ABSTRACT

Objective: The purpose of the current study was to investigate the role of umbilical vein injection of oxytocin compared to saline in the treatment of retained placenta.

Setting: Obstetrics and Gynecology Department, Benha University Hospital.

Design: A Double-blind Randomized Placebo-controlled Clinical Trial

Materials and methods: Retained placenta was reported in 69 cases out of 5858 vaginal deliveries (1.2%). Sixty women fulfilling the inclusion criteria were included in this study and scheduled randomly into two equal groups. Study (Oxytocin) group (n=30) received intraumbilical vein injection of 20 I.U. Oxytocin diluted in 20 ml normal saline and placebo-control group received intraumbilical vein injection of 20 ml normal saline.

Results: There were higher rate of spontaneous expulsion of the retained placenta (46.7% vs. 13.3%; p=0.0087), less need for manual removal of the placenta (53.3%) vs. 86.7%; p=0.0087), less blood loss after intraumbilical vein injection in both groups (200± 26.45mL vs. 200± 26.45mL respectively; p < 0.0001), less need of blood transfusion, shorter injection to expulsion interval, higher hemoglobin level 24 – 48 hours later in favor of oxytocin group compared to Saline group (10.06 ± 0.94 gm/dl vs. 9.63 ± 0.44 gm/dl; p = 0.0270 respectively) and the differences were statistically significant. However, the difference between both groups was not significant regarding the duration of 1st & 2nd stages of labor and the number of women took oxytocin in the 1st stage of labor and the type of vaginal delivery, the occurrence of infection, average blood loss during labor and the duration of hospital stay.

Conclusion: The intraumbilical vein injection of oxytocin is a simple, easy, less invasive and effective choice for treatment of retained placenta.

INTRODUCTION

Retained placenta is regarded as the most common amongst the etiologies of post-partum hemorrhage. It is associ-
ated with the high risk of maternal morbidity and mortality because it has the impending risks of infection and hemorrhage. (Lindsay P. 2004) Consistent with World Health Organization (WHO), the retained placenta is diagnosed once the placenta isn't expelled at half an hour interval from delivery of the baby and the incidence of retained placenta is 3.3 with this definition. The median duration of the normal third stage of labor is 6 minutes. However, the incidence of PPH significantly increases after 30 minutes of the third stage of labor (WHO guidelines 2009). Also, the incidence of retained placenta is raised in preterm delivery (gestation <37 weeks) and markedly increased in extremely preterm delivery (gestation <27 weeks) (Silverman, 2006).

Manual extraction of the placenta, the suggested approach of retained placenta, usually orders obstetrician skills and regional or general anesthesia and may be complicated by infectious morbidity (Tandberg A, et al 1999). The World Health Organization supports the umbilical vein injection (UVI) of saline solution with uterotonic agents, e.g., oxytocin or prostaglandins as a significant first-choice for treatment of retained placenta. This allows the drug to be pointed specifically to the retroplacental myometrium in the area with the failed contractility while saving the rest. (Carroli & Bergel 2001) Unfortunately, this treatment option is not routinely practiced, probably due to the scarcity of large randomized trials and dilemmas about the ideal drug and dosage regimens (Nardin et al., 2012).

The current research endeavored to examine the role of umbilical vein injection of oxytocin compared to saline in the treatment of retained placenta.

**PATIENTS AND METHODS**

This prospective double-blinded randomized placebo-controlled trial was managed at the Obstetrics emergency unit of the Department of Obstetrics and Gynecology, Benha University Hospital, through the period commenced from August 2014 until January 2016. The study protocol was approved by the Internal Ethics Committee and signed knowledgeable consent was taken from each patient before the start of the study. The study was applied to 60 ladies with retained placenta for more than 30 minutes after fetal delivery and fulfilled the subsequent inclusion and exclusion criteria.

**Inclusion criteria were:**

- Women aged ≥ 18 years old.
- Singleton pregnancy.
- Gestational age ≥ 34 weeks who underwent vaginal delivery.
- Retained placenta: failure to deliver the placenta after 30 min of active management of the third stage of labor (10 IU of oxytocin intramuscularly) with the delivery of anterior shoulder, in the presence of an intact umbilical cord.
- Haemodynamically stable women.

**Exclusion criteria were:**

- History of previous PPH.
- History of cesarean section, or any uterine scar.
• Antepartum hemorrhage either placental separation or placenta previa.
• Sonographic evidence of Placenta accreta.
• Dysfunctional labor.
• Polyhydramnios, chorioamnionitis, and instrumental delivery (forceps and vacuum).
• Patients on anticoagulants or those with Coagulopathy.
• Women who underwent painless labor with epidural anesthesia.
• Conditions requiring immediate intervention:

1. Maternal hemodynamic instability
   (pulse > 100 beat/ min or systolic blood pressure < 90 mmHg)
2. PPH requiring immediate intervention.
   • Stillborn baby.
   • All high risk pregnancies with medical disorders i.e. hypertension, diabetes mellitus, cardiac disease, and severe anemia.
   • Known uterine malformations.

METHODS

After thorough clinical and obstetrical examination, patients were randomized according to a computer-based random numerical table into 2 equal groups each included 30 participants. Group I (Study group) and group II (Control group).

Group I (Oxytocin): Included 30 women for whom 201 U. Oxytocin diluted in 20 ml normal saline that was injected into the umbilical vein. Injection was done into the umbilical vein 1 cm from the introitus after placing a haemostat on the cord immediately distal to the site of injection, milking of the cord toward the placenta after injection was carried out to distribute the solution into the placenta.

Group II (Saline): Included 30 women for whom 20 ml normal saline is injected into the umbilical vein. In order to see if placental expulsion is due to the medication, or to the bolus of fluid injected into the umbilical vein and to achieve a placebo effect.

When signs of placental separation occurred, firm contraction of the uterus was ensured and placenta was delivered by Brandt Andrew method and controlled cord traction.

Both the obstetrician and the patient were blinded to the nature of the used medications. The preparation and administration of the medication were carried out by a study nurse who had not been involved in the management of the patient except for drug administration. Data collection sheets with corresponding codes were filled out preoperatively by the operating surgeon. These sheets were completed postoperatively by residents.

Estimation of blood loss:

After the delivery of the baby, amniotic fluid was allowed to drain away; and the separate pad was applied over the episiotomy so that blood did not mix with blood that was lost during and after separation of the placenta. Linen was covered with a plastic sheet under the buttocks to avoid soiling/mixing with blood.
The lower end of plastic cover was molded into a funnel that dipped into a low-profile bedpan (kidney tray with a capacity of 500 ml) for next hour. The collected blood, blood clots and heavily soaked swabs from the pan were decanted into a graduated measuring cylinder and measured by an attending nurse. The blood loss was measured in milliliters (mL).

Outcome measures include:

Intra-partum measures:

- Placental Retention duration
- Successful expulsion of the placenta after the injection.
- Methods of placental delivery with failed study maneuver.
- Amount of blood loss.
- Need for blood transfusion.

Post-partum measures:

- Hemoglobin level at 24 hours.
- Reported complication (PPH, fever).
- Days of hospital stay.

Statistical analysis: the gathered data were statistically analyzed using Statistical Package of Social Science (SPSS) version 16. Numerical data were described as the mean± the standard deviation, and the difference was tested using the Student t-test. Categorical data were described as number and percentage and Chi-square test and Relative risk ratio at a 95% confidence interval were used to test the difference as appropriate. Number Needed to Treat (NNT) is the number of patients needed to be treated for an extra-patient to benefit. The result was considered significant at a p-value <0.05.

RESULTS

During the study period, 69 cases of retained placenta were reported among 5858 vaginal deliveries (1.2 %). Sixty women fulfilling the inclusion criteria were included in this study. Thirty women were included in each group. Table 1 shows no significant differences between the Saline group and oxytocin group in terms of maternal age, gestational age, gravidity, past history of abortion, and fetal birth weight. Table 2 shows no significant differences between the saline control group and oxytocin group as regarding duration of 1st & 2nd stages of labor and number of women took oxytocin in 1st stage of labor and type of vaginal delivery. Table 3 shows a higher rate of spontaneous expulsion of the placenta, less need for manual removal of the placenta, less blood loss after intraumbilical vein injection, less need of blood transfusion, shorter and injection to expulsion interval (minutes), higher hemoglobin level 24 – 48 hours later in favor of oxytocin group compared to Saline group and the difference was statistically significant. However, no significant difference was noted between the two groups regard the occurrence of infection, average blood loss during labor and the duration of hospital stay.
Figure (I): Consort flow chart of participants throughout the trial
Table 1: Patients’ characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oxytocin group (N = 30)</th>
<th>Saline group (N = 30)</th>
<th>Statistical test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>24.06 ± 4.3</td>
<td>24.93 ± 3.05</td>
<td>t=0.904</td>
<td>0.3698</td>
</tr>
<tr>
<td>Gestational age (Weeks)</td>
<td>39.02 ± 1.10</td>
<td>38.82 ± 4.12</td>
<td>t= -0.257</td>
<td>0.7982</td>
</tr>
<tr>
<td>Gravidity {n (%)}</td>
<td>PG</td>
<td>MG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (43.3%)</td>
<td>10 (33.3%)</td>
<td>X= 0.635</td>
<td>0.426</td>
</tr>
<tr>
<td>Past history of abortion</td>
<td>8 (26.7%)</td>
<td>9 (30%)</td>
<td>X= 0.082</td>
<td>0.775</td>
</tr>
<tr>
<td>Birth weight (gm)</td>
<td>3270± 398 (2637 – 4000)</td>
<td>3312± 413 (2750 –3950)</td>
<td>t= 0.401</td>
<td>0.6898</td>
</tr>
</tbody>
</table>

NB: Data are expressed as means ± SD (Standard deviation), number (percent), or rang, t= t test, X= Chi square test, * Significant = (p value < 0.05).

Table 2: Delivery characteristics of the Saline and Oxytocin groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oxytocin group (N = 30)</th>
<th>Saline group (N = 30)</th>
<th>Statistical test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of 1st stage in hours</td>
<td>7 ± 1.41</td>
<td>7.06 ± 1.33</td>
<td>t= 0.17</td>
<td>0.87</td>
</tr>
<tr>
<td>Duration of 2nd stage in minutes</td>
<td>40 ± 12</td>
<td>38 ± 18</td>
<td>t= -0.506</td>
<td>0.615</td>
</tr>
<tr>
<td>Oxytocin given in 1st stage</td>
<td>23 (76.7%)</td>
<td>21 (70%)</td>
<td>X= 0.341</td>
<td>0.56</td>
</tr>
<tr>
<td>Type of vaginal delivery</td>
<td>Spontaneous</td>
<td>Instrumental</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (66.67%)</td>
<td>10 (33.33%)</td>
<td>X= 0.739</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>23 (76.7%)</td>
<td>7 (23.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NB: Data are expressed as means ± SD (Standard deviation), or number (percent), t= t test, X= Chi square test, * Significant = (p value < 0.05).
Table (3): Comparison between Oxytocin group and Saline group regards the outcome measures

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oxytocin group (N = 30)</th>
<th>Saline group (N = 30)</th>
<th>RR (95% CI)</th>
<th>p value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous expulsion of the placenta</td>
<td>14 (46.7%)</td>
<td>4 (13.3%)</td>
<td>0.6154 (0.4281 to 0.8847)</td>
<td>0.0087*</td>
<td>3</td>
</tr>
<tr>
<td>Need for manual removal</td>
<td>16 (53.3%)</td>
<td>26 (86.7%)</td>
<td>0.6154 (0.4281 to 0.8847)</td>
<td>0.0087*</td>
<td>3</td>
</tr>
<tr>
<td>Need of blood transfusion</td>
<td>4 (13.3%)</td>
<td>12 (40%)</td>
<td>0.3333 (0.1211 to 0.9172)</td>
<td>0.0334*</td>
<td>3.75</td>
</tr>
<tr>
<td>Occurrence of infection</td>
<td>5 (16.7%)</td>
<td>6 (20%)</td>
<td>1.2500 (0.3714 to 4.2066)</td>
<td>0.7185</td>
<td>30</td>
</tr>
<tr>
<td>Injection expulsion interval in minutes.</td>
<td>10 ± 0.81</td>
<td>15.5 ± 1.69</td>
<td>&lt; 0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood loss after entry in ml</td>
<td>200 ± 26.45</td>
<td>321 ± 24.16</td>
<td>&lt; 0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average blood loss during labor</td>
<td>970 ± 320</td>
<td>1000 ± 215</td>
<td>0.6715</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level 24 hours later</td>
<td>10.06 ± 0.94</td>
<td>9.63 ± 0.44</td>
<td>0.0270*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days of hospital stay</td>
<td>1.06 ± 0.79</td>
<td>0.93 ± 0.48</td>
<td>0.4443</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NB: Data are expressed as means ± SD (Standard deviation), or number (percent).
* Significant = (p value < 0.05)
DISCUSSION

The current research proposed to examine the performance of the intraumbilical vein injection of oxytocin compared to normal saline in the management of retained placenta. The present study proved significantly higher rates of the spontaneous expulsion of the placenta in the oxytocin group compared to the saline group (46.7% vs. 13.3%; \( p=0.0087 \)). Consequently, the need for manual extraction of the placenta is significantly lower in oxytocin group compared to saline group (53.3% vs. 86.7%; \( p=0.0087 \)). These conclusions are in agreement with Carroli & Bergel 2001, in their meta-analysis that involved 10 trials concluded that there was a significant decrease in the rate of manual removal of the placenta with saline plus oxytocin compared to placebo. Also, Ivalingam & Surinder 2001, observed a reduction in the necessity for hand-operated placental extraction by the use of saline plus oxytocin compared with placebo.

Samanta et al. 2013 reported that umbilical vein injection of 50IU oxytocin in 30mL of NS delivered the retained placenta effectively and this option appears a simple and encouraging procedure to decrease the incidence of a potentially morbid classical interventional procedure and other complications. Nankali et al. 2013 showed that intraumbilical vein injection of 10 IU oxytocin (in 10mL of NS) immediately after fetal delivery was clinically effective in shortening the third stage of labor; nevertheless, its routine use in the management of the third stage of labor is not supported. Lim et al. 2011 proved a significant decline in the rate of consequent manual extraction of placenta (30 vs. 67.7%, \( p < 0.05 \)), incidence of uterine atony (3.3 vs. 25.8%, \( p < 0.05 \)) and the necessity for uterotonics agents (33.3 vs. 64.5%, \( p < 0.05 \)) in the oxytocin group compared with the control group.

In contrary to these conclusions the Cochrane Collaboration review settled the non-effectiveness of the umbilical vein injection of oxytocin for the treatment of RP.

Therefore, further research into the optimal timing of manual removal and into UVI of prostaglandins or plasma expander is warranted. (Nardin et al., 2012) Also, a double-blind, placebo-controlled trial including women in the UK, Uganda, and Pakistan reported that umbilical vein injection of oxytocin had no clinically significant effect on the need for MROP. (Weeks et al., 2010)

Compared to other uterotonics agents, Harara et al. 2011 reported that the overall success rate of spontaneous placental separation within 30 min after intraumbilical injection of uterotonics was 56/78 (71.79%). The success rate was higher with misoprostol when compared to oxytocin and ergometrine but the difference was not significant (20/25 [80%], 19/26 [73.08%], 17/27 [62.96%], respectively, \( P>0.05 \)). The injection-to-separation interval was significantly shorter in the misoprostol group than in the oxytocin and ergometrine groups (7.0±2.2 min, 13.14±3.76 min, 22.5±4.37 min, respectively, \( P<0.001 \)). Also, Elfayomy 2015 showed that the umbilical vein injection of 50 IU oxytocin is as effective as a single intravenous bolus of carbetocin in reducing the need for manual removal of the placenta.
In the current study, there was a significantly lower volume of vaginal blood loss after umbilical vein injection of the oxytocin group compared to the saline group (200± 26.45mL vs. 200± 26.45mL respectively; p < 0.0001). These findings agree with those of (Kore et al. 2000), who reported a mean volume of blood loss of 125 mL in the oxytocin group and 275 mL in the saline group (p = 0.0001).

In the present study, the average vaginal blood loss during labor was insignificantly less in the oxytocin group than in the saline group (970± 320 mL vs. 1000± 215 mL; respectively p = 0.6715). This agrees with Bivins et al. 1993, found no significant difference between the two groups regarding intrapartum blood loss. However, this disagrees with Güngördük et al. 2010, reported significantly lower average blood loss during labor in the oxytocin group.

In the current study, hemoglobin level 24 hours later was significantly higher in oxytocin group compared with saline group (10.06 ± 0.94 ml vs. 9.63 ± 0.44; p = 0.0270 respectively). In line with these findings, Ghulmiyyah et al. 2007 found that the mean drop in Hemoglobin was significantly reduced in oxytocin group (1.3 g/dl compared with 1.9 g/dl). However, these results disagree with Carroli et al. 1998, who reported no difference in the hemoglobin level between the studied groups. However, manual removal of the placenta is associated with higher rate of infectious morbidity.

In the current study, there is no difference in the mean hospital stay (1.06 ± 0.79day vs.0.93 ± 0.48; day p < 0.4443) in oxytocin group compared to saline group, correspondingly. These outcomes agree with the aforementioned study of Carroli et al. 1998,
who reported no difference in the mean of hospital stay between the studied groups.

This disagreement between our results and what was stated by others may be allied to modifications in the infusion procedures used (the amount of volume injected, the dose of oxytocin used, or both) and to the sample size or study design.

The strengths of the study were; 1) prospective, 2) randomized and 3) double-blinded. However, the main limitation of the study is the small sample size.

Conflict of interest: none Acknowledgment:

The author thanks all participants who joined in the study, and the medical providers at the Department of Obstetrics and Gynecology, Benha University Hospital. Conclusion:

The intraumbilical vein injection of oxytocin can be regarded a harmless, simple, easy, noninvasive and efficient alternative for treatment of retained placenta. It increases spontaneous placental expulsion rate, reduces the necessity for manual placental extraction, reduces the need for blood transfusion, reduces the injection expulsion interval, reduces the blood loss after UVI, and preserving higher hemoglobin level 24 hours postoperative in the oxytocin group than the saline group.

REFERENCES


دراسة مقارنة بين حقن الوريد السري بالحبل السري بمادة الأوكسيتوسين المخفف ومادة محلول الملح لعلاج إحتجاز المشيمة داخل الرحم بعد الولادة.

أيمن أحمد عبد الحميد شديد
قسم النساء والتوليد - كلية طب بنها

إن الذئف بعد الولادة من أهم التحديات التي تواجه أطباء التوليد، ومن أسباب الذئف بعد الولادة هو إحتجاز المشيمة داخل الرحم وعدم نزولها بعد تزول الجنين، وتوجد عدة طرق لمحاولة إخراج المشيمة المحتزمة في الرحم في حالة عدم نزولها الطبيعية.

وتهدف هذه الدراسة إلى تقييم ومقارنة إعطاء حقار الأوكسيتوسين المخفف أو محلول الملح في الوريد السري بالحبل السري ليستحث الرحم على نزول المشيمة. وقد أجريت هذه الدراسة في مستشفى بنها الجامعى على تسعون وسبعين حالة إحتجاز مشيمة من ضمن خمسة آلاف وثمانين حالة وفمئية وخمسين حالة وفمئية طبيعية.

وقد أظهرت النتائج مدى فاعلية وسهولة إعطاء حقار الأوكسيتوسين المخفف لعلاج إحتجاز المشيمة داخل الرحم بعد الولادة الطبيعية.

لذلك ينصح بإستخدام حقار الأوكسيتوسين المخفف لعلاج إحتجاز المشيمة داخل الرحم بعد الولادة الطبيعية.