Comparison of the Different Dosages of Rectal Misoprostol On Intestinal Motility and Pain Score in High Risk Cesarean Delivery

Yüksek Riskli Sezaryen Hastalarında Rektal Misoprostolün Farklı Dozlarının İntestinal Motilite ve Ağrı Skoru Üzerine Etkisinin Karşılaştırılması

Filiz ÇAYAN, MD,[a]
Arzu DORUK, MD,[a]
Mehmet Ali SUNGUR, MD,[b]
Saffet DİLEK, MD[a]

Departments of
[a]Obstetrics and Gynecology,
[b]Bioistatistics,
Mersin University Faculty of Medicine,
Mersin

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Yazışma Adresi/*Correspondence:*
Filiz ÇAYAN, MD
Mersin University of Faculty of Medicine,
Department Obstetrics and Gynecology,
Mersin,
TÜRKİYE/TURKEY
filizcayan@yahoo.com

ABSTRACT Objective: To prospectively compare the efficacy of different dosages of rectal misoprostol on pain and intestinal motility in postoperative high risk cesarean delivery. **Material and Methods:** Consecutive 160 pregnant women with two or more previous cesarean sections who underwent cesarean delivery were randomly grouped to receive no drug (n= 40), 200 μg misoprostol (n= 40), 400 μg misoprostol (n= 40) or 600 μg misoprostol (n= 40) rectally before leaving the operating room. Primary outcomes were the time interval between surgery and first bowel movements and first flatus passage. Secondary outcome was the women's satisfaction measured with a visual analogue scale. Patient demographic characteristics, pre- and postoperative findings, pain scores on visual analog scale and adverse effects of the drug were assessed in all groups. **Results:** Time to first bowel movement and the first flatus passage were significantly shorter in the group given 600 μg rectal misoprostol than the others (p< 0.001). There were no significant differences in postoperative pain scores on visual analogue scale and postoperative additional analgesic need among the groups (p= 0.270 and p= 0.906, respectively). The side effects of fever and shivering were found more frequent in the 600 μg misoprostol group, but the difference among the groups did not reach a statistical significance (p< 0.01). **Conclusion:** Single dose rectal misoprostol appears to be effective in recovery of gastrointestinal function after high risk cesarean delivery.

Key Words: Misoprostol; cesarean section

ÖZET Amaç: Yüksek riskli sezaryen hastalarında, rektal misoprostolün farklı dozlarının intestinal motilite ve ağrı skoru üzerine etkisi. **Gereç ve Yöntemler:** Çalışmaya iki veya daha fazla sezaryen geçirmiş olan ve term gebeliği mevcut olan 160 kadın alındı. Hastalar sezaryen operasyonu sonrası randomize olarak dört gruba ayrıldı: Grup 1'de ki olgular herhangi bir rektal ilaç kullanılmazken (n= 40), grup 2'deki olgulara 200 μg misoprostol (n= 40), grup 3'deki olgulara 400 μg misoprostol (n= 40 ve grup 4'deki olgulara 600 μg misoprostol (n= 40) rektal olarak operasyon odasını terketmeden hemen önce uygulandı. Tüm olgularda, operasyon sonrasında bağırsak hareketlerinin ilk başladığı zaman ve ilk gaz çıkış zamanı kaydedildi. Ayrıca postoperatif 24. saatte hastaların memnuniyet derecesi, visual analog scala (VAS) yardımı ile ölçüldü. Tüm olguların demografik özellikleri, pre- ve postoperatif bulguları, visual anolog skala ile belirlenen ağrı skorları ve ilaç yan etkileri belirlendi. **Bulgular:** İlk bağırsak hareketlerinin başlangıç zamanının ve ilk gaz çıkış zamanının 600 μg misoprostol grubunda, diğer gruplara oranla istatiksel anlamlı derecede daha erken olduğu saptandı (p< 0.001). VAS'la değerlendirilen postoperatif 24. saatte ağrı skorları ve ek analjezik ihtiyacı açısından ise gruplar arasında anlamlı bir farklılık bulunamadı (p= 0.270 ve p= 0.906). Ateş ve titreme şikayetleri 600 μg misoprostol grubundaki olgularda diğer gruplardan daha sık görüldü, ancak fark istatistiksel olarak anlamlı değildi (p< 0.01). **Sonuç:** Postoperatif tek doz 600 μg rektal misoprostol, yüksek riskli sezaryen operasyonlarından sonra gastrointestinal fonksiyonların iyileşmesinde faydalı olabilir.

Anahtar Kelimeler: Misoprostol; sezaryen doğum

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Early feeding following cesarean delivery (CD) is associated with higher maternal satisfaction, shortening the hospitalization period and improving the lactation.[1] Historically, patients were fasted following abdominal surgery until return of bowel sounds or passage of flatus. Sometimes it delays more than 48 hour after surgery,[2,3] and this prolonged absence periods is important especially after CD, because it may result in delayed onset of lactation.

Traditionally, it is advised to after an uncomplicated surgery withhold solid food for the first 24 hours in the belief that this would prevent gastrointestinal complications. However, several studies revealed that early feding was as safe as the traditional progressive approach.[4-9] Altough it is well known that early restoration of eating and drinking improves bowel motility after surgery, not much information is available for the complicated and high risk surgery patients.

Misoprostol is a prostaglandin E1 analogue which is used for the prevention and treatment of peptic ulcer disease. Although not registered, it has been widely used for obstetrics and gynaecological indications, such as induction of labor and abortion.[10-12] It is also known to be effective in stimulating intestinal transit both in healthy individuals and chronic constipation patients.[13] However, there are few published data regarding its effects on intestinal motility in the early postoperative period. Therefore, we aimed to evaluate prospectively whether rectal misoprostol induces intestinal motility after high risk CD and if so, at which doses it should be used. To best of our knowledge, this is the first report that compares the effects of different dosages of rectal misoprostol on bowel transit time and patient satisfaction after high risk CD.

MATERIAL AND METHODS

One hundred sixty pregnant women, with two or more previous cesarean deliveries at term (37-40 wks) gestation scheduled for either elective or emergency lower segment CD were recruited in this study, between January 2005 and November 2008 in the University of Mersin School of Medicine. Subjects were randomly divided to four groups immediately following their cesarean delivery. Each group consisted of 40 patients; group 1 (n= 40) received no drugs, group 2 (n= 40) received misoprostol 200 μg rectally, group 3 (n= 40) received misoprostol 400 μg rectally, and group 4 (n= 40) received misoprostol 600 μg rectally before leaving the operating room.

Patient demographic characteristics were recorded and complete blood count was obtained before surgery and 24 hours postoperatively. The bowel sounds in four quadrants were checked every six hours postoperatively by a caregiver. Time to first flatus passage and bowel movement was recorded in hours after the CD, as defined by Patolia et al.[7] The women were examined by a staff physician and obstetrics/gynaecology resident twice daily. The possible side effects of misoprostol (Cytotec; Ali Raif Pharmaceutical Company, İstanbul, Turkey) like fever and shivering were evaluated, and the need of analgesics was noted.

In the morning of the first day after surgery, the women were asked to report on the level of abdominal pain by means of a visiual analogue scale (VAS).[14] According to the VAS, 0 corresponded to no pain and 10 to the greatest pain imaginable. For analyses, numbers have been given to the verbal categories; a total pain score of 0 was evaluated as "no pain", a score of 1 to 3 as "mild pain", a score of 4 to 6 as "moderate pain", and any score greater than 6 as "severe pain". Before starting the the test, the women received an explanation about the scale.

All patients received intravenous infusion of oxytocin 10 IU/hour in 5% dextrose postoperatively for 6 hours, to achieve uterine contraction. The postoperative parenteral analgesia was provided by 100 mg meperidine and 75 mg diclofenac sodium injection inevery 3 hours by turns, and this is the standard of care in our department. All patients were informed that they could receive a rescue dose of a diclofenac sodium injection to breakthrough the pain, if further analgesia was needed. A single dose of prophylactic antibiotic was given to all patients, 30 minutes before the operation. The agents used for induction and maintanance of anaesthesia and analgesics were the same for all patients.

A written informed consent was obtained from all women, and the study protocol was approved by the Medical Ethics Committee of University of Mersin School of Medicine, and we complied with the ethical guidelines of 1975 Helsinki declaration. Any woman who had thyroid diseases, known hypersensitivity to prostoglandins, inflammatory bowel disease (IBD) or other bowel diseases or prior gastrointestinal or bariatric surgery were excluded from the study. General anesthesia was the only anesthetic method used in this study.

Statistical analysis

Statistical analyses were performed using SPSS for Windows statistical package (SPSS/PC software, Chicago, IL, USA). One-Way Anova test was used to compare age, gravida, body mass index (BMI) and fetal weight among the groups. Kruskal-Wallis test was used to compare pre- and postoperative hemoglobin (Hb) concentration, first bowel sounds, first flatus pass time and median visual analog scale pain scores among the groups. Pearson Chi-Square test was used to compare fever, shivering and additional analgesic use. A p-value <0.05 was considered as statistically significant.

RESULTS

Among all subjects, the maternal and gestational ages ranged between 17 to 45 years and 29 to 41 weeks, respectively. Of the total cesarean deliveries, 51.6% (n= 83) were emergency operations. There were no significant differences among the groups with regard to age, BMI, gestational weeks, fetal birth weight and pre- and postoperative Hb concentration as shown in Table 1.

The median time interval between surgery and first bowel sounds and first flatus passage were 19 and 24 hours for the patients receiving no drug, 14.5 and 23 hours for the 200 μg misoprostol group, 17 and 21.5 hours for the 400 μg misoprostol group and 12.5 and 18 hours for the 600 μg misoprostol group. The first bowel movement and first flatus passage time were significantly decreased in 600 μg misoprostol group compared to others (p< 0.001), as shown in Table 2 and Figure 1.

TABLE 1: Demographic features of the patients. Results are expressed as mean ± standard deviation for age, BMI, gestational week and birth weight; median and 25%-75% quartiles for preoperative and postoperative Hb levels.

	no drug (n=40)	200 μg misoprostol (n=40)	400 μg misoprostol (n=40)	600 μg misoprostol (n=40)	P value
Age (year)	30.2 ± 5.9	29.3 ± 5.4	29.9 ± 5.5	30.8 ± 5.5	0.665
BMI (kg/m2)	29.2 ± 4.9	29.1 ± 4.1	28.0 ± 4.1	27.9 ± 4.9	0.478
Gestational week	37.5 ± 2.8	37.6 ± 1.6	37.0 ± 2.3	37.6 ± 1.4	0.590
Birth weight (gram)	3150 ± 625	3017 ± 623	2909 ± 600	3208 ± 816	0.192
Preoperative Hb (g/dL)	11.75 (11-12.65)	11.90 (11-13)	11 (10.25-12)	12 (11-13)	0.130
Postoperative Hb (g/dL)	11 (10-11.8)	11 (10-11.8)	10 (10-11)	11 (10-12)	0.245

TABLE 2: Postoperative findings and side effects of the drug. Note that data are presented as median and 25%-75% quartiles for time to bowel movement and time to passage of flatus and VAS score; n (%) for fever, shivering and additional analgesic use.

	no drug (n=40)	200 μg misoprostol (n=40)	400 μg misoprostol (n=40)	600 μg misoprostol (n=40)	P value
Time to bowel movement.					
mean hours (± SD)	19 (16-24)	14.5 (12-18)	17 (13.2-18)	12.5* (12-14)	<0.001
Time to passage of flatus.					
mean hours (± SD)	24 (18-26.5)	23 (18-27)	21.5 (18-24)	18* (13.2-24)	<0.001
VAS score	3 (2-3)	3 (2-3)	3 (2-3.75)	3 (2-3)	0.270
Fever (n/%)	1 (2.5%)	-	3 (7.5%)	3 (7.5%)	0.137
Shivering (n/%)	2 (5%)	-	2 (5%)	4 (10%)	0.130
Additional analgesic (n/%)	5 (12.5%)	7 (17.5%)	6 (15%)	5 (12.5%)	0.906

*Statistically significant compared with other groups.

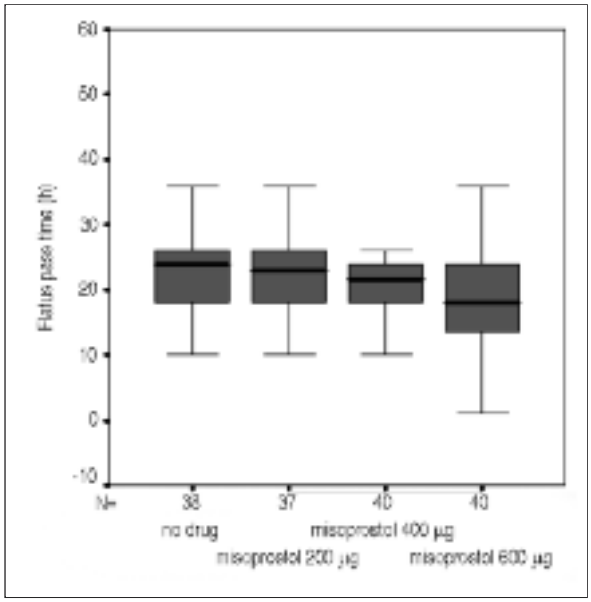

FIGURE 1: The time interval between surgery and first flatus passage time according to the groups. Thick lines represent median values. Boxplots show interquartile range and error bars represent extreme values.

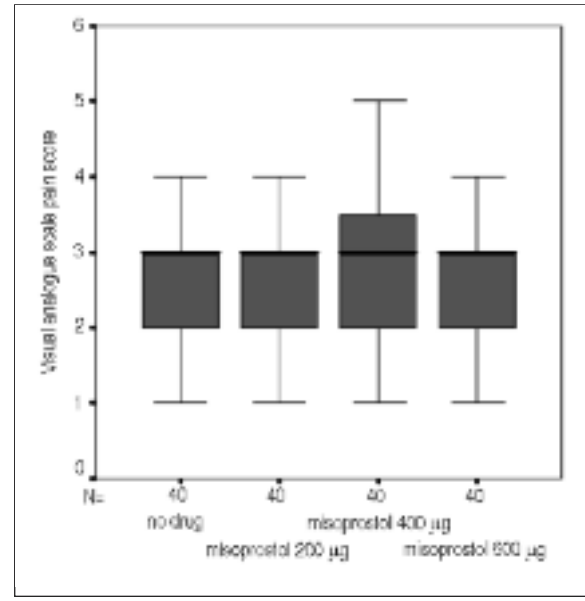

FIGURE 2: Median visual analog scale pain scores of each group.

Pain perceived by the patients in the morning hours of the first day after surgery were similar in all groups (p= 0.270), and the median visual analog scale pain scores of each group are shown in Table 2 and Figure 2.

Incidence of common side effects such as fever (temperature greater than 38ºC within 12 hours of delivery), and shivering were self limiting. These adverse effects were found more frequent in the 600 µg misoprostol group but difference among the groups did not reach statistical significance (p= 0.137 and p= 0.130, respectively). No difference was observed with regard to additional analgesic need and postoperative findings are presented in Table 2.

Intraoperative complications were as follows: two patients had to be hysterectomized due to uterine atony and one patient had bladder injury. However, no major postoperative complications were observed prior to discharge in all subjects. Only one obese woman with two previous abdominal operations, was readmitted due to wound infection on twelwth postoperative day.

DISCUSSION

Early feeding after cesarean delivery is more important than the general surgical population, because postoperative fatigue negatively affects breastfeeding and infant care.[1-9] Various reports have shown that early feeding after uncomplicated cesarean section is as safe as the traditional progressive approach. However after high risk CD, the patients (fasten) cannot eat until the first bowel movement and first flatus passage, to prevent gastrointestinal complications. Because of this absence period can exceed 24 hours, there is a need to search for a new effective medication to provide early maintanance of intestinal motility after these high risk surgeries.

The present study aimed to compare different dosages of intrarectal misoprostol in addition to existing oxytocics to provide early recovery of gastrointestinal function in high risk CD patients. This method was choosen, because of the rectally administered misoprostol achieves a longer peak plasma concentration and avoids side effects. In facts repeated doses may be useful, but this will spoil the blindness of the study and patients.

In previous studies, misoprostol was found to be effective in stimulating intestinal transit. Soffer et al. reported that misoprostol significantly increase frequency of bowel movements[15] and Ruwart et al. showed that the effect of misoprostol on small intestinal transit time depends upon the dosage and route of administration in rats.[16] The usefulness of misoprostol is further corroborated by the findings of Roarty et al. who demonstrated that misoprostol in high doses (400-2400 μg/day) was beneficial for the patients with refractory chronic consitipation.[17] Supporting these results, it was found in the present study that the use of 600 μg single dose rectal misoprostol induces recovery of gastrointestinal function and decreases flatus pass time significantly after cesarean delivery.

Unlike the previous studies, Demirci et al. concluded that rectally administered misoprostol did not improve intestinal motility in the early postoperative period after hysterectomy.[18] However results of the present study showed that transrectal administration of misoprostol achieved early maintanance of intestinal motility after cesarean delivery, consistent with the higher doses. The authors suppose that this difference may be due to low dose use, and the study was confined to hysterectomy operations and the results cannot be generalised to cesarean deliveries.

The most common side effects of misoprostol are vomiting, fever and shivering. These effects are dose-related, depend on the administration route, and often resolve after misoprostol discontinuation.[19-21] Altough the these effects were more frequent in the 600 μg misoprostol group, the difference among the groups did not reach statistical significance. However the incidence of adverse effects in the present study remained lower than previous reports.

The management of postoperative pain after cesarean delivery slightly differs from that of the general surgical population, since women need to recover quickly to take care of their newborn babies.[22] In the morning hours of the first day after surgery, perception of pain intensity was assessed by visual analog scale in each group. Teoh et al. randomised 196 women undergoing cesarean section, to compare the incidence of ileus in early and late oral intake groups. As a secondary outcome, they measured maternal satisfaciton by VAS, and they found a higher rate of satisfaction in the early-fed group.[23] In the present study, pain perceived by the patients in the morning of the first day after surgery were similar in all groups

In conclusion, the present study indicates that the single dose of 600 μg rectal misoprostol improves intestinal motility after high risk cesarean delivery, and has no significant effect on postoperative pain. The incidence of adverse effects with rectal misoprostol was low in the present study, and this finding should increase acceptibility of the procedure by the physicians. It is also important to acknowledge that this trial involved only subjects with high risk CD. The number of cesarean sections performed each year is increasing all around the world and pre-, intra- and postoperative care of these women are of utmost importance and demands due attention.[24,25] Therefore, in addition to existing oxytocics, the administration of rectal misoprostol may provide early recovery of gastrointestinal function to improve patient care and to shorten the hospitalization period.

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REFERENCES

1. Izbizky GH, Minig L, Sebastiani MA, Otaño L. The effect of early versus delayed postcaesarean feeding on women's satisfaction: a randomised controlled trial. BJOG. 2008;115(3): 332-8.
2. Horowitz IR, Rock JA. Postanesthesia and postoperative care. In: Thompson JD, Rock JA, eds. TeLinde's Operative Gynecology. 8thed. Philadelphia, PA: JB Lippincott, 1997, p. 142-63.
3. Cunningham FG, Gant NF, Leveno KJ, Gilstran LC III, Hauth JC, Wenstorm KD. Cesarean delivery and cesarean hysterectomy. In: Cunningham FG, Williams JW, eds. Williams Obstetrics. 21st ed. New York: McGraw-Hill; 2001. p. 537-63.
4. Burrows WR, Gingo AJ Jr, Rose SM, Zwick SI, Kosty DL, Dierker LJ Jr, et al. Safety and efficacy of early postoperative solid food consumption after cesarean section. J Reprod Med 1995;40(6):463-7.

5. Kramer RL, Van Someren JK, Qualls CR, Curet LB. Postoperative management of cesarean patients: the effect of immediate feeding on the incidence of ileus. Obstet Gynecol 1996; 88(1):29-32.
6. Hilliard R, Patolia DS, Toy EC, Baker B. Early feeding after cesarean delivery. Obstet Gynecol 2000;95(4 Suppl):44S.
7. Patolia DS, Hilliard RL, Toy EC, Baker B. Early feeding after cesarean: randomized trial. Obstet Gynecol 2001;98(1):113-6.
8. Weinstein L, Dyne PL, Duerbeck NB. The PROEF diet--a new postoperative regimen for oral early feeding. Am J Obstet Gynecol 1993;168(1 Pt 1):128-31.
9. Guedj P, Eldor J, Stark M. Immediate postoperative oral hydration after caesarean section. Asia Oceania J Obstet Gynaecol 1991; 17(2):125-9.
10. Kulier R, Gülmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev 2004;(2):CD002855.
11. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev 2006;3: CD002253.
12. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev 2006;(2):CD001338.
13. Soffer EE, Metcalf A, Launspach J. Misoprostol is effective treatment for patients with severe chronic constipation. Dig Dis Sci 1994;39 (5):929-33.
14. Revill SI, Robinson JO, Rosen M, Hogg MI. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976;31(9):1191-8.
15. Soffer EE, Launspach J. Effect of misoprostol on postprandial intestinal motility and orocecal transit time in humans. Dig Dis Sci 1993;38(5):851-5.
16. Ruwart MJ, Klepper MS, Rush BD. Prostaglandin stimulation of gastrointestinal transit in post-operative ileus rats. Prostaglandins 1980;19(3):415-26.
17. Roarty TP, Weber F, Soykan I, McCallum RW. Misoprostol in the treatment of chronic refractory constipation: results of a long-term open label trial. Aliment Pharmacol Ther 1997; 11(6):1059-66.
18. Demirci F, Somunkiran A, Gul OK, Demiraran Y, Ozdemir I, Gul OB. Does postoperative misoprostol use induce intestinal motility? A prospective randomised double-blind trial. Aust NZJ Obstet Gynaecol 2007;47(5):410-4.
19. Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev 2004;(1):CD000494.
20. Rutgeerts P, Vantrappen G, Hiele M, Ghoos Y, Onkelinx C. Effects on bowel motility of misoprostol administered before and after meals. Aliment Pharmacol Ther 1991;5(5):533-42.
21. How HY, Leaseburge L, Khoury JC, Siddiqi TA, Spinnato JA, Sibai BM. A comparison of various routes and dosages of misoprostol for cervical ripening and the induction of labor. Am J Obstet Gynecol 2001;185(4):911-5.
22. Lavand'homme P. Postcesarean analgesia: effective strategies and association with chronic pain. Curr Opin Anaesthesiol 2006;19(3): 244-8.
23. Teoh WH, Shah MK, Mah CL. A randomised controlled trial on beneficial effects of early feeding post-Caesarean delivery under regional anaesthesia. Singapore Med J 2007;48(2): 152-7.
24. Avşar AF, Keskin HL, Uzun M. [Pre-and postcesarean care]. Turkiye Klinikleri J Gynecol Obst-Special Topics 2008:1(1):1-6.
25. Çetinkaya ŞE, Söylemez F. [Complications of cesarean section]. Turkiye Klinikleri J Gynecol Obst-Gynecol Obst 2008:1(1):27-32.