Effectiveness of combined use of rectal misoprostol and oxytocin for prevention of postpartum hemorrhage after cesarean section

Nirmala Maniachari1, Sathish Kumar Sure2*, Priyanka Jagadeesh1, Lavanya Agamudi1, Usha Brindhini3

1Department of Pharmacy Practice, Krishna Teja Pharmacy College, Tirupati, Andhra Pradesh, India
2Department of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Education and Research, Anantapur, Andhra Pradesh, India
3Department of Obstetrics and Gynaecology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

ABSTRACT

Post-Partum Hemorrhage (PPH) is defined as the loss of blood which is greater than 500ml after vaginal delivery or greater than 1000 ml after a cesarean section delivery. About 28% of the total maternal deaths were due to PPH particularly in developing countries. Oxytocin has been considered as the ‘gold standard’ drug in the treatment and prevention of PPH. Prophylactic use of prostaglandin analogue i.e., misoprostol in addition to oxytocin during cesarean section is expected to reduce the incidence of PPH. This study aims at comparing the efficacy of combined use of rectal misoprostol and oxytocin infusion with oxytocin in the prevention of PPH. A comparative observational study was conducted on 200 subjects which were divided into two equal groups by Simple Random Selection. One group was treated with Inj. Oxytocin 20IU IV infusion alone while the other group was treated with Tab. Misoprostol 600mcg, rectal route and Inj. Oxytocin 20IU IV infusion. Majority of the subjects were observed under the age group of 21-25years, under primigravidae. A significant decrease in the volume of mean blood loss (740.00 ± 164.00 ml: p = 0.045) and the mean drop of hemoglobin level (Hb) (0.88±0.74gm/dl; p = 0.0001) were observed in group treated with Tab. Misoprostol 600mcg and Inj. Oxytocin and was found to be statistically significant. Preoperative administration of misoprostol per rectal route and oxytocin infusion after the cesarean section have shown, a better control of bleeding and maintenance of hemoglobin level when compared to oxytocin infusion alone. Thus, instead of oxytocin monotherapy combined use of misoprostol and oxytocin would be more effective in prevention of PPH.

INTRODUCTION

Post-Partum Hemorrhage (PPH) is defined as the loss of blood, which is greater than 500ml after vaginal delivery or greater than 1000 ml after a cesarean section delivery (Andolina and Daly, 1999; Ueland, 1976; Rajaei et al., 2014; Stafford et al., 2008). PPH is a major cause of maternal morbidity and mortality, which accounts for about 28% of the total maternal deaths, particularly in developing countries (Drife, 1997). The incidence of PPH has been increasing rapidly and is observed among
5% of the total deliveries where the majority of the deaths due to PPH occurs within 24 hours after the birth (Lu et al., 2005; Callaghan et al., 2010). According to WHO Maternal mortality statistics (2010), it was estimated that about 5,85,000 deaths of women occur due to obstetric conditions out of which 25% of maternal deaths were due to PPH. Oxytocin is considered as the ‘gold standard’ for the prevention of PPH and management of uterine atony. It is a prerequisite to maintain the cold chain to preserve its potency. It has a very short life of 1–6 min and is administered through i.v infusion for a longer period (Dutta and Gupta, 2016). Uterotonics induces uterine contractions and imparts toxicity to the uterus. These are used as the treatment of choice as uterine atony is the leading cause of PPH resulting in loss of uterine musculature tone (Dildy, 2002). Prostaglandin E1 analogue (misoprostol) is also being used for controlling PPH by increasing the tone of uterine musculature. Many studies have proven its efficacy in the management of PPH even the patient is not responding to oxytocin (O’brien, 1998; Bamigboye et al., 1998; Parsons et al., 2007). Despite, several comparative studies conducted to evaluate the efficacy of misoprostol, its ideal dose and route of administration has remained controversial. It can be administered by oral, intrauterine, sublingual, intravaginal and rectal route (el Sharkwy, 2013). Few studies recommend rectal administration of misoprostol over sublingual route despite its slower onset of action, as rectal route maintains longer duration of action, fewer adverse effects and is more convenient among the patients with nausea and vomiting (Bajwa et al., 2012). Prophylactic use of misoprostol administered immediately after peritoneal incision in addition to oxytocin after cesarean section is expected to reduce the incidence of PPH. Though the data regarding the prophylactic dose and efficacy of misoprostol in combination with standard oxytocin is limited, this study aims at comparing the efficacy of oxytocin versus combination of oxytocin and rectal misoprostol with the objectives of estimating the amount of blood loss, post-operative hemoglobin level (Hb), frequency of PPH and drop in hemoglobin level in both treatment groups.

**MATERIALS AND METHODS**

A comparative observational study was carried out prospectively, in the department of Obstetrics and Gynaecology, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati for a period of 6 months after getting approval from Institutional Ethics Committee (IEC NO: 671). Individuals who underwent cesarean section, singleton pregnancy, elective & emergency LSCS and full-term pregnancy were included while the individuals with pre-eclampsia, vaginal delivery, placenta previa and twins were excluded from this study. All the medical records of the patients admitted in the department of Obstetrics & Gynecology were reviewed, and subjects were selected based on inclusion and exclusion criteria. An Informed Consent form has been taken from each subject before their enrollment into the study. Pre-designed patient data collection proforma was used for collection of all the data relevant to the study design which includes demographic details, baseline clinical findings, type of cesarean section, obstetric history, laboratory parameters and amount of blood loss. From the previous studies, (Chaudhuri et al., 2010) we observed that the average amount of blood loss in the group treated with I.V. oxytocin infusion 20 IU was about 710 ml with a standard deviation of 400 ml and assumed that the combined treatment of rectal misoprostol plus oxytocin infusion would reduce it by 200 ml. A sample size of 63 required in each group at a level of significance of 0.05 and power of 80%. A total of 100 participants were enrolled in each study group at a ratio of 1:1 to compensate for the errors which occur due to discontinuation and loss of follow up of the study subjects. The subjects were then divided into two groups by Simple Random Selection (lottery method). One group (Group A) was treated with Inj. Oxytocin 20U I.V infusion alone while the other group (Group B) was treated with Tab. Misoprostol 600mcg, rectal route and Inj. Oxytocin 20U I.V infusion. In both the groups, oxytocin infusion was given after the cesarean section and misoprostol was given immediately after peritoneal incision. The efficacy of both the treatments was determined by comparing the pre-operative hemoglobin levels, amount of blood loss within 24 hours, drop in hemoglobin level and post-operative hemoglobin levels (the sample has to be collected after 48 hours of cesarean Section) Figure 1.

**Estimation of blood loss**

The PPH bag was used for the collection and measurement of the amount of blood loss for a period of 24 hours post - cesarean section (Chaudhuri et al., 2010). The total blood loss (B) was estimated by subtracting the amniotic fluid volume (x) from approximate blood loss (A),

\[
B = \{a + [c - b] - x\}
\]

where approximate blood loss calculated by addition of volume of contents in the bag (a) with the value obtained by subtracting the weight of soaked Lenin (c) and weight of dry Lenin (b).
Figure 1: Flow chart for the allocation, collection and comparison of outcome variables between two groups.

**Statistical analysis**

The mean and standard deviation of the collected data was analyzed using an Excel spreadsheet. The percentage and proportions for all categorical variables were calculated by using SPSS version 20 (Statistical software). The significance of outcome variables was observed using unpaired t-test and chi-square test. P value of < 0.05 was considered as statistically significant value.

**RESULTS AND DISCUSSION**

A total of 200 subjects were recruited and divided into two groups, each having 100 subjects. Group-A subjects were treated with the Inj. Oxytocin 20 IU I.V infusion and Group-B subjects were treated with Tab. Misoprostol 600mcg, rectal route & Inj. Oxytocin 20 IU I.V infusion.

Table 1 represents the categorization of subjects based on age where the majority of the subjects were observed under the age group 20-25 years among which 44% belongs to Group A, and 48% belong to Group B.

Table 2 illustrates the Gravida wise categorization of subjects in both groups where majority of the subjects were under primigravida showing 64% in group A and 68% in group B while in case of multigravida 36% of the subjects belongs to group A and 32% of the subjects belong to group B which is in contrast to the study conducted by Gunjan Singh et al., (2009) where 65% of the total study subjects...
Table 1: Age-wise categorization of subjects in both treatment groups.

<table>
<thead>
<tr>
<th>Age group in (Years)</th>
<th>Group A No. (%)</th>
<th>Group B No. (%)</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-20</td>
<td>20 (20%)</td>
<td>16 (16%)</td>
<td>36 (18%)</td>
</tr>
<tr>
<td>20-25</td>
<td>44 (44%)</td>
<td>48 (48%)</td>
<td>92 (46%)</td>
</tr>
<tr>
<td>26-30</td>
<td>24 (24%)</td>
<td>16 (16%)</td>
<td>40 (20%)</td>
</tr>
<tr>
<td>31-35</td>
<td>4 (4%)</td>
<td>12 (12%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>36-41</td>
<td>8 (8%)</td>
<td>8 (8%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>200 (100%)</td>
</tr>
</tbody>
</table>

Table 2: Gravida wise distribution of subjects in both treatment groups.

<table>
<thead>
<tr>
<th>Type of Gravida</th>
<th>Group A (n = 100)</th>
<th>Group B (n = 100)</th>
<th>Total (N = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primigravida</td>
<td>64 (64%)</td>
<td>68 (68%)</td>
<td>132 (66%)</td>
</tr>
<tr>
<td>Multigravida</td>
<td>36 (36%)</td>
<td>32 (32%)</td>
<td>68 (34%)</td>
</tr>
</tbody>
</table>

Table 3: Distribution of subjects based on the type of Cesarean Section

<table>
<thead>
<tr>
<th>Type of Cesarean Section</th>
<th>Group A (n = 100)</th>
<th>Group B (n = 100)</th>
<th>Total (N = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Section</td>
<td>76 (76%)</td>
<td>84 (84%)</td>
<td>160 (80%)</td>
</tr>
<tr>
<td>Repeat Section</td>
<td>24 (24%)</td>
<td>16 (16%)</td>
<td>40 (20%)</td>
</tr>
</tbody>
</table>

Table 4: Comparison of outcome variables between the two treatment groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group A (n=100)</th>
<th>Group B (n=100)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Loss (ml)</td>
<td>790.00 ± 185.40</td>
<td>740.00 ± 164.00</td>
<td>0.0447a</td>
</tr>
<tr>
<td>Pre-operative Hb (g/dl)</td>
<td>11.48 ± 1.49</td>
<td>11.43 ± 1.60</td>
<td>0.8193</td>
</tr>
<tr>
<td>Post-operative Hb (g/dl)</td>
<td>10.17 ± 2.56</td>
<td>10.55 ± 1.28</td>
<td>0.0379a</td>
</tr>
<tr>
<td>Drop in Hb (gm/dl)</td>
<td>1.31 ± 0.83</td>
<td>0.88 ± 0.74</td>
<td>0.0001a</td>
</tr>
<tr>
<td>PPH</td>
<td>2 (2%)</td>
<td>1(1%)</td>
<td>0.561</td>
</tr>
</tbody>
</table>

PPH: Post-Partum Hemorrhage; a = significant (p < 0.05).

were multigravida. Table 3 represents the distribution of study subjects based on the type of cesarean section in both groups where a majority of the subjects underwent primary section showing 76% in group A and 84% in group B while in case of repeat section 24% of the subjects belong to group A and 16% of the subjects belong to group B.

Various outcome variables like frequency of primary PPH, amount of blood loss, Pre-operative Hb level, Post-operative Hb level and mean drop of Hb were compared between the two groups Table 4. The mean blood loss was observed to be higher in group A and was estimated about 790 ± 185.40 ml while in group B, it was estimated about 740±164.00 ml Table 4. These results showed that the volume of blood loss in the cesarean section was well controlled in group B subjects when compared to group A which was found to be statistically significant (p = 0.0447). The results of this study were similar to other study conducted on rectal misoprostol versus injection oxytocin infusion and found that a significant decrease in mean intra-operative (502.79 ± 178.35 vs 592.41±225.35; P = 0.003) and post-operative blood loss after 8 hours of cesarean section in misoprostol group (73.88 ± 66.62 vs 113.68 ± 166.19 ml; P = 0.045) (Chaudhuri et al., 2010). Some studies compared the effectiveness of sublingual misoprostol 400 mcg, 600mcg, I.V. oxytocin (5IU) and methylergometrine 200 mcg for active management of third stage labor and stated that the treatment group who were on misoprostol 600mcg, reported lowest blood loss of all the groups (Singh © International Journal of Research in Pharmaceutical Sciences 3559
et al., 2009). These study results show that the effective control of blood loss during and after the cesarean section can be done by using misoprostol in either rectal or sublingual route. In contrast, some studies compared sublingual misoprostol (400mcg) plus I.V.oxytocin (20IU) with I.V. carbethocin (100 mcg) and no significant difference in mean blood loss was observed between the treatment groups which might be due to the use of a low dose misoprostol and comparison with carbethocin (el Sharkwy, 2013). A study observed that the mean blood loss was lowest when misoprostol was rectally administered when compared to oral administration (207.2±93.4 vs 232.8±151.2; p=0.016) and the incidence of PPH in misoprostol administered rectally was less versus oral administration (3.2% & 4.9% respectively) which might be due to the maintenance of effective action for a longer duration than administered through sublingual and oral route (Mansouri and Alsahly, 2011).

A randomized clinical trial which compared rectal misoprostol plus oxytocin versus sublingual misoprostol plus oxytocin versus placebo plus oxytocin, concluded that misoprostol along with oxytocin would prevent the occurrence of PPH at a great level through by controlling blood loss during and after cesarean section, whose results coincided with this study (Sweed et al., 2018). Out of 100 subjects enrolled, two cases of primary PPH were observed in group A, while one case was observed in group B. These results were not statistically significant (P = 0.561) Table 4 which was similar to the results obtained by (Badejoko et al., 2012) that 3 cases of PPH in misoprostol group while in oxytocin group, 5 cases of PPH were observed and is statistically not significant (P = 0.49).

The mean pre-operative Hb level in group A was measured to be 11.48±1.49gm/dl while in group B it was found to be 11.43±1.60gm/dl and no significant difference was observed between the two groups (p=0.8193). The mean post-operative Hb level of group A subjects was measured to be 10.17±2.56gm/dl while in group B it was noted as 10.55±1.28 gm/dl (P = 0.0379). It was observed that, the mean post-operative Hb level among group B subjects was greater than that of group A Table 4. These results coincide with the study conducted by (Chaudhuri et al., 2010) that the post-operative Hb level maintained in the group treated with misoprostol was more than that of oxytocin group (9.479 ±1.125g/dl vs 9.068 ±1.26 g/dl; P = 0.029) respectively.

The observed mean drop in Hb level was higher in group A subjects (1.31±0.83gm/dl) when compared to group B subjects (0.88±0.74gm/dl) and was statistically significant (p = 0.0001) Table 4. A randomized controlled trial had conducted and compared treatment groups of sublingual misoprostol plus oxytocin versus oxytocin alone and it showed consistent results to our study as the drop in Hb level was less in misoprostol plus oxytocin group. But the difference is that, we have administered misoprostol per rectal route and oxytocin of 20 IU. The need for additional measures taken (blood transfusion, additional oxytocin), incidence of side effects was least observed in the pre-operative administration of misoprostol when compared to post-operative administration (Fekih et al., 2009). In a randomized controlled trial, the effectiveness of rectal misoprostol versus injection oxytocin was compared and found that the difference between the pre-operative and post-operative Hb levels between the treatment groups after 48 hours of cesarean section was statistically significant (1.10±0.51g/dl vs 1.35±0.49g/dl) which was similar to our study. This suggest that misoprostol with oxytocin provides maximum benefit in pregnant women to prevent or control postpartum hemorrhage during the cesarean section (Sitaula et al., 2017). Further, it would suggest that the use of rectal misoprostol administered as prophylaxis before the surgery prevents the post-partum hemorrhage during the cesarean section. Many studies concluded that the administration of both misoprostol and oxytocin significantly reduced the amount of blood loss after cesarean section when compared to oxytocin alone and use of them was not associated with any serious side effects (Pakniat and Khezri, 2015).

**CONCLUSIONS**

Preoperative administration of rectal misoprostol (600mcg) and oxytocin infusion (20IU) after the cesarean section in the individuals have shown better maintenance of their hemoglobin levels and reduced the amount of blood loss when compared to oxytocin infusion (20IU) alone. Thus, instead of oxytocin monotherapy combined use of misoprostol and oxytocin were observed to be more effective in prevention of PPH. Though the data regarding the dose and prophylactic use of misoprostol are limited, randomized, double blinded studies and meta-analysis on a large population can pave the way for better evidence thus improving the treatment strategies in reducing PPH.

**Conflict of Interest**

None.

**Funding Support**
REFERENCES


