclusion criteria: Women in labour who require augmentation for poor progress of first stage, single viable fetus, rupture of membranes before augmentation, cephalic presentation and term pregnancy. Subjects who were excluded had the following exclusion criteria: Mal presentation, induction of labor, previous any uterine surgery, fetal abnormalities, premature labor, previous caesarean section, any uterine abnormalities, and multiple pregnancy.

**Grouping:**

Patients who need augmentation of first stage of labor will be distributed equally into two groups:

*Group 1 (study group; 66 patients):* Patients are given augmentation by oxytocin in pulsatile method.

*Group 2 (control group; 66 patients):* Patients are given augmentation by oxytocin in continuous method. The progression will be plotted on a partogram.

**Statically consideration (sample size):**

The required sample size has been calculated using the IBM© Sample Power© Software (IBM© Corp., Armonk, NY, USA).

A previous study reported that the mean infusion to delivery time associated with continuous infusion of oxytocin was 7.17 hours with a 95% confidence interval (95% CI) of 6.58 to 7.77 hours versus 9.61 hours (95% CI, 8.95 to 10.27 hours) in association with pulsatile oxytocin. The sample size for either regimen in that study was 240 patients or 241 patients, respectively [7].
Statistical methods:

Results or data collected are presented in diagramed table shape where two end points will appear showing either primary or secondary outcome variables.

Data were analyzed using IBM© SPSS© Statistics version 17 (SPSS© Inc., Armonk, NY, USA).

Normally distributed numerical variables were presented as mean and SD and inter-group differences were compared using the independent samples t-test.

$p$-values $<0.05$ were considered statistically significant.

Pulsatile group:

Pulsatile infusion protocol using a programmable syringe pump the pulsatile regime, oxytocin (Syntocinon, stock solution: 1 iU/mL) administered for 10 seconds every 6 minutes and the dose (2 mU/pulse). Will be doubled every 30 minutes until uterine contractions are established (3/4 in 10).

This regime stems from the observation that physiologic oxytocin may be released in a pulsatile fashion every 4-6 minutes [8].

Continuous group:

Patients were administrated oxytocin (Syntocinon, stock solution: 1 iU/mL) at starting dose (2 mU/min) in a continuous manner and doubled every 30 minutes until uterine contractions would be established (3/4 in 10).

Table (1): Continuous and Pulsatile oxytocin infusion regimes.

<table>
<thead>
<tr>
<th>Infusion mU/min</th>
<th>Continuous infusion mU in 30 min</th>
<th>Pulsatile infusion mU/pulse</th>
<th>Oxytocin infused mU in 30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>60</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>360</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>480</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>20*</td>
<td>600</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>720</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>28</td>
<td>840</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>32</td>
<td>960</td>
<td>160</td>
<td>160</td>
</tr>
</tbody>
</table>

*Continuous infusion above 20 mU/min discussed with obstetric team.

Pulsatile after 1 hour on 32 mU/pulse progress discussed with obstetric team to continue on same or increase up to 96 mU/pulse. Tribe. Pulsatile oxytocin and stimulation of labor. Am. J. Obstet. Gynecol. 2012.

Data collection:

Following admission, all patients will undergo complete clinical examination and detailed medical history will be obtained.

Personal history including: Name, age, marital status, parity, address, occupation, special habits.

Obstetric history: Where the gestational age will be calculated by the date of last menstrual period or by ultrasonography in unreliable dates.

Past history: Medical, surgical, drug, previous blood transfusion, allergy.

Examination: General, abdominal, local, then each patient will have case record form in which the following data will be recorded: (Appendix).

Consent procedures:

Written consent will be taken from all participants or their authorized representatives before recruitment the study after explanation of purpose and the procedure of the study.

Randomization:

Will be done as computer generated list (appendix).

Allocation and concealment:

120 Opaque Envelopes will be numbered serially, in each envelope the corresponding letter in randomization table will be put inside, then will be closed and put in one box. When the first woman arrives, the first envelope will be opened and she will be allocated to the group according to the letter inside.

Results

This table shows that there was no statistically significant difference between the two study groups as regard age, height, weight, gestational age, parity ($p$-values were more than 0.05).

This table shows that the time taken for augmentation in the pulsatile infusion group was higher than the time taken for augmentation in the continuous infusion group and there was statistically significant difference between them ($p$-value less than 0.05).

Moreover, it shows that there was no statistically significant difference between the two groups as regard cervical dilatation before augmentation and reaching full cervical dilation after augmentation ($p$-value more than 0.05).

This table shows that the total dose of oxytocin used in augmentation of the study group is markedly lower than the oxytocin used in augmentation in control group and there is statistically significant difference between them ($p$-value less than 0.05).
This table shows that there was no statistically significant difference in the failure of vaginal delivery between the study group and the control group. ($p$-value 0.32).

There were 19 cases failed to continue as normal vaginal delivery in the case group, 17 cases had a delay in the 1st stage time (beyond action line of the partogram) and 2 cases showed fetal distress and caesarean sections were done.

There were 16 cases failed to continue as normal vaginal delivery in the control group, 16 cases had a delay in the 1st stage time (beyond action line of the partogram) and caesarean sections were done.

This table shows that there was no statistically significant difference in hyperstimulation rates in both groups, ($p$-value more than 0.05).

Moreover, it shows that there was no statistically significant difference between the two study groups as regard post partum hemorrhage rates, maternal ICU admission rates ($p$-value more than 0.05).

This table shows there was no statistically significant difference between the two groups as regard fetal birth weight, apgar score, infants discharged with their mother and NICU admission. ($p$-value is more than 0.05).

Table (2): Characteristics of patients in both study groups.

<table>
<thead>
<tr>
<th></th>
<th>Pulsatile oxytocin group (n=60)</th>
<th>Continuous oxytocin group (n=60)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>24±2.61</td>
<td>28±2.09</td>
<td>0.465</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170±6.41</td>
<td>166±6.65</td>
<td>0.727</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80±8.07</td>
<td>75±7.9</td>
<td>0.665</td>
</tr>
<tr>
<td>GA (Wk)</td>
<td>37±0.33</td>
<td>39±0.42</td>
<td>0.368</td>
</tr>
<tr>
<td>Parity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PG</td>
<td>24 (40%)</td>
<td>19 (31.7%)</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>34 (56.7%)</td>
<td>38 (63.3%)</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>2 (3.3%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD or number (%). $p$-value is significant if less than 0.05.

Table (3): Duration of 1st stage of labour, cervical dilatation before starting augmentation and reaching full cervical dilatation after augmentation.

<table>
<thead>
<tr>
<th></th>
<th>Pulsatile oxytocin (study) group (n=60)</th>
<th>Continuous oxytocin (control) group (n=60)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of first stage of labour from starting of the augmentation till end of the 1st stage of labour (h)</td>
<td>8.95±0.75</td>
<td>7±0.80</td>
<td>0.001</td>
</tr>
<tr>
<td>Cervical dilatation before augmentation (cm)</td>
<td>3</td>
<td>4</td>
<td>1.101</td>
</tr>
<tr>
<td>Reaching Full Cervical Dilatation after augmentation</td>
<td>42 (63.3%)</td>
<td>50 (75%)</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or number (%). ($p$-value is significant if less than 0.05).
**Discussion**

The aim of this study was to find an alternative more efficient method for augmentation of delayed 1st stage of labour. The effects of pulsatile versus continuous intravenous oxytocin for the augmentation of 1st stage of labour is evaluated. Specifically to determine the time taken from starting...
Pulsatile Versus Continuous Oxytocin for the Augmentation of First Stage of Labour

augmentation to end of 1st stage of labour. Additionally, the increase in the rate of vaginal delivery and reduction in fetal morbidity with the use of pulsatile versus continuous intravenous oxytocin.

After application of inclusion and exclusion criteria 132 women in prelabor ward were chosen and assorted into the two groups.

The current study reported these items: Time of the first stage of labour in both study groups, total dose of oxytocin used in the augmentation in both groups, Caesarean section rates in both groups, Maternal and neonatal outcomes.

The mean age of the study groups was (24 year ± 2.61) which was lower than the mean age of control group (28±2.09 year). The mean height of the study group was (170cm ± 6.41) and in the control group was (166 cm ±6.65). The mean weight of the study group was (80 kg ±8.07) and in control group was (75kg ±7.9). The mean gestational age of the study group was (37 weeks ±0.33) and in control group was (39 weeks ±0.32). There was no statistically significant difference between them as regard age, height, weight and gestational age.

In the current study the time of the augmentation of the 1st stage of labour was (8.95 H) in study group compared to (7h) in control group. It was higher than control group with a statistically significant difference (p=0.001).

The present results are keeping with the results of [7] which reported the failure of vaginal birth in continuous infusion oxytocin group was 37% and in pulsatile oxytocin group was 47% with no statistically significant difference.

In the current study there was no hyperstimulation (more than 5 contractions in 10min) noted in both groups with no statistically significant difference (p>0.05). These results are keeping with the results of [9] who reported the absence of a statistically significant difference with respect to maternal characteristic and no hyperstimulation was noted in either groups.

In the current study, there was only one case in the study group that was admitted to ICU unit as she had severe primary (atonic) postpartum hemorrhage after delivery with no statistically significant difference between the two groups (p=0.406).

As for postpartum haemorrhage, 3 cases were noted in the study group (2 cases atonic pph and one case was a cervical tear) and 2 cases in the control group (2 cases of atonic pph), with no statistically significant difference (p=0.651).

The mean birth weight in the study group reached (2.8kg) compared to (3.0kg) in control group with no statistically significant difference (p-value=0.135).

Two neonates (low apgar score) were admitted to NICU for the study group reached (2.8kg) compared to (3.0kg) in control group with no statistically significant difference (p-value=0.173).

It was reported that admission to NICU was higher in pulsatile group 6.5% versus 2% in continuous group with p-value (.009) was statistically significant [7,11].
The results of the present work suggested that administration of pulsatile oxytocin versus continuous oxytocin had not any beneficial effect in labour outcomes as regard the time of augmentation of 1st stage of labour.

Moreover, the rates of maternal ICU admission, postpartum haemorrhage, hyper stimulation achieved, birth weights and admission of neonates to NICU showed no statistically significant difference between the two tested groups.

However, further studies with larger numbers of subjects and blinded observers are needed to validate the efficacy of pulsatile oxytocine in augmentation of 1st stage of labour.

In conclusion: Our study demonstrated that pulsatile oxytocin regimen was less effective than continuous oxytocin regimen in augmentation of the 1st stage of labour with lower total dose of oxytocin and mostly the same maternal and neonatal outcome.

References


مقارنة بين طريقة إعطاء الأوكسيتوسين بالتنقيط الوريدي المستمر والتنقيط الوريدي على دفعات تعزيز المرحلة الأولى في الولادة

لعلاج التأخر في المرحلة الأولى في الولادة غالباً ما يعطى الأوكسيتوسين عن طريق التنقيط الوريدي المستمر. الأوكسيتوسين هو هرمون يخرج من الغدة النخامية الخلفية عند حدوث الولادة على دفعات كل ثلاث إلى أربع دقائق. وعاء الأوكسيتوسين بالتنقيط الوريدي المستمر يؤدي إلى تنخفض عدد مستقبلات الأوكسيتوسين في خلايا عضلات الرحم مما يضعف تأثيره.

في إعطاء الأوكسيتوسين بطريقة تفاعلية تمثل طريقة خروجه من الغدة النخامية بإعطاءه على دفعات كل ثلاث إلى أربع دقائق يؤدي إلى تعزيز فعالية
وتقصير المرحلة الأولى في الولادة وإعادة جرعات أقل مما يقلل من حدوث اضطرابات للجنين وتبقي زمن المرحلة الأولى من الولادة.

وقد أجريت هذه الدراسة في جامعة عين شمس مستشفى النساء والتوليد عن ما قبل الولادة في الفترة من مارس 2016 حتى نوفمبر 2016.

هدف الدراسة: تهدف هذه الدراسة إلى مقارنة تأثير تعزيز المرحلة الأولى من الحمل باستخدام الأوكسيتوسين بالتنقيط على دفعات والتنقيط المستمر لعلاج تأخر المرحلة الأولى.

مجموعات الدراسة: تضم الدراسة 132 حالة في ولادة ثقافية في كشف الولادة مجموعة التنقيط على دفعات: باستخدام سريرة حقن وريدي مبرمجة بالأوكسيتوسين سوف يعطى لمدة 10 ثوان كل 1 دقائق ونسبة كل نصف ساعة لحين الوصول للعدد الأقصى لطلقات الرحم 3-4 في كل 10 دقائق (باستخدام محلول 10 وحدات/مل).

مجموعة التنقيط المستمر: سوف يعطى الأوكسيتوسين الوريدي باستمرار ويضاف كل 2 دقيقة لحين الوصول للعدد الأقصى لطلقات الرحم في كل 10 دقائق (باستخدام محلول 10 وحدات/مل).

نتائج الدراسة: في الدراسة الحالية وجد فرق ذات دلالات إحصائية بين مجموعة الأوكسيتوسين في مجموعات الأوكسيتوسين المستمر من حيث زمن تعزيز المرحلة الأولى من الولادة، وتصلح (H=8.95) في مجموعات الأوكسيتوسين على دفعات و (H=7.6) في مجموعة الأوكسيتوسين المستمر بقيمة (0.01) بالناكونية فإن زمن تعزيز في مجموعة الأوكسيتوسين على دفعات أطول من زمن التعزيز في مجموعة الأوكسيتوسين المستمر.

وفي الدراسة الحالية معدل فشل الولادة الطبيعية كان 27٪ في مجموعة الأوكسيتوسين على دفعات و 20٪ في مجموعة الأوكسيتوسين المستمر. وبالتالي فإن مجموعات الأوكسيتوسين على دفعات تزيد من معدل الولادة الجراحية عن مجموعات الأوكسيتوسين المستمر.

في الدراسة الحالية لم يوجد فرق ذات دلالات إحصائية بين فرق التتبيه للرحم ونسبة دخول الأمهات إلى الرعاية المركزية وحCTRLح الزمن الذي يمر به المولود بعد الولادة.

في الدراسة الحالية وجد أنه لا يوجد فرق ذات دلالات إحصائية من حيث وزن حديثي الولادة أو دخولهم إلى الحضانات.