Rectal Misoprostol versus Oxytocin in The management of the third stage of labor

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ABSTRACT:

Objective: To compare the effectiveness of rectally used misoprostol in the active management of third stage of labor with intramuscular oxytocin.

Methods: A comparative prospective study was performed at 2 hospitals in Basrah, 200 pregnant women in active labor were enrolled. Women were randomized to receive rectal misoprostol 600µg or intramuscular oxytocin 10 IU with delivery of the anterior shoulder. The primary outcome measures were the incidence of postpartum hemorrhage or change in Hb. concentration before delivery and 12 hour after delivery. Secondary outcomes included the need for additional uterotonic agents, severe post partum hemorrhage, blood transfusion, and medication side effects.

Results: The percentage of PPH was 5% in the misoprostol group and 6% in oxytocin group (p >0.05). There were no significant difference among the groups in the drop of Hb. conc. (p>0.05). Secondary outcome measures including severe PPH and the duration of the 3rd stage of labor and medication side effects were similar in both groups.

Conclusion: Rectal misoprostol 600µg is as effective as 10 IU intramuscular oxytocin in minimizing blood loss in the 3rd stage of labor. This confirms the utility of misoprostol as a safe and effective uterotonic drug for use in some areas where other pharmacologic agent may be less feasible.

Introduction:

Third stage of labor is associated with high incidence of post partum hemorrhage (PPH), which is the most common cause of maternal morbidity and mortality in developing countries. Even in developed countries, although maternal mortality rates are much lower, PPH remains a major concern\(^1\). It ranks just behind thromboembolic events and hypertensive disease as a common cause of maternal death in developed countries, this is not because embolism is more common, but because improvements in prevention and treatment have decreased markedly deaths due to hemorrhage\(^1\). The duration of third stage of labor is important, because the prevalence of post partum hemorrhage increase as the duration lengthen\(^2\). Two large series of consecutive deliveries showed that the average length of third stage of labor was five to six minutes , and that 90%
of placenta were delivered within 15 minutes and 97% were delivered within 30 minutes of birth\(^2,3\). Failure of the uterus and retact following childbirth has for centuries been recognized as the most striking cause of post partum hemorrhage. Powerful efficient contractions of the myometrium are essential to arrest blood loss after delivery\(^4\). The optimal approach to management of 3\(^{rd}\) stage of labor is an active management which is include\(^5\):

1. administration of a prophylactic uterotonic agent during or immediately after the delivery of the baby.
2. early cord clamping and cutting.
3. controlled cord traction to deliver the placenta.

**Drugs (uterotonic agents) used in the active management\(^6\):**

1- **Oxytocin:** Owing to its short plasma half – life (mean 3 min ), a continuous intravenous infusion is required in order to maintain the uterus in a contracted state. The onset of action is almost instantaneous and plateau concentration is achieved after 30 min . By contrast , intramuscular administration results in a slower onset of action (3-7 min) but a longer lasting clinical effect (up to 60min)\(^6\). Furthermore , rapid intravenous bolus administration of undiluted oxytocin results in relaxation of vascular smooth muscle , which can lead to hypotension\(^7\). It is therefore best given intramuscularly or by dilute intravenous infusion . Oxytocin is stable at temperatures up to 25°C but refrigeration may prolong its shelf – time\(^7\).

**The disadvantages of oxytocin\(^7\):**
- Its short half – life.
- The need for refrigerated storage

2- **Misoprostol:**
It is an orally active, stable synthetic PGE1 analogue, has entered clinical use in Obstetrics and gynecology on wide scale \(^8\). **It has several advantages\(^9\):**
- Stability in ambient temperature.
- Long shelf-lift.
- Low cost.

Plasma levels of misoprostol acid vary considerably, over the range of 200-400 µg.\(^{10}\). After oral administration, the peak level of misoprostol acid is reached within 12# 3 min, with a terminal half-life of 20-40 min\(^{10,11}\). The maximum serum concentration was achieved 23 min later in rectal administration and the peak levels were lower compared to oral administration of misoprostol\(^12\).

Toxic doses of misoprostol have not been determined, however, pregnant women have tolerated cumulative dose up to 2200 µg administered over an period of 12 hr without any serious adverse effects\(^13\).

**Contraindication\(^12\):**
- Hypersensitivity.
- Medical disorder: asthma, epilepsy and heart diseases.

**Aim of study:**
To compare the effectiveness of rectally used misoprostol in the active management of third stage of labor with intramuscular oxytocin.


**Materials and Methods**

A comparative prospective study carried out in two hospitals in Basrah (Al-Mawani general hospital and Basrah maternity and child hospital) during the period from September 2009 to September 2010. Two hundred pregnant women in active labor were enrolled in this study. Informed consent was obtained from the women using standardized form after admission to the labor word when it was clear that a vaginal delivery was very likely. The exclusion criterion were any known contraindication to prostaglandin administration (hypersensitivity or medical conditions, including asthma or epilepsy), preterm labor (gestational age before completed 37 week), Hemoglobin less than 8gm/dl and coagulation abnormalities. Women at perceived high risk for PPH were not excluded, but the factors that increased the risk were recorded on the data sheet, they were as follows; grand multiparty (greater than para 5), multiple gestation, previous PPH, precipitous labor (less than 3 hours), polyhydramnious, chorioamnionitis, previous caesarian section and oxytocin augmentation of labor. The information included in this study were; maternal age, parity, gestational age determined by last menstrual period or by ultrasound, episiotomy, laceration, birth weight, duration of 3rd stage of labor and maternal temp. was noted if it is >37.5℃. The initial maternal blood sample was drown to determine the hemoglobin concentration (Hb.) before delivery. Women were included in this study divided into two groups:

**Group 1 (misoprostol group):** 100 women were given 600µg misoprostol (three 200 µg tablet) rectally after slight moistening with water.

**Group 2 (oxytocin group):** 100 women were given 10 IU oxytocin IM injection.

The treatment in each group was administered as soon as feasible after delivery of the baby (i.e. within 1 to 2 minutes). After delivery, women were monitored for any additional blood loss. In our study the blood loss was assessed subjectively by the person attending the delivery or by obstetrician.

If a woman had a significant blood loss, the usual hospital protocol would be initiated, this protocol included use of intravenous oxytocin, attention to Laceration, removal of retained piece of placental tissue, and blood transfusion as required and not included in our study.

Expected side effect as nausea, vomiting, diarrhea, shivering and hyperthermia were assessed in each group.
At approximately 12 hours postpartum, second blood sample was drawn to determine postpartum hemoglobin concentration in 47 women in (group 1) and 44 women in (group 2) and the differences in Hb. concentration were estimated. Because it was standard practice at our hospital to discharge patients within 24 hours of normal vaginal delivery, measuring Hb. levels at 24 hours postpartum was not feasible.

The primary outcome measures were the proportion of PPH and drop in Hb. concentration in both groups. Secondary outcome measures were the need for additional uterotonic, the length of 3rd stage of labor, blood transfusion and medication side effects. PPH was recorded when subjective estimated blood loss (EBL) in excess of 500 ml or 10% drop in Hb. concentration.

**Statistical Analysis:**
Primary outcome and continuous variable secondary outcome were tested using a two-sided student t-test. The primary outcome was considered statistically significant at an α-level of 5% (P < 0.05). P-value were reported for secondary outcomes.

**Results:**
A total of 200 women were enrolled in this study to receive either rectal misoprostol (100) or I.M. Oxytocin (100) during the study period. All of the 200 women (the misoprostol group "100" and the oxytocine group "100") had pre-delivery Hb., but only (47) women, 44 women in misoprostol and oxytocin group respectively had a postpartum Hb. Concentration.

Table (1) describe the demographic characteristic and risk factors for PPH, there was no significant difference between the two groups.

Table (2) describe the primary and secondary outcome measures indicative of blood loss. The percentage of PPH in misoprostol group was 5% while it was 6% in oxytocin group (P = 0.75). There was no significant difference between the groups for change in Hb. conc. The mean (± standard deviation) decrease in HB conc. was 0.83 (0.24) g/dl for the misoprotol group and 0.81 (0.24) for oxytocin group (risk difference 25%; 95% CI-7.8% -12.9%; p=0.62). Secondary outcome measures did not show significant difference between the groups (Table 2). Specifically in length of 3rd stage, clinical diagnosis of severe PPH.

There was only one case had estimated blood loss greater than 1000 ml in oxytocin group and it was the only one case of blood transfusion. There was no significant difference between the two groups in the use of additional uterotonic drugs with relative risk of 1.13 (95% CI 0.42 -3.07) p=0.8.

There was no maternal death recorded, no other women required an operative intervention (such as manual removal of placenta, dilatation and curettage, laprotomy or hysterectomy). Table (3) describe medications side effects where the two groups were similar in the incidence of nausea, vomiting, temp > 37.5°.

Although there was difference between two groups in the incidence shivering (4% vs 1%; relative risk 2%; 95% CI 0.31 -6.35) but it was not significant (P=0.17).
Table 1. Demographic characteristics of both studied groups

<table>
<thead>
<tr>
<th>Title</th>
<th>MISOPROSTOL 600µG</th>
<th>OXYTOCIN 10 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>25.75 (6.15)</td>
<td>25.62 (6.63)</td>
</tr>
<tr>
<td>Gravida</td>
<td>3 [1, 4]</td>
<td>3 [2, 4]</td>
</tr>
<tr>
<td>Para</td>
<td>2 [0, 3]</td>
<td>2 [1, 3]</td>
</tr>
<tr>
<td>Gestation in weeks</td>
<td>38.9 (0.8657)</td>
<td>39.04 (0.81)</td>
</tr>
<tr>
<td>Laceration</td>
<td>6/100 (6%)</td>
<td>8/100 (8%)</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>37/100 (37%)</td>
<td>28/100 (28%)</td>
</tr>
<tr>
<td>Pre-delivery HB</td>
<td>9.94 (0.4968)</td>
<td>9.93 (0.51)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>3188 (381.4592)</td>
<td>3121 (271.19)</td>
</tr>
<tr>
<td>PPH (Risk Factors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grand multiparty</td>
<td>12/100 (12%)</td>
<td>11/100 (11%)</td>
</tr>
<tr>
<td>Current multiple</td>
<td>2/100 (2%)</td>
<td>3/100 (3%)</td>
</tr>
<tr>
<td>Previous PPH</td>
<td>1/100 (1%)</td>
<td>1/100 (1%)</td>
</tr>
<tr>
<td>Precipitous labor</td>
<td>1/100 (1%)</td>
<td>0/100</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>0/100</td>
<td>0/100</td>
</tr>
<tr>
<td>Polyhydramnia</td>
<td>0/100</td>
<td>0/100</td>
</tr>
</tbody>
</table>

Values are given as mean (standard deviation), median [quartiles]
### Table 2. Primary and secondary outcome measures indicative of blood loss

<table>
<thead>
<tr>
<th>Title</th>
<th>Misoprostol</th>
<th>Oxytocin</th>
<th>Relative Risk (95 % CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HB in g/dl</td>
<td>0.83(0.24)</td>
<td>0.81(0.24)</td>
<td>2.5 % (-7.8 % -12.9%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Postpartum HB</td>
<td>9.1 (0.5)</td>
<td>9.02(0.7)</td>
<td>10.5% (-18.1% -39.1%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Length of 3rd stage of labor</td>
<td>5.6 (3.4)</td>
<td>5.7 (3.6)</td>
<td>5% (-11% -83%)</td>
<td>0.76</td>
</tr>
<tr>
<td>EBL &gt; 500 ml</td>
<td>5 / 100(5%)</td>
<td>5 / 100(5 %)</td>
<td>1 % (0.28-3.5)</td>
<td>1</td>
</tr>
<tr>
<td>EBL &gt; 1000 ml</td>
<td>0 / 100</td>
<td>1 /100(1%)</td>
<td>0.49 (0.43-0.572)</td>
<td>0.316</td>
</tr>
<tr>
<td>Additional uterotonic</td>
<td>8 / 100(8%)</td>
<td>9 / 100 (9%)</td>
<td>1.13 (0.42- 3.07)</td>
<td>0.8</td>
</tr>
<tr>
<td>Clinical diagnosis of ppH</td>
<td>5/100 (5%)</td>
<td>6/100 (6%)</td>
<td>1.2 (0.35-4.11)</td>
<td>0.75</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0/100</td>
<td>1/100 (1%)</td>
<td>0.49(0.43-0.57)</td>
<td>0.31</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>0/100</td>
<td>0/100</td>
<td>0.49(0.43-0.57)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Values are given as mean (standard deviation) , Relative Risk (95 % CI), P-value.

### Table 3. Medication side effects

<table>
<thead>
<tr>
<th>Title</th>
<th>Misoprostol</th>
<th>Oxytocin</th>
<th>Relative Risk</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1 / 100(1%)</td>
<td>2 / 100 (2%)</td>
<td>0.5(0.49 - 5.32)</td>
<td>0.56</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 / 100(1%)</td>
<td>1 / 100(1%)</td>
<td>1(0.12 - 3.71)</td>
<td>1</td>
</tr>
<tr>
<td>Shivering</td>
<td>4 / 100(4%)</td>
<td>1 / 100(1%)</td>
<td>4(0.46 - 7.49)</td>
<td>0.17</td>
</tr>
<tr>
<td>Temperature &gt;37.5°C</td>
<td>2 / 100(2%)</td>
<td>1 / 100(1%)</td>
<td>2(0.31 – 6.35)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Values are given as relative risk (95 % CI), P-value.


**Discussion:**

In developing countries, PPH is regarded as one of the major causes of maternal mortality and morbidity consequently, the active management of the 3rd stage of labor should be practiced routinely. To substitute for oxytocin and to prevent PPH misoprostol was chosen because it has similar advantages with minimal side effect. This study has confirmed the utility of rectal misoprostol for routine management of 3rd stage of labor. Misoprostol was shown in several randomized controlled trials to be effective in preventing PPH because of its strong uterotonic effects, moreover, it is inexpensive and easy to administer. Our study had confirmed the utility of rectal misoprostol for routine management of 3rd stage of labor, as the percentage of PPH was 5% in misoprostol group compared to 6% in the oxytocin group determined by subjective evaluation of blood loss and the change in Hb. concentration before delivery and 12 hr after delivery. We included high risk patients in the study. The absorption of rectally administrated tablet may not be quick and probably take 15 minutes especially when using tablet design for oral use. Recent studies has shown that rectal misoprostol is useful in the management of 3rd stage of labor and may be effective in the treatment of PPH. Karakin et al. studied 240 women who received 400µg rectal misoprostol after the delivery or parenteral oxytocin (5 IU) I.V. or (10 IU) I.M. with the delivery of the baby. No difference in Hb. concentration was observed between the groups. The duration of the 3rd stage of labor did not differ between the two groups, these results were similar to the result in our study. Also our results were similar to the trial done by Bugalho et al. studied 663 women with uncomplicated vaginal delivery were received 400µg rectal misoprostol or oxytocin 10 IU after observed between groups, before and 72 hr after delivery, they concluded that rectal misoprostol appear to be effective as parenteral oxytocin in preventing PPH. The rectal route has been chosen in our study because of the ease of administration, and can avoid gastrointestinal side effects of nausea, vomiting and diarrhea, so it can be given to nauseated women. In our study, the observed incidence of shivering was only 4%, although this was higher than the 1% observed in oxytocin group but it was not significant. Higher doses (800µg) of misoprostol rectally was used by Parsons et al. in Ghana and he found that there is higher incidence of shivering 7.5% and it was significantly higher than the 0.9% in 10 IU oxytocin intra muscular group. A study was done by Parsons et al. compared between 800µ of oral misoprostol with 10 IU oxytocin intramuscular and he founded the higher rate of shivering and fever with oral misoprostol (shivering 80.7% vs. 3.6%, fever 11.4% vs. 0%) . The low incidence of side effect with 600µg dose of rectal misoprostol in the current study (nausea 1%, vomiting 1%, shivering 4% and fever 2%) is encouraging and suggests that the rectal misoprostol may be superior to oral for limiting gastrointestinal and thermo-regulatory side effects while maintaining uterotonic properties. Our study along the available literatures on rectally administered misoprostol illustrate that rectal misoprostol seems to be effective like oxytocine in reducing the like hood of PPH after vaginal delivery at dose of 600µg.
Conclusion:
Misoprostol 600µg given rectally is effective in minimizing blood loss when utilized in active management of the 3rd stage of labor, as measured by change in Hb concentration before the delivery and 12 hr after the delivery. This dose and route of administration are well tolerated, and the usual side effects of shivering and increased temperature were noted only infrequently.

References
1-DK James, PJ steer, CP Weiner and B Gonik. Postpartum hemorrhage; High risk pregnancy. 2nd ed. W.B. Saunders, 1999:1229
3-Combs CA, Laros RK Jr, prolonged third stage of labor: morbidity and risk factors, Obstetrics Gynecology 1991; 77:863
الخلاصة

د. ادوار خوشو ود. وئام المحفوظ

الهدف: لمقارنة فعالية عقار الميزوبرستول عن طريق الشرج مع الأوكسيتوسين العضلي في معالجة المرحلة الثالثة من مراحل الولادة.

الطريقة: أجريت الدراسة في اثنتين من مستشفيات مدينة البصرة (م. البصرة للولادة والطفل و م. الموانئ العام) على 200 نسمة من النساء الحوامل. وقد تم تقسيم النساء اللواتي أجريت لهن الدراسة إلى مجموعتين:

المجموعة الأولى: وعددهن (100) تم إعطاؤهم (600 مايكروغم) ميزوبرستول عن طريق الشرج.

المجموعة الثانية: وعددهن (100) تم إعطاؤهم الأوكسيتوسين العضلي (10 وحدات).

وكانت النتائج الأساسية المطلوبة دراستها في هذا البحث هي نسبة حدوث النزف، والتغير في نسبة الهيموغLOBين بين ما قبل وبعد الولادة. أما النتائج الثانية فكانت مدة المرحلة الثالثة للولادة وعدد الذين احتاجوا إلى نقل الدم وحالات النزف الشديد. وقد شملت الدراسة الحالات المعرضة لخطرة حدوث النزف بعد الولادة.

النتائج: كانت نسبة النزف بعد الولادة في المجموعة الأولى هي (5%) أما نسبة النزف بعد الولادة في المجموعة الثانية (6%). أما النتائج المتعلقة بالتفجر في نسبة الهيموغLOBين ونسبة الدرجة الثالثة وحالات نقل الدم والأعراض الجانبية كالإعاقة مقارنة.

الاستنتاج: لقد تم الاستنتاج من هذه الدراسة أن استخدام عقار الميزوبرستول (600 مايكروغم) عن طريق الشرج قد ثبت كفاءته بالمقارنة مع عقار الأوكسيتوسين المستخدم عضلياً بفضل حالات النزف بعد الولادة، وأثبتت الدراسة كفاءته كعقار أمن وفعال للاستخدام كعلاج روتيتي من ضمن الأدوية المستعملة في معالجة المرحلة الثالثة لمراحل الولادة.