Rectal misoprostol after cesarean delivery: does it affect recovery of bowel functions? A prospective randomized trial

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Summary

Aim: To assess the efficacy of rectally administered misoprostol in the improvement of bowel function recovery after cesarean delivery (CD). Methods: This prospective randomized trial was conducted among 171 pregnant women subjected to term elective CD. Patients were divided equally into 3 groups by simple randomization. Participants in group A were given misoprostol 200 μg rectally; those in group B were given misoprostol 400 μg rectally just after CD but before leaving the operating theater, while the participants in group C did not receive any rectal drug. The study outcome measures were: duration before first bowel movement and start of the regular oral diet. Adverse effects, need for additional analgesics, and post-CD hospital stay period were also recorded. Results: The mean times to first audible intestinal sounds and to the first passage of flatus were significantly lower in group B (14.1 ± 1.4 h and 16.7 ± 2.3 h, respectively) when compared to both groups A and C [21.9 ± 5.3 h and 24.9 ± 5.7 h (A) vs. 23.6 ± 6.9 h and 27.1 ± 7.9 h (C)] (p = 0.001). It was found that notably, patients in group B resumed diet more quickly, with a mean period of 20.5 h, which was significantly faster than the remaining groups (29.8 h and 33.1 h in groups A and C, respectively). Of great interest, patients in group B had a lower post-CD hospital stay (38.5 h vs. 59.2 h in group A and 64.8 h in group C). Conclusion: For the recovery of bowel functions after CD, rectal administration of 400 μg misoprostol appears to be more effective than 200 μg of rectally administered misoprostol or traditional feeding regimens.

Key words: Misoprostol; Bowel motility; Cesarean section; Post-CS recovery.

Introduction

In modern obstetrics, cesarean delivery (CD) is an everyday practice, with increasing worldwide incidence. Despite the high prevalence of CD, the optimal time to start oral feeding after CD has yet to be determined; our knowledge is based on experience rather than any evidence-based medicine [1]. Following cesarean delivery, normal bowel movement is temporarily interrupted in the early postoperative period; bowel function ordinarily returns within the first 24 hours. Occasionally, this phenomenon is delayed and results in post-operative paralytic ileus leading to abdominal distension with discomfort, vomiting, agonizing abdominal pain, as well as increased hospitalization resulting in increased healthcare burden and costs [2].

Enhanced recovery after surgery (ERAS) is considered a standard protocol for perioperative care currently being followed within multiple surgical disciplines. ERAS has resulted in clinical benefits (reductions in length of stay, complications, and readmissions) as well as in health system benefits (reduction in cost) [3, 4].

Postoperative feeding regimens vary considerably among obstetricians and surgeons, ranging from a trend of early administration of diet to delayed feeding regimens [5]. Traditionally, patients with cesarean delivery are maintained on exclusive IV fluids for the initial 24 hours. On the first postoperative day, if intestinal sounds are audible with no abdominal distension, the patients are allowed to start with fluids [6]. However, this delayed feeding regimen increases the risk of gaseous retention of the colon and prolonged hospital stay, resulting in increased economic cost [2, 7]. On the other hand, early oral feeding exhibited a significant reduction in thirst and hunger, better maternal satisfaction, early ambulation and shorter hospital stay with no impact on readmissions or gastrointestinal symptoms or infections [4]. This practice also improves and maintains a positive caloric balance, enhances wound healing and boosts postoperative recovery, leading to earlier hospital discharge [8, 9]. However, some obstetricians delay the post-cesarean delivery oral intake until the recovery of regular bowel function due to fears of complications such as vomiting with the possibility of aspiration, pneumonia and wound dehiscence [2, 10].

Misoprostol, a synthetic prostaglandin E1 analogue, was originally prescribed for the management of peptic ulcer disease through inhibition of acid production and the increase of gastric mucosa protection [11, 12]. Subsequently, it gained popularity in the field of obstetrics for the management of medical abortion, induction of labor, and prevention and management of atonic post-partum hemorrhage [12]. As is well documented in the literature, misoprostol has shown a remarkable capacity to improve intestinal and colonic motility with increased intestinal fluid secretion and movement, resulting in decreased colonic transit time in refractory chronic constipation patients [12, 13].
Although there is scant published data as to misoprostol’s potential influence on intestinal motility after cesarean delivery, considering the current financial pressure on health resources, it is understandable that there is widespread interest in introducing some agents after cesarean delivery to facilitate earlier hospital discharge [4, 14]. Accordingly, we set out to determine whether rectally administered misoprostol can improve bowel function recovery after cesarean delivery, a major determinant of early hospital discharge.

**Participants and Methods**

This prospective randomized trial has been conducted among women subjected to term elective cesarean delivery during the period from July 1, 2018 to August 31, 2019 at the Obstetrics department of Maternity Hospital KSA.

All willing term pregnant patients undergoing elective CD during the aforementioned study period were included in the trail. The different indications for cesarean delivery were previous cesarean deliveries (n = 132), abnormal presentations (n = 21), cephalopelvic disproportion (n = 11), and previous classical repair and/or complete perineal tear (n = 7). Exclusion criteria were: Women with a past history of thyroid diseases, chronic constipation, irritable bowel diseases, bowel surgery, abdominal irradiation, use of epidural analgesia, those suffering from systemic medical diseases (cardiac, hepatic, renal, etc.), and women who had general anesthesia by choice or contraindicated for spinal anesthesia.

All pregnant women fulfilling the inclusion criteria were advised as to the purpose of the study and encouraged to participate; informed written consent was then obtained in Arabic form. Based on an expected difference of 4 h to the time of the first intestinal sound between groups A and C, [2] and on the power of the study of 80% and \( \alpha \) error of 0.05 [15], the required sample size was at least 57 women in each study arm after a 5% allowance was made for attrition (Figure 1). The trial included 171 women who were equally divided into 3 groups by simple randomization method. Participants who were assigned into group

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Figure 1. — Consort flow chart of participants through the study.
Table 1. — Baseline maternal characteristics of the studied participants.

| Variables               | Group A (n = 57) | Group B (n = 57) | Group C (n = 57) | p value  
|-------------------------|-----------------|-----------------|-----------------|---------
| Age (years)             | Mean ± SD       | 29.2 ± 4.3      | 28.4 ± 2.5      | 27.6 ± 3.9 | 0.06 (NS)  
| BMI (kg/m²)             | Mean ± SD       | 28.5 ± 2.9      | 29.1 ± 3.5      | 27.8 ± 2.7 | 0.08 (NS)  
| Gestational age (weeks) | Mean ± SD       | 38.2 ± 1.1      | 37.9 ± 1.7      | 38.1 ± 1.4 | 0.06 (NS)  
| Previous CD            |                 | 58%             | 56%             | 55%       | 0.08 (NS)  
| Mal-presentation        |                 | 17%             | 18%             | 15%       |          
| CPD                     |                 | 14%             | 12%             | 13%       |          
| Previous CR             |                 | 11%             | 14%             | 17%       |          
| Non scared uterus       |                 | 42%             | 44%             | 45%       | 0.06 (NS)  
| Number of previous CD (%) |             |                 |                 |          
| Previous 1-2 CD         |                 | 28%             | 25%             | 27%       |          
| Previous ≥ 3 CD         |                 | 30%             | 31%             | 28%       |          
| Gravida PG              |                 | 7 (12.3%)       | 9 (15.8%)       | 9 (15.8%) |          
| Gravida 2-3             |                 | 21 (36.8%)      | 18 (31.6%)      | 17 (29.8%)| 0.09 (NS)  
| > Gravida 3             |                 | 29 (50.9%)      | 30 (52.6%)      | 31 (54.4%)|          

NS: No statistically significant difference. BMI = Body Mass Index, PG = Primigravida, CR = Classic Repair, CD = Cesarean Delivery, CPD = Cephalo-pelvic disproportion.

Table 2. — Main outcome measures among the studied participants.

| Variables                        | Group A (n = 57) | Group B (n = 57) | Group C (n = 57) | p value |
|----------------------------------|-----------------|-----------------|-----------------|---------|
| Time to the first audible intestinal sound (h) (Mean ± SD) | 21.9 ± 5.3<sup>a</sup> | 14.1 ± 1.4<sup>b</sup> | 23.6 ± 6.9<sup>a</sup> | 0.001* |
| Time to the passage of first flatus (h) | 24.9 ± 5.7<sup>a</sup> | 16.7 ± 2.3<sup>b</sup> | 27.1 ± 7.9<sup>a</sup> | 0.001* |
| Time to the first meal (h) (Mean ± SD)          | 29.8 ± 8.3<sup>a</sup> | 20.5 ± 3.1<sup>b</sup> | 33.1 ± 10.2<sup>a</sup> | 0.001* |
| Hospital stay (h) (Mean ± SD)                       | 59.2 ± 12.9<sup>a</sup> | 38.5 ± 2.7<sup>b</sup> | 64.8 ± 18.4<sup>a</sup> | 0.001* |

Adverse effects of misoprostol

| Nausea | Vomiting | Distension | Shivering |
|--------|----------|------------|----------|
| 2 (3.5%) | 3 (5.3%) | 3 (5.3%) | 2 (3.5%) |
| 3 (5.3%) | 3 (5.3%) | 5 (8.8%) | 3 (5.3%) |
| 3 (5.3%) | 4 (7.1%) | 0 (0%) | 1 (1.8%) |

<sup>a</sup>Statistically significant difference (ANOVA test). (a, b) Superscripts denote statistically significant difference within groups (post hoc test).

A received 200 µg per rectal administration of misoprostol and group B received 400 µg per rectal administration of misoprostol [12], immediately following surgery but before leaving the operating room, while patients in group C did not receive any rectal drug. The author was responsible for the randomization method as well as confirmation of administration of the drugs in the operating room. To eliminate any study bias, the post-operative follow-up team (outcome assessors) was all blinded to the study groups.

Pre-operative care was the same for all study participants and all cesarean deliveries were performed under regional spinal anesthesia. Upon delivery of the fetus, all women received 1 amp of ergometrine (Methergine, Novartis CO.) IM as per protocol in addition to 10 units of oxytocin (Syntocinon, Novartis CO.) in 500 mL dextrose 5% given by IV drip over 30 min. Additional oxytocin was administered, if deemed necessary. Then, on the basis of the study assignment, participants were divided into groups A, B and C.

Similarly, all study participants received the same post-operative care in the form of regular intravenous fluids and routine analgesia: two doses of 75 mg diclofenac sodium were given IM immediately and 12 h postoperatively. During the postoperative period, vital signs and auscultation of intestinal sounds in all four abdominal quadrants were periodically recorded every two hours, as usual. Oral feeding was delayed until passage of flatus and/or audible intestinal sounds were observed. Serum levels of sodium, potassium, hemoglobin and hematocrit were measured both pre-op and two days following the cesarean delivery.

The following outcomes were recorded for all the 3 groups: time to first detection of intestinal sounds, time to first passage of flatus, and duration of hospital stay. The length of hospital stay was defined as the time interval between the end of surgery and hospital discharge [2]. Any adverse effects of misoprostol (nausea, vomiting, abdominal distension or shivering) were also recorded. Data were processed using SPSS version 22.
operative hospital stay, whether through rectal misoprostol or traditional feeding regimen after cesarean delivery. The Enhanced Recovery After Surgery (ERAS) Society provides recommendations to facilitate early and safe maternal hospital discharge [4]. To the best of our knowledge, their study is the first trial to compare the efficacy of 3 different regimens on the early recovery of bowel function and postoperative hospital stay, whether through 200 μg of rectally administered misoprostol, 400 μg of rectally administered misoprostol, or traditional feeding regimen after cesarean delivery.

Rectal administration of 400 μg misoprostol in our trial entailed reduced times to the first flatus passage and audible intestinal sounds, indicating its valuable effect on energizing intestinal recovery following cesarean delivery. Recovery of intestinal function after cesarean delivery is an essential parameter for early postoperative feeding and reduced hospital stay [2]. That early recovery of bowel function in our study group could be explained by the pharmacologic effects of misoprostol on increased bowel motility and intestinal fluid movement [16] which was to be expected with 400 μg rather than 200 μg of rectal misoprostol, in addition to the routine post cesarean delivery use of non-steroidal anti-inflammatory drugs which was found to be closely related with a significant decrease in bowel activity [17]. Finally, cesarean delivery was performed under local regional spinal anesthesia which blocks sympathetic nerve activity that may help in the efficacy of bowel movements [18].

We compared our findings with the only two reported research trials and were in agreement with Adanikin et al. who assessed bowel motility after cesarean delivery by the administration of 600 μg of rectal misoprostol; their misoprostol group had a short mean postoperative interval to the passage of flatus (20.27 ± 7.77 hours) and commencement of regular diet (21.08 ± 7.69 hours) [19]. However, Demirci et al. contradicted our findings. They administered 200 μg and 400 μg of rectal misoprostol after abdominal hysterectomy, recorded intervals between surgery and flatus pass (21.6 ± 6.9 h and 23.8 ± 14.6 h, respectively) and concluded that misoprostol did not affect intestinal movements after surgery [12]. Research methodology, sampling techniques, duration of surgery and extent of bowel handling may account for that difference.

Adverse gastrointestinal effects tended to be higher when 400 μg misoprostol was rectally administrated vs. 200 μg, and both were higher than the control group, although the differences did not reach clinical or statistical significance. Of great interest, incidence of these adverse effects was much lower than in previously reported studies [12, 19], as we elected to use minimal rectally administered misoprostol doses of a type reported to have low-circulation blood levels, possibly accounting for the reduction in the adverse effects, in comparison to oral route [20]. However, appropriate and prompt simple and supportive measures were given to eliminate those adverse effects. Although adverse effects were not significant in the study, it is important to check for such effects when rectal misoprostol is used in larger studies in the future.

### Results

The socio-demographic characteristics of all participants in the 3 groups are presented in Table 1. Maternal age, gravidity, gestational age and body mass index were matched without any statistical significance. Previous cesarean delivery was the most common indication for elective cesarean delivery (58 %, 56% and 55% in groups A, B and C, respectively).

The main study outcome measures are presented in Table 2. The mean times to first audible intestinal sounds and to the first flatus passage were significantly less for women in group B (14.1 ± 1.4 h and 16.7 ± 2.3 h, respectively) as compared to both groups A and C (21.9 ± 5.3 h and 24.9 ± 5.7 h (A), while 23.6 ± 6.9 h and 27.1 ± 7.9 h (C)). Patients in group B resumed regular diet significantly earlier (20.5 h) than the remaining groups (29.8 h and 33.1 h in groups A and C, respectively). Furthermore, patients in group B had shorter postoperative hospital stays (38.5 h vs. 59.2 h in group A and 64.8 h in group C). Adverse effects were higher in group B as nausea and vomiting were 5.3% vs. 3.5% & 5.3% in group A and 0% & 1.8% in group C, respectively. Abdominal distention and shivering were 8.8% and 7.1% in group B vs. 5.3% & 3.5% in group A and 3.5% & 0% in group C, respectively. However, these differences were not statistically significant. Lastly, there were no adverse neonatal outcomes recorded (Table 2).

All variables that may affect the recovery of postoperative bowel function are shown in Table 3. The mean duration of cesarean delivery as well as mean pre- and postoperative hematocrit values were not statistically different among the study groups. There was no reported use of additional pain relief such as pethidine among study participants.

### Discussion

Post-operative bowel care is considered an essential component of postoperative care in cesarean delivery. The Enhanced Recovery After Surgery (ERAS) Society provides recommendations to facilitate early and safe maternal hospital discharge [4]. To the best of our knowledge, their study is the first trial to compare the efficacy of 3 different regimens on the early recovery of bowel function and postoperative hospital stay, whether through 200 μg of rectally administered misoprostol, 400 μg of rectally administered misoprostol, or traditional feeding regimen after cesarean delivery.

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### Table 3. — Operative characteristics of the studied participants.

| Variables                        | Group A (n = 57) | Group B (n = 57) | Group C (n = 57) | p value |
|----------------------------------|-----------------|-----------------|-----------------|---------|
| Duration of surgery (minutes)    | 49.3 ± 8.3      | 52.8 ± 7.4      | 50.1 ± 9.9      | 0.07 (NS)|
| Preoperative hematocrit (mean ± SD) | 37.2 ± 1.8      | 37.4 ± 1.4      | 37.7 ± 1.7      | 0.3 (NS)|
| Postoperative hematocrit (mean ± SD) | 36.8 ± 1.3      | 36.7 ± 2.8      | 36.9 ± 1.5      | 0.8 (NS)|

NS: No statistically significant difference.
Traditionally, mothers might be discharged on the third post-operative day. However, the early hospital discharge of some cases after cesarean delivery was suggested as a logical, secure and cost-effective choice. Recovery of healthy intestinal activity after cesarean delivery was an essential parameter of early hospital discharge, as had been shown in the 400 µg of rectally administrated misoprostol group when compared to the remaining study groups. The National Institutes for Health (NIH) recommend the discharge of uncomplicated cesarean delivery after just 24 hours [21], as the economic impact of early hospital discharge following an uncomplicated cesarean delivery cannot be overstated, especially in developing countries with limited resources [2, 14].

In conclusion, our trial demonstrated that rectal administration of 400 µg misoprostol appears to be superior to 200 µg of rectal administration of misoprostol or traditional feeding regimens. This protocol permits a more rapid recovery of bowel function after term-elective cesarean delivery, with use of non-steroidal anti-inflammatory drugs to help the recovery of bowel functions [2, 4]. The study’s limitation is that the score levels of patients’ satisfaction were not assessed as an outcome. Further community-based longitudinal studies with more elaboration of patient’s satisfactions are recommended.

Ethics Approval and Consent to Participate
All subjects gave their informed consent for inclusion before they participated in the study. The study was carried out in accordance with the ethical principles for medical research involving human subjects included in the Helsinki declaration; ethical approval was taken as per hospital ethical committee policy (Ethics approval number: 153/18).

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Conflict of Interest
The author declares no conflict of interest.

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