Comparison between the Effect of Sublingual and Rectal Misoprostol on Hemoglobin Level Change before and after Caesarean Section

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Abstract
Cesarean delivery is the commonest women surgery worldwide. Postpartum hemorrhage is blood loss >1000 ml after SC. This study conducted to assess the efficacy of sublingual versus rectal misoprostol on intraoperative and postoperative blood loss and the subsequent effect on hemoglobin values. This was a prospective study that included 100 pregnant women divided randomly into two equal groups, 50 participants each admitted to the department of obstetrics and gynecology, Beni-Suef university hospital- Egypt from August 2018 to May 2019. Participants received 400 mcg rectally or sublingually before SC after induction of spinal anesthesia. The primary outcome measure perioperative hemoglobin and hematocrit values regarding blood loss. Comparisons between groups were carried out by Student’s t-test (parametric data), Mann Whitney test (Non-parametric data), and Chi-Square test. $P<0.05$ was considered statistically significant

Keywords: Caesarean delivery, Misoprostol, Postpartum hemorrhage.

1. Introduction
Cesarean delivery is the commonest major women's surgery worldwide [1]. The incidence ranges from 20-30% all over the world [2]. Postpartum hemorrhage defined as loss of >1,000 ml after cesarean delivery (uterine atony cause about 75%) [3], with incidence range from 5-10 % [4]. Postpartum hemorrhage is a major cause of maternal mortality, mainly in developing countries and is the cause of about 25% of maternal deaths worldwide [5]. Using traditional uterotonics is accepted in the prevention of PPH after cesarean delivery [6]. Misoprostol [PGE1]) is one of the synthetic PGE1 analogs with strong uterotonic activity and few side effects at therapeutic doses [7]. Misoprostol is safe, stable, rapidly absorbed, easy to be used (oral, vaginal, buccal, or rectal), of low cost, and its effect on the uterus [8].
Misoprostol has been considered an alternative to injectable uterotonic agents for the prevention of PPH after vaginal or cesarean deliveries [9]. Sublingual misoprostol reaches the highest peak plasma concentration within the shortest time [6], with no adverse neonatal effects after the preoperative use of sublingual misoprostol in cesarean delivery [10].

2. Patients and Methods

This was a prospective study performed in Beni-Suef university hospital and Maghagha General hospital within Nine months from August 2018 to May 2019 involving 100 pregnant women divided randomly into two equal groups. Participants have undergone a CS under spinal anesthesia. Group (I): Sublingual misoprostol: cases administrated preoperatively 400 mcg misoprostol sublingually at the time of induction of spinal anesthesia. Group (II): Rectal misoprostol: cases administrated preoperatively 400 mcg misoprostol rectally after insertion of the urinary catheter. Written consents were obtained.

2.1 Inclusion criteria:

1. Age from 18 to 35 years.
2. Uncomplicated singleton pregnancy.
3. Term pregnancy of gestational age (37-40 wks.).
4. Elective or an emergency section.
5. Parity ≤ 4.
6. Hb ≥ 9 g/dl.
7. Previous CSs ≤ 2.

Exclusion criteria:

1. Known history of the medical disease (hypertension, cardiac, pulmonary, chronic endocrine or metabolic disease).
2. Risk factor for postpartum hemorrhage.
3. Contraindication to prostaglandins (severe asthma, hypersensitivity to the drug).
4. Placenta previa or abruption.
5. Blood diseases affecting coagulation profile.

2.2 All patients were subjected to the following:

1. Full history taking: Personal history, history of chronic medical disorders, obstetric history.
2. Clinical examination including:
   A. General, local and physical examination, and measurements (weight, respiration rate, and heart rate, and routine obstetric examination).
   B. Obstetric ultrasonography was performed for all patients to make sure of gestational age using (TOSHIBA SSA-340A diagnostic ultrasound).
3. Laboratory investigations:

   A volume of 3 ml blood sample was collected under the fully sterile condition from all cases in a tube containing EDTA for assessment of CBC. Blood samples were collected from all patients before & 24 hours after the CS. CBC determined by using automated cell counter Sysmex, NE (TAO, Medical Incorporation, Ono) stressing on hemoglobin (Hb) and packed cell volume or Heamatocrit (Hct).
The outcomes measured were the change of Hct and Hb values, the estimation of the intraoperative blood loss, the incidence of severe PPH (> 1000 ml), the need for blood transfusion and the need for further uterotonics. The surgical towels were weighed (g) with its wrapping before and after the operation via using a highly accurate digital balance (National, Xiamen Yukexiang Trading Co., Ltd.) and the differences in weight between dry and soaked linen towels were calculated. Blood loss was estimated accordingly: volume of the contents of the suction bottle (ml) (A), the weight difference of linen towels (g) (B) [weight of soaked linen towels (g) − weight of dry linen towels (g)], AFV (ml) (C). Thus, blood loss during operation (ml) = (A + B) – C [11].

2.3 Sample size determination

Sample size calculation was done using the comparison of Hb deficit between cases undergoing Cesarean section pretreated with sublingual versus rectal misoprostol as it was the primary outcome of our study. we calculated that the minimum proper sample size was 17 cases in each arm to achieve 80% power in detecting a difference of 0.6g/dl with a pooled SD of 0.65 g/dl, at α = 0.05 level using Student’s T-test for independent samples. Sample size calculation was done using Stats Direct statistical software version 2.7.2 for MS Windows, Stats Direct Ltd., Cheshire, UK.

Statistical methodology

All statistical analyses were performed using Statistical Package for Social Science (SPSS) version 21 under Windows 7 operating system. Results were expressed as means ± SD for quantitative data and by No. (%) for qualitative data. Comparisons between the groups were conducted by Student’s t-test for parametric data and by Mann Whitney test for Non-parametric data. Chi-Square test was used to test the significance between groups regarding qualitative data or Fisher exact test when appropriate. Probability level (P-value) was assumed significant if less than 0.05 and highly significant if P-value was less than 0.01. P-value was considered non-significant if greater than or equal to 0.05.

3. Results

The present study included a total of 100 pregnant women with an age range of 18:35 years that were randomly divided into two equal groups: Group (I): Sublingual misoprostol (n=50): Women administrated preoperatively with misoprostol sublingually at the time of induction of spinal anesthesia. Group (II): Rectal misoprostol (n=50): Women administrated preoperatively with misoprostol rectally after insertion of the urinary catheter. The primary objective of this study was to compare the effect of sublingual and rectal misoprostol administrated before the cesarean section on hemoglobin level change due to intraoperative and postoperative blood loss.
Table (1): Comparison between groups regarding baseline characteristics.

| Variable                        | Groups | P. value (Sig.) |
|---------------------------------|--------|-----------------|
|                                | Group (I) | Group (II)     |
|                                | Sublingual Misoprostol (n=50) | Rectal Misoprostol (n=50) |
| Age (year) Mean ± SD            | 27.4 ± 5.4 | 26.8 ± 4.6     | 0.55NS          |
| Parity                          | Primigravida | 13 (26.0%) | 14 (28.0%) | 0.94NS          |
|                                | G2 P1 + 0  | 13 (26.0%) | 11 (22.0%)  |
|                                | G2 P0 + 1  | 0            | 1 (1.0%)     |
|                                | G3 P1 + 0  | 1 (2.0%)     | 1 (2.0%)     |
|                                | G3 P2 + 0  | 12 (24.0%)   | 13 (26.0%)   |
|                                | G4 P1 + 2  | 1 (2.0%)     | 0            |
|                                | G4 P2 + 1  | 6 (12.0%)    | 6 (12.0%)    |
|                                | G4 P3 + 0  | 4 (8.0%)     | 4 (8.0%)     |
| Gestational age (wks.) Mean ± SD | 38.2 ± 0.92 | 38.4 ± 1.0    | 0.60NS          |
| Number of previous Caesarean deliveries | No history of previous CS | 18 (36.0%) | 14 (28.0%) | 0.64NS          |
|                                | Previous one CS | 21 (42.0%) | 22 (44.0%)  |
|                                | Previous two CS | 11 (22.0%) | 14 (28.0%)  |

NS: P-value > 0.05 (Non-significant)

Table (1) showed a comparison between groups regarding baseline characteristics. The results demonstrated that there were no significant differences between groups as regard age (27.4 ± 5.4 year in group I vs. 26.8 ± 4.6 year in group II, p=0.55) (fig. 8), parity (p=0.94), gestational age (38.2 ± 0.92 wks. in group I vs. 38.4 ± 1.0 wks. in group II, p=0.60) and number of previous caesarean delivery sections (p=0.64).

Table (2): Comparison between groups regarding intraoperative blood loss.

| Variable     | Groups                        | P. value (Sig.) |
|--------------|-------------------------------|-----------------|
|              | Group (I) Sublingual Misoprostol M ± SD | Group (II) Rectal Misoprostol M ± SD |
| Blood loss (ml) | 456 ± 187                     | 581 ± 196       | < 0.01**        |

**Significant (P<0.01).

Table (2) showed that women of rectal misoprostol group (group II) had a significantly higher amount of intraoperative blood loss compared to cases of sublingual misoprostol group (group I), (581 ± 196 vs. 456 ± 187 ml in group II and I, respectively), (P≤0.01).
Table (3): Comparison between groups regarding pre and post-operative Hb.

| Variable               | Groups                          | P. value (Sig.) |
|-----------------------|--------------------------------|-----------------|
|                       | Group (I)                       |                |
|                       | Sublingual Misoprostol M ± SD   |                |
| Preoperative Hb (g/dl)| 10.86 ± 0.90                   | 0.74 NS         |
| Postoperative Hb (g/dl)| 10.28 ± 0.88                   | 0.39 NS         |
| P. value (Sig.)       | < 0.01**                        |                |
| Percentage of Hb decrease| 5.34                         |                |

*NS: P-value > 0.05 (Non-significant)

**Significant (P<0.01).

Table (3) showed that no significant differences were found between groups regarding preoperative Hb level (10.86 ± 0.90 g/dl in group I vs. 10.92 ± 0.92 g/dl in group II, p=0.74) and also postoperative Hb level (10.28 ± 0.88 g/dl in group I vs. 10.14 ± 0.67 g/dl in group II, p=0.39). But, an obvious highly significant reduction was noticed in the postoperative Hb level in both groups (P≤0.01). The percentage of Hb decrease in rectal misoprostol group (group II) was higher than the sublingual misoprostol group (group I).

Table (4): Comparison between groups regarding pre and post-operative Hct.

| Variable               | Groups                          | P. value (Sig.) |
|-----------------------|--------------------------------|-----------------|
|                       | Group (I)                       |                |
|                       | Sublingual Misoprostol M ± SD   |                |
| Preoperative Hct (%)  | 33.4 ± 2.1                      | 0.64 NS         |
| Postoperative Hct (%) | 32.1 ± 2.1                      | 0.21 NS         |
| P. value (Sig.)       | < 0.01**                        |                |
| Percentage of Hct decrease | 3.89                         | 6.52           |

*NS: P-value > 0.05 (Non-significant)

**Significant (P<0.01).

Table (4): showed the results of the comparison between groups regarding pre and post-operative Hct. At the same line of the results of Hb, the results revealed that there were no significant differences between groups regarding preoperative Hct (33.4 ± 2.1 % in group I vs. 33.7 ± 1.9 % in group II, p=0.64) and also postoperative Hct (32.1 ± 2.1 % in group I vs. 31.5 ± 2.7 % in group II, p=0.21). However, a highly significant reduction was found in postoperative Hct % in both groups (P≤0.01). Also, the percentage of Hct reduction was higher in the rectal misoprostol group (group II) compared to the sublingual misoprostol group (group I).
Table (5): Comparison between groups regarding side effects and need for uterotonics.

| Variable         | Group (I) Sublingual Misoprostol (n=50) | Group (II) Rectal Misoprostol (n=50) | P. value (Sig.) |
|------------------|----------------------------------------|--------------------------------------|----------------|
| Shivering        | 46 (92.0%)                             | 40 (80.0%)                           | 0.09 NS        |
| Nausea           | 50 (100.0%)                            | 50 (100.0%)                          | 1.0 NS         |
| Vomiting         | 15 (30.0%)                             | 6 (12.0%)                            | 0.03*          |
| Need for uterotonics | 3 (6.0%)          | 7 (14.0%)                            | 0.18 NS        |

NS: P-value > 0.05 (Non-significant)

*Significant (P≤0.05).

Table (5) presented the comparison between groups regarding side effects and the need for uterotonics. Shivering and nausea were almost similar between groups with no significant difference. However, the incidence of vomiting was significantly higher in the group (I) compared to group (II) (15 cases vs. 6 cases). The results showed that 7 cases (14.0%) in rectal misoprostol group needed uterotonics versus only 3 cases (6.0%) in the sublingual misoprostol group, the difference between the group was not significant (p=0.18)

4. Discussion

Cesarean delivery is the commonest major surgical procedure all over the world for females with a comparable incidence in both high and most low-income countries ranging from 20-30% worldwide [2]. PPH after CS is the commonest cause of maternal morbidity &mortality, even in highly resourced countries and is continuously increasing in incidence [12]. Misoprostol is a synthetic analogue of PGE1 that acts as a uterine contractile agent. It is efficient in the prevention and treatment of PPH [13]. Sublingual misoprostol has the shortest onset of action, the highest peak concentration, and the greatest bioavailability among all routes of administration [14]. Rectally administered misoprostol is accompanied with slower absorption, lower peak levels, and decreased side effects in comparison with the oral & sublingual routes [15]. The results of the present study revealed that there were no significant differences between groups as regard age (p=0.55), parity (p=0.94), gestational age (p=0.60), and the number of previous CSs (p=0.64). This nonsignificant difference was important to ensure the homogenization of the studied groups to get accurate results from the comparison between groups. In this study, women of rectal misoprostol group (group II) had a significantly higher amount of intraoperative blood loss compared to cases of sublingual misoprostol group (group I), (581 ± 196 vs. 456 ± 187 in group II and I,
respectively), (P≤0.01). These results are completely in agreement with another study [5] that found the estimated blood loss in rectal misoprostol group was 457.5 ± 140.7 mL compared to 357.8 ± 129.7 mL in sublingual misoprostol group, they found that this difference between groups was significant (P≤0.01). In the current study, the difference between the rectal and sublingual groups in blood loss may be related to the rapid absorption and high bioavailability of misoprostol when given sublingually [16]. Sublingual misoprostol is known to reach the highest peak plasma concentration within the shortest time [5].

It has been reported that sublingual misoprostol observed to be more effective than the intravenous infusion of OXT in reducing blood loss during and after CS [17]. The rectal route of misoprostol had slow uptake, but the prolonged duration of action. The buccal and sublingual routes had a rapid intake, prolonged duration of action, and the greatest total bioavailability. It was concluded from the data reviewed that the most promising route of administration was the sublingual route [18].

In our study, no significant differences were found between groups regarding preoperative Hb level (10.86 ± 0.90 g/dl in group I vs. 10.92 ± 0.92 g/dl in group II, p=0.74) and also postoperative Hb level (10.28 ± 0.88 g/dl in group I vs. 10.14 ± 0.67 g/dl in group II, p=0.39). However, an obvious, highly significant reduction was noticed in the postoperative Hb level in both groups (P≤0.01). The percentage of Hb decrease in rectal misoprostol group (group II) was higher than the sublingual misoprostol group (group I). These results agreed with a recent study [5], that study found that preoperative Hb was 10.7 ± 1.0 g/dl in the sublingual misoprostol group in comparison with 10.5 ± 1.0 g/dl in the rectal group with no significant difference between groups. However, postoperative Hb was decreased to 10.3 ± 1.0 and 10.1 ± 1.0 g/dl in both sublingual and rectal misoprostol groups, respectively.

The difference between groups in postoperative Hb was not significant. However, the reduction in postoperative Hb was highly significant in both groups (P≤0.01). Also, they reported that the percentage of Hb decrease in rectal misoprostol group was higher than that of the sublingual misoprostol group. Also, our results are in harmony with another study [15] that compares the effect of sublingual versus rectal administrations of misoprostol on blood loss in cases undergoing an elective CS. They documented that preoperative Hb was 11.17 ± 1.03 in the sublingual misoprostol group versus 11.32 ± 0.97 g/dl in the rectal misoprostol group (P=0.512). However, the mean postoperative Hb was higher in the sublingual group (10.00 ± 1.13 g/dl vs. 9.63 ± 0.76 g/dl, p=0.463), it is
obvious that the fall in Hb level was significantly higher in the rectal misoprostol group.

In our study, the same trend of results of Hb was found in Hct, the results demonstrated that there were no significant differences between groups regarding preoperative Hct (33.4 ± 2.1 % in group I vs. 33.7 ± 1.9 % in group II, p=0.64) and also postoperative Hct (32.1 ± 2.1 % in group I vs. 31.5 ± 2.7 % in group II, p=0.21).

However, a highly significant reduction was found in postoperative Hct % in both groups (P≤0.01). Also, the percentage of Hct reduction was elevated in the rectal misoprostol group (group II) compared to the sublingual misoprostol group (group I).

Regarding the side effects of misoprostol, shivering, and nausea were almost similar between groups with no significant difference. However, the incidence of vomiting was significantly higher in the group (I) compared to the group (II) (15 cases vs. 6 cases). These findings corroborate with other studies [15,19]. As regards the need for additional uterotonics, the results showed that 7 cases (14.0%) in rectal misoprostol group needed uterotonics versus only 3 cases (6.0%) in sublingual misoprostol group, the difference between the group was not significant (p=0.18).

The need for additional uterotonic agents was less in the sublingual misoprostol group in our study, and this finding is similar to other studies [5, 20 and 21].

Finally, oral, buccal, rectal, and sublingual routes have been used in different studies. The sublingual route was chosen because it avoids oral intake, doesn't disrupt the operative field, and ensures continuous plasma levels of a potent uterotonic agent over a prolonged period. Pharmacokinetic studies on different routes of administration have shown that sublingual route achieved the highest serum peak concentration (C max), the shortest time to peak concentration (T max), and the highest area under the curve (AUC) of misoprostol acid, the active metabolite of misoprostol [22, 23].

5. Conclusion and Recommendations

The sublingual route of administration of misoprostol is more effective in reducing intraoperative blood loss and postoperative Hb and Hct level decrease at CS than the rectal route but with no significant difference between groups postoperatively, and with more adverse effects in the sublingual group. Also, sublingual misoprostol reduces the need for additional uterotonics. Sublingual administration of misoprostol is recommended because it is favorable for patients and convenient of use than rectal one. Funding This Study did not receive any funds from any organization.
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