Research Article

Side Effects of Misoprostol Per Rectal for Treating Postpartum Hemorrhage in Vaginal Delivery versus Cesarean Section: What Do We Know So Far?

Efek Samping Misoprostol Per Rektal untuk Pengobatan Perdarahan Pascasalin pada Persalinan Normal versus Seksio Sesarea: Apa yang Sudah Kita Ketahui?

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Abstract

Objective: To compare the incidence and profiles of misoprostol side effects given per rectal for treating postpartum haemorrhage in vaginal delivery versus cesarean section.

Methods: A prospective observational study involving 40 women delivered by vaginal birth (VD) and 40 by Cesarean Section (CS) was undertaken in a gynecology ward of a hospital in West Java. The incidence of misoprostol's side effects was identified through patient observation and medical note review. The side effect probability was rated by the panellists of healthcare providers. Patient characteristics and side effect data were summarized descriptively. The incidence rates of misoprostol's side effect between the two groups were compared using Z-test.

Results: Thirty-four patients (85.0%) in the VD group experienced side effects, whilst all CS patients reported at least one side effect. There was no significant difference in the proportion of patients having side effects in the two groups (p=0.366). There were 135 and 164 side effects in the VD group and CS group, respectively. There was no discernible difference in side effect profile between the two groups. Gastrointestinal side effects accounted for the most frequent side effects. Regarding the side effect probability, the panellists rated all side effects in VD patients as probable. Meanwhile, around70% of side effects in CS patients were regarded as probable leaving the remaining as definite.

Conclusions: High incidence of misoprostol's side effects was documented both in VD and CS patients. The incidence rates and side effect profile between the two delivery modes were quite similar.

Keywords: cesarean section, misoprostol, postpartum haemorrhage, side effect, vaginal delivery.

Abstrak

Tujuan: *Membandingkan insiden dan profil efek samping misoprostol per rektal untuk pengobatan perdarahan pascasalin pada persalinan pervaginam versus seksio sesarea.*

Metode: *Penelitian observasional prospektif melibatkan 40 perempuan yang melahirkan melalui persalinan pervaginan (VD) versus 40 pasien melalui Seksio Sesarea (CS) dilakukan di bangsal ginekologi sebuah rumah sakit di Jawa Barat. Insiden efek samping misoprostol diidentifikasi melalui pengamatan pasien dan kajian rekam medis. Probabilitas efek samping dinilai oleh panel tenaga kesehatan. Karakteristik pasien dan profil efek samping dianalisis secara deskriptif. Proporsi insiden efek samping misoprostol antara dua metode persalinan dibandingkan menggunakan uji Z.*

Hasil: *Tiga puluh empat pasien (85,0%) pasien di kelompok VD mengalami efek samping, sementara semua pasien CS melaporkan setidaknya satu efek samping. Tidak ada perbedaan yang signifikan terkait proporsi pasien yang mengalami efek samping di kedua kelompok (p=0,366). Secara keseluruhan terdapat 135 dan 164 efek samping pada kelompok VD dan CS secara berurutan. Tidak ada perbedaan yang nyata dalam profil efek samping kedua kelompok. Efek samping terkait saluran cerna merupakan efek samping yang palings sering ditemukan. Terkait probabilitas kejadian efek samping, panelis menilai semua efek samping pada kelompok VD sebagai "mungkin". Sementara itu, sekitar 70% efek samping pada pasien CS dikategorikan "mungkin" dan selebihnya "sangat mungkin".*

Kesimpulan: *Insiden tinggi efek samping misoprostol ditemukan baik pada pasien VD maupun CS. Proporsi insiden dan profil efek samping cukup seragam pada dua kelompok tersebut.*

Kata kunci: *efek samping, misoprostol, perdarahan pascasalin, persalinan pervaginam, persalinan seksio sesarea.*

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INTRODUCTION

Primary Postpartum Hamorrhage (PPH) is defined as blood loss from the genital tract of 500 mL or more following a normal vaginal delivery (NVD) or 1,000 mL or more following a cesarean section within 24 hours of birth.[1] PPH contributes significantly to maternal morbidity and mortality. PPH is a leading cause of maternal deaths globally, contributing to a quarter of the deaths annually.[2] In the developed world, PPH is a largely preventable and manageable condition.[3] In developing countries, mortality from PPH remains high and recent studies have shown that PPH causes up to 60% of all maternal death. In Indonesia, PPH is responsible for 43% of maternal death cases.[4]

Some key women's health organizations including International Federation of Gynecology and Obstetrics(FIGO), World Health Organization (WHO) and Royal College of Obstetricians and Gynecologists have supported the use of injectable uterotonics (i.e. oxytocin, ergometrine) as the first-line treatment for PPH due to their effectiveness and safety evidence.[5-7] Indonesia Society of Obstetrics and Gynecology has released its guideline in PPH management which was in accordance with the aforementioned international organizations.[8] Oxytocin and ergometrine are proven effective and safe in pregnant women even in those with hypertension and preeclampsia. Unfortunately, these drugs should be administered via injection only and require refrigeration to maintain stability. Additionally, their administration needs skilled health care professionals. These features may result in their limited availability particularly in a resource-poor environment such as rural and isolated areas.[9]

Misoprostol, a stable prostaglandin E1 (PGE1) analogue, has been shown to effectively stimulate uterine contractility in early pregnancy and at term. Misoprostol is known as alternative uterotonic agents in a situation where the first-line treatment is not available and feasible[9]. This drug is registered in Indonesia for the treatment of gastric and peptic ulcer. It is not approved yet by the Indonesian National Agency of Food and Drug Control to be used for the prevention and treatment of PPH. However, the use of misoprostol in the management of PPH is quite common among gynecologists. In low resource settings (e.g. developed countries), the use of misoprostol has attracted considerable attention due to its cheaper price, heat stability and longer half-life as opposed to conventional injectable uterotonics being used as the first-line treatment for PPH. In addition, misoprostol can be administered in multiple routes (including oral, buccal, vaginal, sublingual and rectal)supporting its ease of administration and making it more popular in health facilities with limited skilled health care providers. Understandably, misoprostol was added to Essential Medicines WHO Model List for PPH treatment.[10] Nevertheless, the administration of misoprostol poses certain risks to its questionable effectiveness and safety. A systematic review of ten randomized-controlled trials (RCTs) using oxytocin and misoprostol for PPH treatment highlighted that the use of misoprostol as an adjunct treatment to oxytocin conferred no additional benefit for patients.[11] In regards to its safety, misoprostol is frequently associated with some transient side effect such as chills and pyrexia.[12] Moreover, some randomized controlled trials of misoprostol have reported maternal death and severe morbidity presumably linked to its use.[13, 14]

It has been evident that misoprostol should be reserved in certain condition where the first line PPH treatment was impractical. However, the use of misoprostol for PPH treatment in the study hospital was prevalent and not in line with the existing evidence where the access to first-line treatment in the hospital was immediately available. It is of importance to note that the side effects related to misoprostol ranked third of the adverse drug event report in the study hospital. Additionally, little research has been undertaken to evaluate the side effects of misoprostol in two modes of delivery (cesarean versus vaginal delivery). Based on the aforementioned reasons, the study was conducted to compare the incidence and profile of misoprostol side effects in vaginal delivery and cesarean section.

METHODS

This was a prospective observational cohort study. Subjects were pregnant women admitted to gynecology ward in a district hospital in West Java during the period of June-August 2018. The inclusion criteria were patients undergoing

vaginal delivery or cesarean section who was diagnosed with PPH and received misoprostol via rectal route within 24 hours of delivery. The exclusion criteria were referral patients who delivered in other hospitals, those receiving misoprostol via other routes in addition to per rectal administration and deceased patients. Sampling size was calculated using Slovin's formula as follows:

$$n = \frac{N}{1 + Ne^2}$$

Denote:
n : sample size for each group
N : Population size
e : Margin of error

Sample size for group of vaginal delivery:

$$\frac{n = N}{(1 + Ne^2)} = \frac{40}{(1 + 40 \times 0.05^2)} = \frac{40}{1.1} = 36.36 \sim 40 \text{ patients}$$

Sample size for group of cesarean section:

$$\frac{n = N}{(1 + Ne^2)} = \frac{45}{(1 + 45 \times 0.05^2)} = \frac{45}{1.1} = 40.9 \sim 40 \text{ patients}$$

The principal researcher identified the occurrence of side effects through patient observation and medical note review. The probability of side effects was rated by a panel consisting of gynecologist, midwife and pharmacist. The rating was done using Naranjo algorithm[15] and the consensus among the panel members was used as the final rating. The study was approved by the Human Ethics Committee of the study hospital. Written informed consent was obtained from the patients prior to observation.

Patient characteristics and side effect data were summarized using descriptive statistics. The proportion of misoprostol's side effect incidence between two modes of delivery was compared using Z-test. Statistical data analysis was undertaken using statistical Product and Service Solutions (SPSS) for Windows version 22.0. The level of significance was set at a probability value of $p < 0.05$.

RESULTS

There were 40 patients observed in each group during this three-month study. Patients' maternal and obstetric characteristics are summarized in Table 1. As seen in Table 1, there was no discernible difference in maternal age and gestational age between the two groups. With regard to parity, patients in CS group tend to have more birth experience with nearly 40% having their third parity compared with 22.5% of those in VD group. Four patients in CS group had comorbidities (i.e. hypertension, human immunodeficiency virus infection, hepatitis B, brain tumour) with only one patient taking regular medicine. Meanwhile, none of the patients in the VD group reported any comorbidities and took any routine medicine.

Table 1. Patients' Maternal and Obstetric Characteristics

Characteristics	Vaginal Delivery Group (N=40 Patients)	Cesarean Section Group (N=40 Patients)
Maternal age in years (±SD)	29.05 (±7.172)	29.58 (±7.510)
Gestational age in weeks (±SD)	37.65 (±1.099)	36.83 (±2.899)
Parity, N (%)		
1	15 (37.5)	10 (25.0)
2	16 (40.0)	15 (37.5)
≥3	9 (22.5)	15 (37.5)
Presence of comorbidities, N (%)	-	4 (10.0)
Routine consumption of medicines, N (%)	-	1 (2.5)

Table 2. Patients' Pre-and Postpartum Clinical Data

Clinical Parameters	Vaginal Delivery Group (N=40 Patients)		Cesarean Section Group (N=40 Patients)	
	Prepartum	Postpartum	Prepartum	Postpartum
Temperature, N (%)				
Normal (36.1-37.2 ^{0}C)	40 (100.0)	5 (12.5)	37 (92.5)	1 (2.5)
Above normal (>37.2 ^{0}C)	-	35 (87.5)	3 (7.5)	39 (97.5)
Pain Scale (5-point), N (%)				
3	40 (100.0)	40 (100.0)	39 (97.5)	39 (97.5)
4	-	-	1 (2.5)	1 (2.5)
Hemoglobin level, N (%)				
8-12 g/dL	25 (62.5)	39 (97.5)	22 (55.0)	40 (100.0)
12-16 g/dL	15 (37.5)	1 (2.5)	18 (45.0)	
Hamorrhage volume, N (%)				
>500 mL	-	40 (100.0)	-	-
>1000 mL	-	-	-	40 (100.0)

Side Effects of Misoprostol

All patients in the VD group received misoprostol per rectal 400 mcg given in a single dose. Meanwhile, the majority of CS patients (N=38, 95.0%) was given a higher total dose of misoprostol (i.e. 600 mcg single dose) via rectal route and two patients received total dose 800 mcg divided into two doses (600 mcg followed by 200 mcg). The second dose was given due to persistent hamorrhage despite the administration of first dose. Patients were observed before and after delivery to evaluate the patient's clinical status and identify the presence of misoprostol's side effects. The clinical data are detailed in Table 2.

It can be seen from Table 2 that after delivery the majority of VD patients (87.5%) and nearly all CS patients experienced increased body temperature above the normal range. Both groups showed a similar pattern in pain severity where there was no change in pain scale before and after delivery. Nonetheless, one patient in CS group reported slightly more severe pain (i.e., scale of 4) compared to other patients in both groups. Concerning the hemoglobin (Hb) level, just over 60% of VD patients had Hb < 12 g/dL and the proportion increased enormously to 97.5%. The similar condition was documented in the CS group with all patients having low postpartum Hb level. The high proportion of patients with decreased Hb level could be partly explained due to the volume of blood loss (i.e.>500 mL in the VD group and >1000 mL in CS group).

Thirty-four patients (85.0%) patients in the VD group experienced side effects, whilst all CS patients reported at least one side effect after receiving misoprostol. There was no significant difference in the proportion of patients having side effects in the two groups (p=0.366). Totally, there were 135 and 164 side effects in the VD group and CS group, respectively. The details of side effects of misoprostol in the two study groups can be seen in Table 3. As described in Table 3, gastrointestinal side effects (e.g. nausea, vomiting, diarrhoea) accounted for the most frequent side effects in the two groups. In terms of side effect profile, there was no discernible difference between the two groups. However, abdominal pain and fatigue were observed in CS patients only.

Table 3. Side Effects of Misoprostol Per Rectal in Vaginal Delivery and Cesarean Section

Types of Side Effects N (%)	Vaginal Delivery Group (N=40 Patients)	Cesarean Section Group (N=40 Patients)	*P-value*
Nausea	31 (77.5)	34 (85.0)	0.438
Vomiting	31 (77.5)	34 (85.0)	0.432
Pyrexia	27 (67.5)	33 (82.5)	0.366
Shivering	20 (50.0)	23 (57.5)	0.432
Diarrhea	10 (25.0)	8 (20.0)	0.454
Abdominal pain	-	2 (5.0)	0.454
Headache	16 (40.0)	29 (72.5)	0.228
Fatigue	-	1 (2.5)	0.477

**Z-test was applied to compare the proportion of each side effect occurrence experienced by patients in the group of vaginal delivery versus that of cesarean section.*

Concerning the probability of side effect occurrence, there were slight differences between VD and CS patients. The panellist rated all side effects in VD patients as probable. Meanwhile, more than 70% (N=115/164) of the side effects in CS patients were regarded as probable leaving the rest of the proportion as definite. Further, abdominal pain and fatigue, which were absent in VD patients, were rated as definite in CS group.

DISCUSSION

Misoprostol can be administered through many routes including oral, vaginal, sublingual, buccal or rectal. A pharmacokinetic study comparing the profiles of misoprostol administration in three different routes (i.e. oral, rectal, vaginal) showed that vaginal misoprostol had a greater area under curve (AUC) and circulated in the body longer than the oral route. Rectal misoprostol showed similar profiles to the vaginal route but with lower AUC. Oral misoprostol had a higher peak plasma concentration and more rapid absorption than either vaginal or rectal route highlighting the higher rates of gastrointestinal-related side effects (nausea, diarrhoea) associated with oral misoprostol compared to the vaginal and rectal route. [11, 16] The present study used misoprostol

tablet designed for oral administration instead of the specifically-designed rectal formulation. However, a study done by Khan and colleagues revealed that oral misoprostol tablet can be absorbed by rectal and vaginal route.[16]

It is challenging to compare our findings with other studies despite numerous studies have been done to evaluate misoprostol's side effects. To the best of our knowledge, little research has been done to compare the side effects of misoprostol between VD and CS patients. Regarding the profile of side effect, the results of this present study were in line with the WHO Adverse Reaction Database that the most common frequent adverse events related to misoprostol were as follows: diarrhoea, abdominal pain, nausea, hamorrhage, abortion, vomiting, dyspepsia, flatulence, abortion, vomiting, dizziness, menorrhagia, vaginal hemorrhage and fever.[17] Similarly, pooled data from Cochrane review showed that misoprostol given in treatment doses had increased risk of side effects in comparison to placebo. According to the review, patients taking misoprostol had approximately two-fold risk to experience vomiting and shivering, and three-fold risk of pyrexia. Nevertheless, the reported side effects were transient in nature.[11]

The safety profile of misoprostol in obstetrics is linked to the pharmacokinetic profile of PGE1analogue.[9] In addition to its uterotonic mechanism, misoprostol has shown pharmacologic effects on several organ systems. It can inhibit platelet-activating factors and affects metabolic and physiologic processes.[18] PGE1 like misoprostol acts on the central thermoregulation centres which may explain the incidence of pyrexia in misoprostol use.[19] A systematic meta-analysis done involving 33 trials found that the incidence of pyrexia after administration of misoprostol is largely determined by its dosage and route.[20] That study reported that the highest incidence of pyrexia was noted in sublingual route (15%) with lower rates with the oral (11.4%) and rectal (4%) which was contradictory with our finding showing high incidence of pyrexia more than 60%. In line and colleagues found sublingual route had the highest bioavailability of all administration modes and this route was associated with the highest incidence of side effects compared to other routes.[21] Further, the study underlined vital finding that patients taking misoprostol had the five-time risk of pyrexia as opposed to those given placebo or other uterotonic agents.[20]PGE1 effect on central thermoregulatory system also has an impact on the incidence of shivering. A randomized placebo-controlled trial of misoprostol for PPH prevention reported shivering was more common in the misoprostol group than in that of placebo (19% vs 5% respectively).[22]Corresponding to the result of our study, higher rates of shivering were uncovered in other studies where shivering was documented in 32%-57% of women receiving misoprostol.[13,14] Other common side effects of misoprostol included diarrhoea and nausea which occurred due to the impact of prostaglandin on the smooth muscle of the gastrointestinal tract including increased orocaecal transit time.[23]

The current study also revealed that patients in CS group received a higher dose of misoprostol (600 mcg as a single dose and two patients took total dose of 800 mc) than those in VD group (i.e., 400 mcg). A meta-analysis comparing misoprostol 400 mcg vs 600 mcg showed no evidence of using misoprostol with higher dose for reducing blood loss. Moreover, the incidence of pyrexia was higher among women receiving misoprostol compared with those taking other uterotonics. Higher dose of misoprostol (600 mcg) was associated with more incidence of pyrexia than the lower dose (400 mcg).[17] Our study confirmed the finding of the meta-analysis in which CS patients showed higher rate of pyrexia (82.5%) than those in the VD group (67.5%). Further, it has been found that studies reporting maternal death after taking misoprostol, the patients in those studies were administered with higher dose (i.e., ≥600 mcg).[13,14,17] In fact, some trials uncovered significant finding that there was no significant efficacy between misoprostol 400 mcg vs higher doses. Conversely, the findings highlighted the safety concerns pertinent to the use of high dose of misoprostol as the frequency and severity of adverse events were dose-related.[17, 24]

It is quite unfortunate that there is no clinical pathway for PPH management in the study hospital. The findings of this study confirm the existing evidence to obstetricians and gynecologists as to the safety of misoprostol for treating PPH. Further, the results can be used as essential information for the clinicians

to develop clinical pathway in the study hospital to guide them when treating patients with PPH. Nonetheless, there are some limitations in the study. Firstly, this study was conducted in one hospital with modest number of samples which diminished the generalization of the findings. Our findings highlight that more research is required to better understand the rate and pattern of misoprostol's side effects in two modes of delivery. Future studies should include larger sample size with various routes of misoprostol and multiple institutions to provide a broader picture of the side effects and to identify the influence of delivery mode on the side effects. Secondly, the panellists rating the side effect probability were selected for convenience and there was no formal training provided. Nevertheless, the panellists were deemed to have the adequate clinical knowledge and professional experience, and the panellists were asked to read through the Naranjo algorithm prior to the panel meeting. The results might be different if the formal training on how to use the Naranjo algorithm had been provided to the panellists.

CONCLUSIONS

In summary, the study uncovered high incidence of misoprostol-related side effects both in VD and CS patients and the rate of incidence was not significantly different between the two delivery modes. In addition, there was no discernible difference in the profile of side effects documented in the two groups. This study raises the concern on the importance of judicious use of misoprostol for obstetric and gynecological indications in appropriate clinical settings to ensure its effectiveness and safety. In addition, the frequent occurrence of side effects related to its use requires active pharmacovigilance involving the front-line healthcare professionals particularly doctors, nurses and pharmacists.

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