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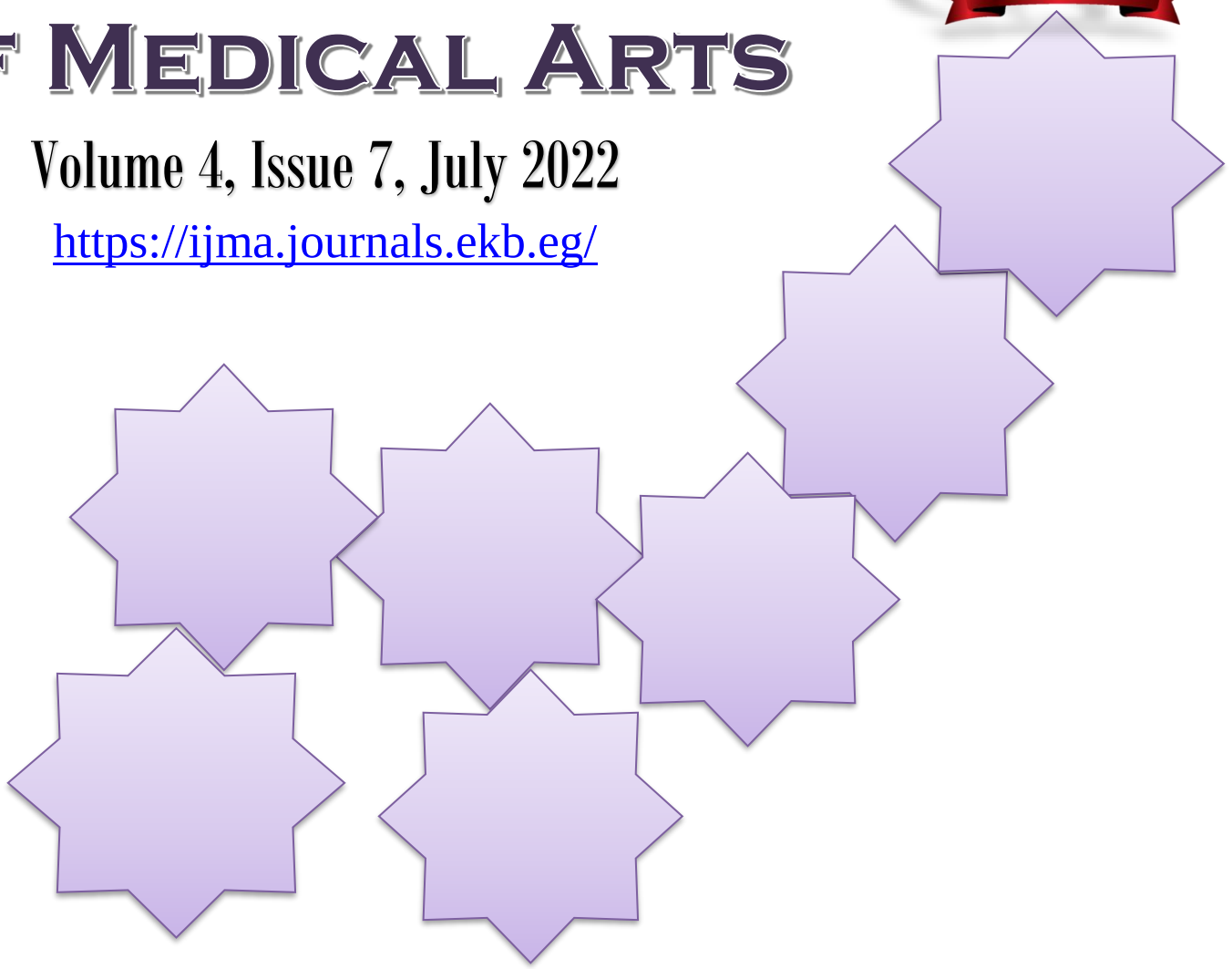

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Original Article

Prostaglandin E1 Analog: Comparison between Two Different Routes of Administration for the Prevention of Post-Partum Hemorrhage

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ABSTRACT

Background: Postpartum hemorrhage [PPH] is considered as the major cause of maternal death worldwide. A Prostaglandin E1 analog, Misoprostol, has been demonstrated to be useful in lowering intra and postoperative blood loss. However, the proper timing of administration is still up for debate.

Objective: Comparative study of Prostaglandin E1 analog [misoprostol] administration via two distinct routes: preoperative rectal and intraoperative intrauterine administration to reduce blood loss during and after cesarean delivery.

Patients and Methods: This is a randomized clinical trial that involved 100 pregnant women attending Alzhraa University Hospital, all of them were eligible for elective cesarean section. All participants were randomized into two groups: Group [1]: which involved 50 women who received 400 ug misoprostol intrauterine intraoperative, and Group [2]: which involved 50 women who received 400 ug misoprostol rectally preoperative.

Results: The two groups were not statistically significant different regarding the amount of blood loss or the occurrence of postpartum hemorrhage P-value [P<0.05]. The Apgar scores were considerably higher in the intrauterine Group compared to the rectal Group at both 1 and 5 minutes.

Conclusion: Both preoperative rectal and intraoperative intrauterine administration of Misoprostol [400ug] have the same effect on the amount of blood loss during caesarean delivery; however, it is more convenient to be administrated during caesarean delivery with a safer neonatal outcome.

Keywords: Post-partum; Bleeding; Intrauterine, Rectally; Misoprostol

INTRODUCTION

Cesarean section [CS] is a crucial life-saving intervention when vaginal delivery may represent a fetal or maternal risk according to the World Health Organization [1]. The prevalence of CS in Egypt has recently been found to be 52%, according to Egypt Demographic and Health Survey [EDHS], showing a considerable increase in the prevalence of CS conditions over the past decade [2].

Primary post-partem hemorrhage [blood loss of more than 1000ml during the first 24 hours] is considered one of the most common complications nationwide, especially in resource-limited countries [3], with an overall incidence of 6% [4].

In the last years, several preventive measures have been applied based on the use of uterotonics to reduce the incidence of uterine atony by 60% [5]. Recombinant Oxytocin is an Oxytocic. Its physiological effect is by increasing uterine smooth muscle contraction. In the postpartum period, oxytocin is used to induce uterine contractions in the 3rd stage of labor and hence control postpartum hemorrhage. It is considered the treatment of choice for prophylaxis and treatment of PPH; however, repeated injections of oxytocin will lead to receptor desensitization [6].

In cases of refractory uterine atony, approximately 3-25% of patients require other uterotonics after oxytocin injection [7].

Misoprostol is an artificial analog of prostaglandin-E_1 with uterotonic characteristics, making it useful for the treatment and prevention of PPH. Because of its features, such as long half-life, stability without refrigeration, low cost, readily available, and simplicity to administer, Misoprostol can be efficiently used for prevention and treatment of PPH, especially in countries with low resources [8].

Misoprostol can be taken orally, sub-lingually, rectally, buccally, vaginally, and intrauterine to reduce blood loss during cesarean delivery [9]. The use of intrauterine Misoprostol and oxytocin during cesarean section decreases the amount of blood lost during the procedure, prevents postpartum hemorrhage, and reduces the necessity for additional uterotonic drugs [10].

Both beneficial effects, such as uterine contraction, and the side effects, which include nausea, diarrhea, and chills, are dosage-dependent [11]. Previous studies suggested that Misoprostol is helpful in lowering blood loss during and after CS, independent of the route of administration [12]. However, the proper timing of administration is still up for debate.

THE AIM OF THE WORK

The aim of this study was to assess the effectiveness of preoperative and intra-operative Misoprostol administration through rectal and intrauterine routes, respectively, for reducing blood loss during cesarean section.

PATIENTS AND METHODS

This is a prospective randomized clinical trial that involved 100 pregnant women attending Alzhraa University Hospital, between September 2021 to April 2022. All participants are candidates for elective cesarean section. All participants were randomly divided into two groups [randomization is based on computer-generated random numbers]: Group [1]: involved 50 woman who received Prostaglandin E1 analog [Misoprostol] 400 ug [Cytotec Pfizer] intrauterine intraoperative [200ug at each cornue] inserted after delivery of placenta, and Group [2]: involved 50 woman who received Prostaglandin E1 analog [Misoprostol] 400 ug [Cytotec Pfizer] rectally preoperative.

The primary objective was to determine the amount of blood loss during the CS, while the secondary objectives were to determine whether bleeding occurred within the first postoperative 24 hours. and whether or not there were any adverse effects on the mother or the fetus.

Inclusion criteria: women are aged between 20–40 years with a single, viably born, full-term pregnancy [Confirmed pregnancy of at least 37 weeks gestational age by 1st day of the last menstrual cycle or 1st trimester ultrasono-graphy].

Exclusion criteria: patients with more than previous two cesarean section, antepartum hemorrhage, bleeding tendency, severe anemia, preterm delivery, concurrent anticoagulant therapy, fetal distress, known allergies to prostaglandins or people with preexisting comorbidities diseases [e.g., coagulopathies, cardiac, hepatic, or renal illness].

Ethical consideration

Al-Azhar University Ethical Committee authorized the current research. All eligible women provided their informed written consent.

All participants were submitted to a comprehensive patient history, physical and obstetrician examination [including menstrual period data, BMI, and vital signs], followed by ultrasound for gestational age identification and pregnancy eligibility confirmation. Preoperative investigation including CBC, PT, PTT liver, kidney function tests, random blood sugar, and virology testing.

Spinal anesthesia was used in all the caesarean sections that were performed. All women who were recruited underwent a caesarean section using the same procedure, which consisted as the subsequent steps: Pfannenstiel incision to skin, transverse incision to lower uterine segment and visceral peritoneum, delivery of fetus, immediate cord clamping, delivery of placenta and membrane, closure of both uterus, and anterior abdominal wall in layers, with adequate hemostasis for all operative steps. The patients in both groups didn't receive oxytocin.

All towels were counted and weighed before and post-CS, the difference in weight was determined, and the blood volume in the suction unit was recorded. Blood loss intraoperatively was estimated in the suction unit in millilitres, all towels used were the same size and weight, and each 1g increase in weight was equated to 1ml of blood loss. Total intraoperative blood loss was determined [blood loss in suction apparatus plus weight difference of used towels].

During the first 24 hours, postoperative external blood loss is measured by weighing soaked towels put in the vulval region.

Apgar score was observed at 1 and 5 minutes, neonatal intensive care unit admission and neonatal death were also observed. In addition to that, monitoring of fluid input and output was carried out. Every patient was followed for the 1st 24 hours post-delivery to monitor the amount of blood loss, blood transfusion requirement, the need to use another ecbolic, or any misoprostol-related adverse effects in the 1st six hrs. [fever, shaking, headache, nausea, vomiting]."CBC was done post-operatively to detect changes in Hb level. Both groups' data were gathered, processed, and compared.

The estimated blood loss volume that resulted during the cesarean section was the primary outcome, whereas the 1st 24 hours' postoperative blood loss were secondary outcomes, followed by identification of the necessity for blood transfusions, utilization of additional uterotonics, presence of any fetal or maternal side effects and changes in hemoglobin level.

Statistical analysis

Using version 23.0 of the statistical program, data were examined [SPSS Inc., Chicago, Il, USA]. The quantitative information was reported as mean± standard deviation and ranges. In addition, qualitative factors were reported in numerical and percentage form. Using the Kolmogorov-Smirnov and Shapiro-Wilk tests, the normality of the data was examined. For comparing two means, a t-test for significance based on independent samples was utilized. In order to compare proportions between qualitative parameters, the Chi-square [x2] significance test was utilized. The confidence interval was set to 95%, and the acceptable margin of error at 5. p-value <0.05 considered significant.

RESULTS

No statistically significant difference existed among the included groups in terms of socio-demographic factors, hematologic profile, or the primary outcome [amount of blood loss], as shown in tables [1-3].

There was a statistically significant higher mean of Apgar score at 1 & 5 min when comparing the intrauterine Group versus the rectal Group [p<0.05 significant]; while Excessive blood loss >1000ml in the first 24hr and the need for the use of extra ecbolic is insignificant [table 4].

There was an insignificant higher frequency of side effects in the rectal Group compared to the intrauterine Group [table 5].

Table [1]: The Socio-demographic characteristics of the study participants

Variables	Group [1]	Group 2	t-test	p-value
Maternal age [Years]	26.98±5.11	27.51±4.46	0.553	0.582
BMI [kg/m²]	29.22±4.98	30.89±4.72	1.721	0.088
Gestational age [weeks]	38.35±1.92	38.60±0.72	0.862	0.391
Number of previous CS	1.42±1.24	1.40±1.33	0.078	0.938
Parity	3.20±1.10	3.50±1.90	0.966	0.336
Neonatal Weight [gm]	3280.1±133.29	3300.12±102.47	0.842	0.402
Duration of CS [min]	60.33±4.66	61.53±5.67	1.156	0.250

Table [2]: Hematological alterations profile among included groups

Variables	Group [1]	Group [2]	t-test	p-value
Preoperative Hb [gm/dl]	11.22±1.24	11.71±1.32	1.913	0.059
Postoperative Hb [gm/dl]	10.47±1.06	10.71±1.07	1.127	0.263
Drop in Hb	0.75±0.63	1.00±0.69	1.892	0.061
Preoperative HCT [%]	31.53±3.66	32.16±2.27	1.034	0.304
Postoperative HCT [%]	29.29±2.39	30.15±2.01	1.947	0.054
Drop in HCT	2.24±0.96	2.01±0.87	1.255	0.212

Table [3]: Loss of blood among included groups

Outcome	Group [1]	Group [2]	t-test	p-value
Blood Loss in Towels [ml]	176.11±31.9	167.54±26.3	1.466	0.146
Blood loss in suction [ml]	265.0±70.9	237.0±83.6	1.806	0.074
Intra-operative blood Loss [ml]	421.0±84.7	394.0±75.6	1.682	0.096
Post-operative vaginal bleeding	172.4±33.1	169.5±32.5	0.442	0.659
Total estimated blood loss [ml]	593.40±117.7	563.5±108.1	1.323	0.189

Table [4]: Secondary outcome of both studied groups

Outcomes	Group [1]	Group [2]	Test value	p-value
Excessive blood loss >1000ml in the first 24hr.	3 [6%]	2 [4%]	x^2:0.208	**0.648**
The need to use extra ecbolic	6 [12%]	3 [6%]	x^2:2.187	**0.139**
Apgar score at 1 min.	7.54±0.65	7.17±0.90	t:2.357	**0.020***
Apgar score at 5 min.	9.55±0.50	9.18±0.73	t:2.957	**0.004***

Table [5]: The adverse side effects of the drug in both Studied groups

Side effects	Group [1]	Group [2]	x^2	p-value
Pyrexia	5 [10%]	7 [14%]	0.375	0.540
Shivering	8 [16%]	10 [20%]	0.268	0.605
Vomiting	2 [4%]	3 [6%]	0.208	0.648
NICU admission	3 [6%]	4 [8%]	0.306	0.580

DISCUSSION

In the present study, Prostaglandin E1 analog [Misoprostol] in a dose of 400 ug administered intrauterine has similar efficacy as preoperative rectal misoprostol 400 ug during cesarean section in reducing both intraoperative and postoperative blood loss. **Abd-Ellah *et al*.** [13] proved that preoperative rectal Misoprostol is more effective than postoperative administration

in reducing blood loss and in decreasing the need for other uterotonic drugs in cesarean delivery [10]. They Examined the efficacy of intrauterine Misoprostol in conjunction with oxytocin versus oxytocin alone in preventing postoperative hemorrhaging following cesarean delivery, and concealed that intrauterine Misoprostol decreased hemoglobin by 39.6% and the requirement for further uterotonics by 50%. In addition, 13% of patients who got oxytocin alone saw a significant sharp reduction in hemoglobin [>3g%], compared to 3% of those who were treated with intrauterine Misoprostol. It has been suggested oxytocin in conjugation with intrauterine Misoprostol decreases excessive loss of blood during and after post-cesarean birth.

Similar findings were shown by **Alalfy *et al.*** [14], who reported significantly reduced blood loss in the patients receiving intrauterine Misoprostol combined with oxytocin versus oxytocin alone. The same as with **Bahadur *et al.*** [15], who found that the use of intrauterine Misoprostol in conjunction with oxytocin infusion dramatically reduced blood loss in women undergoing both intraoperative and postoperative CS.

Majed *et al.* [12] demonstrated the efficacy and safety of preoperative misoprostol administration via the rectal route.in reducing blood loss intra-operative and postoperative. It has been reported that the buccal routes have a faster absorption rate than the oral and rectal routes by way of peak levels occurring greater than an hour post-delivery, therefore achieving a high peak level towards the end of the intervention.

It is considered, however, that the pre-operative pathway may have a negative impact on the fetus, particularly if the delivery of the fetus is delayed in cases of difficult operation with significant adhesion from multiple previous surgeries. In order to avoid any adverse effects on the fetus, intrauterine administration was chosen.

It is thought that the decidua's large surface area and many feeding capillaries allow for efficient absorption, as the mucosal absorption of the sublingual, vaginal, and rectal routes. This hypothesis was validated when it was shown that the intrauterine rectal routes were equally effective in reducing blood loss during and post-cesarean delivery.

This study concurs with all prior studies regarding the efficacy of intrauterine Misoprostol for blood loss reduction during and after post-cesarean delivery and, consequently, PPH.

Based on the current study, participants who were administered with rectal Misoprostol preoperatively had lower Apgar scores at 1 & 5 min compared to those treated with intrauterine Misoprostol. The present finding agrees with the study of **El-Sherbini *et al.*** [16], who observed that the combined usage of Misoprostol with oxytocin intrauterine or rectally lowers operational blood loss and PPH as effectively as the use of either agent alone. Misoprostol has no side effects other than shivering, fever, and nausea, regardless of whether a rectal-intrauterine route of administration is used. However, the intrauterine route is preferable since it is fetus safe than the rectal route, particularly during a lengthy interval of misoprostol administration and delivery. Furthermore, the rectal route eliminates the possibility of contamination.

This study assessed the safety and effectiveness of Misoprostol administered via the rectal and intrauterine routes in low-risk pregnancies. Both approaches were shown to be equally effective in minimizing blood loss intra and post-cesarean delivery. Moreover, newborn infants to moms who received intrauterine Misoprostol had a higher considerable Apgar scoring at 1 & 5 min.

The limitation of the present study is the exclusion of patients with a high risk for PPH and patients with higher than two previous cesarean sections.

Conclusion

Administration of Prostaglandin E1 analog [Misoprostol] by preoperative rectal and intraoperative intrauterine for minimizing blood loss regarding the operational level and post-cesarean delivery was found to have the same efficacy. Either intrauterine or rectal administration of Misoprostol is equally safe except for shivering, and pyrexia could still happen, but it is mild and self-limiting. Intrauterine Misoprostol is preferred over the preoperative rectal route as it is fetus safe, particularly when there is a long time between the administration of misoprostol and delivery.

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