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Review Article

Comparison of the effects and side effects of misoprostol and oxytocin in the postpartum period: A systematic review

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ABSTRACT

Follow-up of the side effects of uterotonics used for postpartum hemorrhage is one of the most important roles of health care providers. In this review, it is aimed to compare the side effects of misoprostol and oxytocin that are used to prevent postpartum hemorrhage. This systematic review was carried out in accordance with the guidelines for the Center for Reviews and Dissemination 2009 (CRD). Articles published in the PubMed, CINAHL, Wiley Interscience, Science Direct and Cochrane databases between 2010 and 2016 were examined. Finally, although 2277 articles were found to be related to misoprostol and oxytocin, only 12 randomized controlled (n = 6290) articles were included in the review. Results: In the misoprostol group, the rate of >500 mL blood loss was lower than that in the oxytocin group ($p < 0.05$). The groups were similar in terms of ≥500 mL blood loss were similar ($p > 0.05$). Although misoprostol was more effective than oxytocin in preventing PPH, the side effects of misoprostol were more. The incidence of drug-induced shivering, nausea and increase in body temperature were significantly higher in the misoprostol group than the oxytocin and placebo groups ($p < 0.05$). Shivering was most frequently seen in the 600 mg of sublingual misoprostol group (56.4%).

Severe side effects of uterotonics used to prevent postpartum hemorrhage on maternal health were determined. Nurses and midwives should be aware of the side effects of uterotonic drugs and should develop care guidelines that explain the interventions to be performed in case of side effects.

Introduction

Blood loss of more than 500 ml in the first 24 h after vaginal delivery is defined as postpartum hemorrhage (PPH), while blood loss more than 1000 ml is defined as severe PPH. The incidence of excessive bleeding after vaginal delivery is between 5% and 7%. Therefore, prevention and treatment of PPH are vital for women's health [1,2].

The World Health Organization (WHO) reported that, in 2015, around 303,000 maternal deaths occurred worldwide, and 25% of these deaths were caused by PPH. In a study conducted in Turkey (2016), 19.2% of maternal mortality has been reported to occur as a result of bleeding. Waterstone et al. (2001) emphasized that PPH is one of the causes of maternal death and should be prevented [3–5].

Prevention and management of postpartum hemorrhage:

It is known that only 40% of PPH cases have an identifiable risk factor, and therefore, a wide variety of interventions have been used in prevention and treatment of PPH. These interventions may be classified as conservative, pharmacological (uterotonic drugs) and surgical interventions [6,7].

Uterotonic drugs:

WHO recommends oxytocin for the intrapartum and postpartum periods. Intravenous/Intramuscular (IV/IM) synthetic oxytocin bolus or a combination is used to prevent postpartum atonic hemorrhage and provide uterine contractions. When oxytocin is given as oxytocin IV, it should be given slowly, since it causes a temporary decrease in blood pressure [1,8,9].

PPH may be reduced by administering prostaglandin analogs. Prostaglandins (misoprostol) may be administered in various ways (IV, oral, sublingual, vaginal or intracervical channels).

It was stated that misoprostol may be beneficial in cases where competent obstetricians are not sufficiently available [9,10].

The guidelines of WHO and the International Federation of Gynecology and Obstetrics recommend the use of a single 600 μg

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oral or sublingual prophylactic dose of misoprostol. However, it was determined that misoprostol may develop side effects (fever, shivering and intestinal complaints) on various levels depending on the dose and route of administration. For this reason, oxytocin use is recommended for prophylaxis of PPH [1,9,11].

Application of uterotonics, which are used in prevention of postpartum hemorrhages, monitoring their effects and side effects, is among the care responsibilities of nurses and midwives. In this review, the following question was asked: "What are the effects and side effects of oxytocin and misoprostol which are used in prevention of PPH?"

Materials and methods

Search strategy: The aim of this systematic review was to determine the effects and side effects of misoprostol and oxytocin, which are used in prevention of postpartum hemorrhage. The review was performed in accordance with the guidelines of the Center for Reviews and Dissemination (CRD 2009) developed by the National Institute for Health Research, the University of York. The articles published in the international literature (Pubmed, CINAHL, Wiley Interscience, Science Direct and Cochrane databases) were scanned for articles published between 2010 and 2016. The keywords that were used in screening are given in Table 1. Screening was performed using the English language (postpartum hemorrhage, bleeding prevent, vaginal birth, misoprostol, oxytocin, effect, side effect randomized controlled trial).

The criteria of this systematic review were randomized controlled trials involving vaginal delivery, oxytocin and misoprostol or oxytocin, misoprostol and control groups.

Qualitative studies, descriptive, cohort studies, dissertations, verbal or poster papers, case reports, case reports, meta analyses and review articles were the exclusion criteria of the review.

Data analysis: Reachable articles: As a result of the literature review, 2277 articles on the subject were reached, and in this review, 12 articles that met the research criteria were examined.

The flow chart of the study is given below (Table 1).

The following information was collected from the included studies:

1. Study characteristics: persons engaged in the study, publication year, origin country and study design
2. Characteristics of the women: number of women (randomized)
3. Drugs used: use-induced (empiric/prophylactic) dose, route of application
4. Results obtained: ≥500 or ≥1000 ml incidence of blood loss, additional uterotonic and blood transfusion requirements, surgical procedures performed and maternal mortality
5. Side effects: Although different side effects were reported in the studies, the most common side effects were shivering, fever and/or nausea and/or vomiting, headache, abdominal pain and diarrhea.

Comparisons

1. Comparison of oxytocin and misoprostol efficacy for reducing bleeding
2. The route of administration of oxytocin and misoprostol (different routes: intravenous, intramuscular, oral sublingual, rectal).
3. Comparison of the side effects of oxytocin and misoprostol.

Limitations of the study: In this systematic review, it was possible to reach all studies that met the criteria, but some studies might not have been reached.

Results

Search outcomes: As a result of the literature review, 2277 articles were reached at the beginning. In this systematic review, 12 studies that compared the effects and/or side effects of misoprostol and oxytocin that met the research criteria were included in the review (Fig. 1).

Study characteristics:

Twelve studies: sublingual misoprostol in 5 studies, oral misoprostol in 2 studies, rectal misoprostol in 5 studies (at least 200 μg and not more than 1000 μg misoprostol). In 6 studies, intramuscular oxytocin was administered, and intravenous oxytocin was administered in 6 studies (at least 3 IU and up to 20 IU oxytocin). The largest sample size was n: 1800 in the examined articles, while the smallest sample size was n: 100 (Fig. 1).

Study quality: In this systematic review, the features, data, Results and interpretations of the twelve studies that were examined are provided comprehensively (Table 1).

Routes of uterotonic administration and blood loss: Shrestha et al. (2011) found that the difference in the mean blood loss in the 1000 μg rectal misoprostol and 10 IU intramuscular oxytocin groups was significant ($p = 0.012$); Mirteimouri et al. (2013) found that the difference between the bleeding rate of >500 ml in the 400 μg rectal misoprostol and 3 IU intravenous oxytocin groups was significant (19%; 31.3%) ($p = 0.005$); Firouzbakht et al. (2016) found a significant difference in the 200 μg rectal misoprostol and 20 IU intravenous oxytocin groups in terms of postpartum blood loss ($p = 0.017$) [13–15].

Badejoko et al. (2012) determined that there was no significant difference between the 600 μg rectal misoprostol and 20 IU oxytocin infusion groups in terms of blood loss ($p = 0.80$). Nagasree and Smitha (2015) found a difference between the 800 μg rectal misoprostol and 5 IU intravenous oxytocin groups in terms of postpartum blood loss ($p = 0.56$) (Table 1) [16,17].

Uthman et al. (2011) compared 600 μg oral misoprostol and 10 IU intravenous oxytocin groups and found more blood loss in the oxytocin group (17.9%, 8.9%, respectively) ($p < 0.001$). Rajaei et al. (2014) compared 400 μg oral misoprostol and 20 IU oxytocin groups and found significant differences in blood loss ($p = 0.007$) (Table 1) [18,19].

Bellad et al. (2012) compared 400 μg powder sublingual misoprostol and IM oxytocin group and reported a lower incidence of PPH in the misoprostol group (3.1%, 9.1%, respectively) ($p = 0.002$). Atukunda et al. (2014) found that there was a difference the between 600 μg sublingual misoprostol + 1 mL placebo injection and 10 IU intramuscular oxytocin + sublingual placebo groups in terms of ≥500 ml blood loss in 24 h (respectively: 28.6%; 17.4%) ($p = 0.001$). Priya et al. (2015) compared 400 μg sublingual misoprostol and 10 IU intramuscular oxytocin groups and detected more blood loss in the oxytocin group ($p = 0.04$) (Table 1) [20–22].

Al-Sawaf et al. (2013) compared 200 μg sublingual misoprostol, 5 IU intramuscular oxytocin groups and a control group, whereas they found less bleeding in the oxytocin group than in the misoprostol and control groups. Chaudhuri et al. (2012) determined no difference in the incidence of 500 mL of bleeding between the 400 μg sublingual misoprostol and 10 IU intramuscular oxytocin groups ($p = 0.85$) (Table 1) [23,24].

Table 1
Findings about the characteristics, Results and interpretations of the studies (n = 12).

Author, Publication Year, and Country	Objective	Study Design	Example (n)	Drugs and Delivery Form	Results				Results Obtained and Comments	Suggestions
					Bleeding Amount; mL (%)	Hb (g/dL/%)	Additional Uterotonic	Side effects		
Shrestha et al., 2011 Nepal [13]	Comparison of rectal misoprostol efficacy with intramuscular oxytocin in preventing postpartum bleeding	Randomized trials	200 women Misoprostol (n = 100) Oxytocin (n = 100)	1000 μg rectal misoprostol 10 IU intramuscular oxytocin	>500 mL (4%) >500 mL (6%)	Hb level 10.7 ± 1.5 Hb level 10.6 ± 1.4	–	1: Fever with shivering 2: Abdominal pain Misoprostol 1: 25% 2: 2% Oxytocin 1: 10% 2: 3%	The estimated blood loss means in the misoprostol and oxytocin groups were significantly different (p = 0.012). There was no difference between the groups in terms of hemoglobin reduction (p > 0.05). Six-hour side effect differences between misoprostol (41%) and oxytocin (14%) were<!–Soft-enter Run-on– > significant (p = 0.003), 24-hour side effect differences were not significant (p = 0.106). Rectal misoprostol is as effective as intravenous oxytocin in prevention of PPH, though the incidence of side effects is similar, but it has been found to be useful as a uterotonic agent in routine management of the third stage of labor.	The use of rectal misoprostol has been proposed as an alternative to oxytocin.
Uthman et al., 2011 Nigeria [18]	To compare the efficacy of 600 μg oral misoprostol and 10 IU intravenous oxytocin in prevention of PPH	Randomized multi-center study	1800 women Misoprostol (n = 900) Oxytocin (n = 900)	 600 μg oral misoprostol 10 IU intravenous oxytocin	Bleeding amount (%) Misoprostol 8.9% Oxytocin 17.9%	Postpartum Hb mean Misoprostol 11.449 ± 0.03 Oxytocin 11.135 ± 0.04	Additional uterotonic (ergometrine 0.5 mg) Misoprostol 3.6% Oxytocin 16.4%	Side effect Not evaluated	Postpartum blood loss was significantly higher in oxytocin group (17.9) than in misoprostol group (8.9) (p < 0.001). Mean hemoglobin drop level was significantly different (p < 0.001). The additional uterotonics requirement was significant in the oxytocin group (16.4) and misoprostol group (3.6). (p < 0.05), and the difference was significant.	
Chaudhuri et al., 2012 India [24]	Comparison of intramuscular oxytocin and sublingual misoprostol in prevention of postpartum bleeding in low-risk women with vaginal delivery	Prospective double-blind randomized study	530 women Misoprostol (n = 265) Oxytocin (n = 265)	In a minute after birth 400 μg sublingual misoprostol 10 IU intramuscular oxytocin	Bleeding amount; mL (%) ≥500 mL (6.0%) ≥1000 mL (0.3%) ≥500 mL (5.7%) ≥1000 mL (0.8%)	1: Postpartum Hb, g/dL 2: Blood transfusion Misoprostol 1: 10.05 ± 1.47 2: 1.9% Oxytocin 1: 9.95 ± 1.04 2: 1.1%	Additional oxytocin Misoprostol 7.5% Oxytocin 8.7%	Side effect 1: Severe shaking 2: Fever> 38 °C 3: Nausea 4: Vomiting 5: Diarrhea Misoprostol 1: 19% 2: 2.3% 3: 0.8% 4: 1.9% 5: 0.8% Oxytocin 1: 0.8% 2: 0.0% 3: 0.8% 4: 0.8% 5: 0.0%	The incidence of ≥500 mL postpartum bleeding was similar in the two groups (6%; 5%, p = 0.85). Shivering was more common in the misoprostol group (shivering 19%, 0.8%) (p = 0.001). In low-risk vaginal delivery, the efficacy of oxytocin of 10 IU with 400 μg misoprostol was equivalent to the prevention of PPH.	To determine the efficacy and potential benefits of sublingual misoprostol, it was concluded that larger studies including high-risk populations are necessity.
Badejoko et al., 2012 Nigeria [16]	To evaluate the efficacy of additional rectal misoprostol with oxytocin infusion in prevention of primary postpartum	Double-blind randomized controlled study	264 women	After third phase of birth	Bleeding amount; mL (%)	1: Hematocrit 2: Blood transfusion within 24 h	Additional uterotonic (ergometrine)	1: Pyrexia 2: Severe shaking 3: Vomiting	There was no difference in blood loss (p = 0.80). There was a difference between the two groups in terms of postpartum hematocrit means (p < 0.001).	

	bleeding in women with uterine atony risk factors		Misoprostol (n = 132) Oxytocin (n = 132)	600 μg rectal misoprostol 20 IU of oxytocin into oxytocin Infusion (500 mL)	>500 mL (22.2%) >1000 mL (2.4%) >500 mL (20.9%) >1000 mL (3.9%)	Misoprostol 1: 34.94 ± 2.96 2: 0.8% Oxytocin 1: 31.76 ± 4.24 2: 0%	Misoprostol 5.6% Oxytocin 4.7%	Misoprostol 1: 22.2% 2: 27% 3: 23% Oxytocin 1: 5.4% 2: 13.2% 3: 5.4%	There was less postpartum hematocrit reduction in the misoprostol group (1%; 2.9%). There was no significant difference between the two groups in the need for additional oxytocin or surgical intervention (p = 0.74), blood transfusion within 24 h was not significant (p=0.31). The incidence of postpartum fever was higher in the misoprostol group (p < 0.001). Vomiting and shivering were higher in the misoprostol group (p < 0.001). A woman in misoprostol group, was applied bilateral uterine artery ligation, and a woman in the oxytocin group received obstetric hysterectomy.	
Bellad et al., 2012 India [20]	To compare the amount of postpartum blood loss	Double-blind randomized controlled study	652 women	After standard care, application with intramuscular oxytocin	Mean amount of bleeding (mL)	1: >10% reduction in hemoglobin 2: Blood transfusion	Additional uterotonic (Carboprost)	1: Shivering 2: Fever > 38 °C 3: Nausea 4: Vomiting	The incidence of PPH in the misoprostol group was (3.1%), and that in oxytocin group was (9.1%) (p = 0.002). No woman had blood loss ≥1000 ml.	It was reported that further research is needed to confirm these Results.
			Misoprostol (n = 321)	400 μg powder sublingual misoprostol	Misoprostol 192 ± 124 Oxytocin 366 ± 136	Misoprostol 1: 9.7% 2: 0.3%	Misoprostol 0.3%	Misoprostol 1: 53.9% 2: 1.2% 3: 3.7% 4: 1.6%	There was a significant difference between the groups in terms of the transient side effect of the misoprostol group (shivering p < 0.001, fever p = 0.04, nausea p < 0.001, vomiting p = 0.02). A blood transfusion was made to a woman from each group. Sublingual misoprostol was found to be more effective than intramuscular oxytocin in reducing PPH.	
			IM oxytocin (n = 331)	Standard maintenance with IM oxytocin		Oxytocin 1: 45.6% 2: 0.3%	Oxytocin 2.4%	Oxytocin 1: 4.2% 2: 0% 3: 0% 4: 0%		
Mirteimouri et al., 2013 Iranian [14]	To evaluate the efficacy of rectal misoprostol in prevention of PPH.	Double-blind randomized study	400 women	After the birth		1: Postpartum Hb mean 2: Blood transfusion	Over oxytocin	1: Shivering 2: Nausea 3: Headache	>500 mL bleeding rate was significantly different between the two groups (p = 0.005). There was a difference between the two groups in terms of postpartum Hb means (p < 0.001). Excess oxytocin requirement was significantly lower in the misoprostol group (p = 0.003). There was no difference between the groups in terms of side effects (nausea, vomiting diarrhea, shivering, etc.). Blood transfusion groups were similar (p = 0.18). A woman had hysterectomy from in the oxytocin group that was present. Misoprostol was more effective than oxidase in reducing the incidence of Postpartum blood loss. Rectal misoprostol was seen to be safe, effective and inexpensive in reducing the incidence of PPH as an alternative to prophylactic intravenous oxytocin.	It was concluded that more comprehensive studies containing high-risk populations are necessary.
			Misoprostol (n = 200) Oxytocin (n = 200)	400 μg rectal misoprostol 3 IU intravenous oxytocin 1 L ringer serum	>500 mL 19% >500 mL 31.3%	Misoprostol 1: 10.83 ± 1.1 2: 8 (4%) Oxytocin 1: 10.25 ± 1.1 2: 14 (7.1%)	Misoprostol 18% Oxytocin 30.8%	Misoprostol 1: 0.5% 2: 3.5% 3: 15.5% Oxytocin 1: 0% 2: 2.5% 3: 19.2%		

(continued on next page)

Table 1 (*continued*)

Author, Publication Year, and Country	Objective	Study Design	Example (n)	Drugs and Delivery Form	Results				Results Obtained and Comments	Suggestions
					Bleeding Amount; mL (%)	Hb (g/dL/%)	Additional Uterotonic	Side effects		
Al-Sawaf et al., 2013 Egypt [23]	To evaluate the efficacy and side effects of 5 IU intramuscular oxytocin with 200 μg sublingual misoprostol in prevention of PPH	Randomized controlled study.	104 women Misoprostol (n = 28) Oxytocin (n = 37) Control (n = 39)	 200 μg sublingual misoprostol 5 IU intramuscular oxytocin Control group	Mean amount of bleeding (mL) 348.0 ± 112.0 314.7 ± 94.6 438.6 ± 130.2	Postpartum Hb mean Misoprostol 12.1 ± 3.8 Oxytocin 12.3 ± 4.1 Control 12.4 ± 0.9	Additional uterotonic 1: 20 IU oxytocin IV infusion 2: 2.0 mg of methylergometrine IM Misoprostol 1: 10.7% 2: 7.1% Oxytocin 1: 5.4% 2: 2.7% Control group 1: 20.5% 2: 15.3%	Minor side effects such as fever, nausea or vomiting occurred in the misoprostol group.	The amount of PPH was significantly lower in the oxytocin group than in the misoprostol group and the control group. Postpartum hemoglobin and hematocrit values were not significantly different. Additional uterotonic requirement was the highest in the control group. When misoprostol and oxytocin groups were compared to the control group, the incidence of shivering, nausea and/or vomiting was significant. Fever was observed in a woman in the misoprostol group, and tachycardia was observed in a woman in the oxytocin group. There was no difference among the three groups about diarrhea frequency. A woman in the control group required blood transfusion (500 mL).	5 IU IM may be recommended just after cordoc-lampsine IM oxidase as a prophylactic measure against PPH in low-risk vaginal births. Sublingual misoprostol is supposed to be a potentially usable drug in prevention of stage 3 and PPH, especially in areas with limited medical facilities.
Firouzbakht et al., 2013 Iranian [15]	To evaluate the efficacy and safety of misoprostol with oxytocin in prevention of PPH	A randomized controlled study.	100 Misoprostol (n = 50) Oxytocin (n = 50)	200 μg rectal misoprostol 20 IU intravenous oxytocin (in 1000 mL saline)	≥500 mL (12%) ≥500 mL (10%)	Postpartum Hb Misoprostol 11.8 ± 1.03 Oxytocin 11.53 ± 1.34	Additional uterotonic Misoprostol 6% Oxytocin 8%	Shivering Misoprostol 14% Oxytocin 4%	Estimated blood loss was significantly reduced in the third phase of birth (p = 0.003) in the misoprostol group, but no difference for postpartum blood loss was observed. There was no difference between the two groups in terms of hematocrit values and additional uterotonic uptake. There was a difference between the groups in terms of shaking (0.035), but it was similar in terms of nausea, vomiting and headache. None of the females required surgical intervention (manual removal of placenta, dilatation, abortion, laparotomy or hysterectomy), and blood loss did not occur. >1.000 ml (p = 0.737). Misoprostol provides a simple treatment option for healthcare providers as an effective uterotonic in developing countries.	Rectal misoprostol is suggested be safe and effective in preventing PPH and recommended to be used at the third stage of delivery.
Atukunda et al., 2014 Uganda [21]	To compare the efficacy of oxytocin and 600 mg sublingual misoprostol recommend especially in the prevention of PPH during active management of birth.	Double-blind, double artificial randomized controlled study	1140 Misoprostol (n = 570) Oxytocin (n = 570)	 600 μg sublingual misoprostol +1 mL placebo injection 10 IU intramuscular oxytocin + sublingual placebo	Bleeding amount; mL (%) ≥500 mL (28.6%) ≥1000 mL (3.6%) ≥500 mL (17.4%) ≥1000 mL (2.7%)	1: <12 Hb g/dL 2: Blood transfusion Misoprostol 1: 35.8% 2: 1.2% Oxytocin 1: 29.1% 2: 2.9%	Additional uterotonic Misoprostol 8.2% Oxytocin 5.4%	1: Shivering 2: Body temperature > 37.5 °C 3: Nausea/vomiting 4: Headache 5: Diarrhea Misoprostol 1: 56.4% 2: 9.3% 3: 24.2% 4: 1.8% 5: 1.1% Oxytocin 1: 26.5% 2: 2.1% 3: 15.1% 4: 1.9% 5: 0.4%	There was a significant difference between the groups in terms of blood loss of ≥500 ml within 24 h (p = 0.001). Postpartum hemoglobin changes and additional uterotonics requirement were similar in the blood transfusion groups. Side effects (shivering and fever) were more frequent in the misoprostol group (p = 0.001, p = 0.005). There was no difference between groups in terms of diarrhea. Two groups were similar in terms of blood transfusion and retention of placenta.	Further studies that can explain in which subpopulations the use of oxytocin should be preferred to sublingual misoprostol should be focused on.

Rajaei et al., 2014 Iranian [19]	To compare the safety and efficacy of oxytocin and misoprostol when used in prevention of PPH	Double-blind, randomized controlled study	400 women		Mean amount of bleeding	1: Hemoglobin mean 2 Blood transfusion	Additional Oxytocin	1: Shivering 2: Body temperature > 37.5 °C	Bleeding rate mean ($p = 0.007$). Additional oxytocin use ($p = 0.018$). There was a significant difference between the groups in terms of side effects ($p = 0.001$).	Because misoprostol is cost-effective and easy to administer, it is recommended to be used in low-income areas when oxytocin is not available.
			Misoprostol (200) Oxytocin (200)	400 μg oral misoprostol 20 IU Oxytocin (1000 mL ringer solution)	Misoprostol 157.0 ± 84.9 Oxytocin 182.4 ± 101.3	Misoprostol 1: 10.7 ± 1.4 2: 0.5% Oxytocin 1: 10.9 ± 1.5 2: 2.0%	Misoprostol 7.5% Oxytocin 10.5%	Misoprostol 1: 1.1% 2: 14.5% Oxytocin 1: 1.1% 2: 2%	Blood transfusion groups were similar (0.184). Misoprostol was determined to be more effective in reducing the amount of blood loss.	
Priya et al., 2015 India [22]	To evaluate misoprostol that is safe, effective and easily applicable but is not parenteral medicine for prevention of postpartum bleeding	A randomized controlled study.	500 women		Bleeding amount (%)				Women in the oxytocin group had more blood loss than the misoprostol group ($p = 0.04$). No additional oxytocin was required in both groups. Surgical intervention was not required because of blood transfusion, surgical removal of the placenta by hand or atony. There were 23 side effects in the misoprostol group and 17 in the oxytocin group, and the difference was significant ($p = 0.004$). Nausea was significantly more prevalent in the oxytocin group than the misoprostol group ($p = 0.003$). Surgical intervention was not required because of blood transfusion, surgical removal of the placenta by hand or atony in both groups. Other side effects such as vomiting, diarrhea and fever were not significantly different.	Sublingual misoprostol was found to be as effective as prophylactic intramuscular oxytocin in active management of the third phase of birth.
			Misoprostol (n = 250) Oxytocin (n = 250)	400 μg sublingual misoprostol 10 IU intramuscular oxytocin	Misoprostol 70 mL (0.4%) Oxytocin 75 mL (0.4%)					
Nagasree and Smitha 2015 East Godavari [17]	To compare the safety and efficacy of oxytocin and misoprostol when used in preventing PPH	Double-blind, randomized study	200 women			Hemoglobin mean			There was no difference in hemoglobin values. 21 women in the misoprostol group and 5 in the oxytocin group had fever, and the difference was significant ($p < 0.001$). There was no difference between the groups in terms of other side effects.	Because misoprostol is cost-effective and easily applicable, its use in low-income areas is recommended when oxytocin is not available.
			Misoprostol (n = 100) Oxytocin (n = 100)	800 μg Rectal misoprostol 5 IU intravenous oxytocin		Misoprostol 9.8 ± 1.2 Oxytocin 10.3 ± 1.4				

PPH (Postpartum Hemorrhage), RCS (Randomized Controlled Study), μg (microgram), Hb (Hemoglobin).

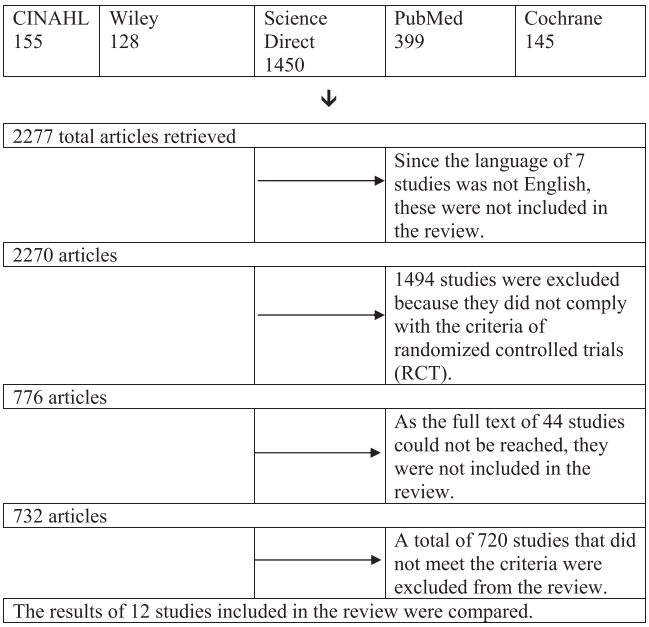

Fig. 1. PRISMA flow chart [12].

Administration routes for uterotonics and hemogram changes: Badejoko et al. (2012) found that postpartum hematocrit means were significant in the 600 μg rectal misoprostol and 20 IU oxytocin infusion groups ($p = 0.001$). Mirteimouri et al. (2013) reported that postpartum Hb mean was significant in the 400 μg rectal misoprostol and 3 IU intravenous oxytocin groups ($p = 0.001$). Shrestha et al. (2011) found a difference in hematocrit decline between the 1000 μg rectal misoprostol and 10 IU intramuscular oxytocin groups ($p > 0.05$). Nagasree and Smitha (2015) stated that there was a significant difference between the hemoglobin values of the 800 μg rectal misoprostol and 5 IU intravenous oxytocin groups ($p = 0.87$). Firouzbakht et al. (2016) examined 200 μg of rectal misoprostol and 20 IU intravenous oxytocin groups in terms of the changes in the values of hematocrit, but no difference was determined ($p = 0.28$) (Table 1) [13–17].

Uthman et al. (2011) found a significant difference in 600 mg oral misoprostol and 10 IU intravenous oxytocin groups in terms of the decreases in their mean hemoglobin levels ($p = 0.001$) (Table 1) [18].

Al-Sawaf et al. (2013) found no difference in 200 μg sublingual misoprostol, 5 IU intramuscular oxytocin and control groups in terms of postpartum hemoglobin and hematocrit values. Atukunda et al. (2014) explained that postpartum hemoglobin changes were similar in the 600 μg sublingual misoprostol + 1 mL placebo injection and 10 IU intramuscular oxytocin + sublingual placebo groups (Table 1) [21,23].

Administration routes of uterotonics and additional uterotonics: Mirteimouri et al. (2013) compared 400 μg of rectal misoprostol and 3 IU intravenous oxytocin, and the need for excess oxytocin was significantly lower in the misoprostol group ($p = 0.003$). Uthman et al. (2011) found that the difference between the additional uterotonic requirement in the 600 μg oral misoprostol group (3.6%) and the 10 IU intravenous oxytocin group (16.4%) was significant ($p < 0.05$). Rajaei et al. (2014) reported a difference in the 400 %g oral misoprostol and 20 IU oxytocin groups in terms of additional oxytocin use (7.5%; 10.5%, respectively) ($p = 0.018$). There was no difference between the groups in some other studies in terms of additional uterotonics use (Table 1) [15,21,22,24].

Administration routes of uterotonics and side effects: Shrestha et al. (2011) found that the 6-hour side effect difference was significant in the 1000 μg rectal misoprostol (41%) and 10 IU intramuscular oxytocin (14%) groups ($p = 0.003$). They found that the 24-hour side effect difference was not significant ($p = 0.106$) Badejoko et al. (2012) stated that the incidence of fever, vomiting and shivering was higher in the 600 μg rectal misoprostol group in comparison to the 20 IU oxytocin infusion group ($p < 0.001$) [13,16]. Nagasree and Smitha (2015) reported fever in 21 women in their 800 μg rectal misoprostol group and in 5 women in the 5 IU intravenous oxytocin group ($p < 0.001$), while there was no difference between the groups in terms of other side effects. Firouzbakht et al. (2016) found that there was a difference in shivering between the groups that were applied 200 μg rectal misoprostol and 20 IU intravenous oxytocin (in 1000 ml saline) (0,035), and nausea, vomiting and headache were similar in terms of the groups. Mirteimouri et al. (2013) compared 400 μg rectal misoprostol and 3 IU intravenous oxytocin groups and found no difference between the groups in terms of side effects (nausea, vomiting, diarrhea, shivering) (Table 1) [14,15,17,19].

Rajaei et al. (2014) found a higher transient side effect in their 400 μg oral misoprostol group and 20 IU oxytocin group, and the difference was significant (shivering $p < 0.001$, fever $p = 0.04$, nausea $p < 0.001$, vomiting $p = 0.02$). Chaudhuri et al. (2012) found that, in the 400 μg sublingual misoprostol group, shivering was significantly more common than the 10 IU intramuscular oxytocin group (shivering 19%; 0.8%) ($p = 0.001$). Bellad et al. (2012) observed that side effects were higher in their 400 μg powder sublingual misoprostol group in comparison to the standard maintenance group with IM oxytocin treatment (shivering $p < 0.001$, fever $p = 0.04$, nausea $p < 0.001$, vomiting $p = 0.02$). Al-Sawaf et al. (2013) compared 5 IU intramuscular oxytocin, a control and 200 μg sublingual misoprostol groups and reported that small side effects such as fever, nausea or vomiting occurred in the misoprostol group. Atukunda et al. (2014) compared 600 μg sublingual misoprostol + 1 mL placebo injection and 10 IU intramuscular oxytocin + sublingual placebo, and shivering and fever were more frequent in the misoprostol group ($p = 0.001$; $p = 0.005$), whereas they found that the groups were similar in terms of diarrhea (Table 1) [19–21,23,24].

Priya et al. (2015) reported that 23 women in their sublingual misoprostol group (400 μg) had side effects with 17 women in the 10 IU intramuscular oxytocin group ($p = 0.004$), and nausea was more prevalent in women in the oxytocin group ($p = 0.003$) (Table 1) [22].

Administration routes of uterotonics and other interventions: Badejoko et al. (2012) reported that one woman in the 600 μg rectal misoprostol group underwent bilateral uterine artery ligation, and one woman in the 20 IU oxytocin infusion group underwent obstetric hysterectomy. Mirteimouri et al. (2013) found that blood transfusion was similar in the 400 μg rectal misoprostol and 3 IU intravenous oxytocin groups ($p = 0.18$), and hysterectomy was performed in a woman in the oxytocin group. Firouzbakht et al. (2016) observed that no woman in the 200 μg rectal misoprostol and 20 IU intravenous oxytocin groups required a surgical intervention (such as manual removal of the placenta, dilatation-abortion, laparotomy or hysterectomy) and there was no more than 1000 ml of blood loss ($p = 0.737$) (Table 1) [14–16].

Rajaei et al. (2014) found that the 400 μg oral misoprostol and 20 IU groups were similar in terms of blood transfusion in the oxytocin groups (0.184). Bellad et al. (2012) found that the 400 μg sublingual powder misoprostol and IM oxytocin were given to one woman from both groups. Al-Sawaf et al. (2013) compared 200 μg sublingual misoprostol and 5 IU intramuscular oxytocin, 20 IU oxytocin and control groups and determined that a woman in the control

group needed blood transfusion (500 mL). Atukunda et al. (2014) compared 600 μg sublingual misoprostol, 1 mL placebo injection and 10 IU intramuscular oxytocin sublingual placebo groups, and blood transfusion and placental retention were similar among the groups. Priya et al. (2015) examined 400 oxytocin sublingual misoprostol and 10 IU intramuscular oxytocin groups, and they reported no need for surgical intervention because of blood transfusion, manual removal of the placenta or atony (Table 1) [19–23].

Discussion

The use of routine uterotonics in prevention and management of postpartum hemorrhage has a wide range. This review was carried out to evaluate the efficiency of misoprostol and oxytocin that are used in prevention of postpartum hemorrhage and reach scientific generalizations by synthesizing the findings. In this systematic review, a total of twelve (five randomized-controlled and seven double-blind randomized/controlled) studies were considered appropriate for inclusion. As a result of the review, important findings from 12 studies are discussed below.

When the findings in this systematic review are compared in terms of blood loss: Shrestha et al. (2011) reported that there was a difference in misoprostol and oxytocin groups in terms of >500 mL blood loss ($p = 0.012$). It was stated that rectal misoprostol was as effective as intravenous oxytocin, and it could be useful to use as an uterotonic agent at the third stage of labor [13].

Firouzbakht et al. (2016) reported that there was a difference between the misoprostol and oxytocin groups in terms of postpartum blood loss (0.017) In management of the third stage of labor, rectal misoprostol was recommended [15].

Uthman et al. (2011) reported that the amount of blood loss was higher in their 10 IU oxytocin group compared to the 600 μg oral misoprostol group ($p < 0.001$) [18]. Bellad et al. (2012) found that the incidence of PPH in the misoprostol group was lower than that of the oxytocin group ($p = 0.002$) [20]. Although sublingual misoprostol was more effective than IM oxytocin in reducing PPH, it was indicated that further research is required [18,20]. Mirteimouri et al. (2013) found that their misoprostol group had less incidence of >500 mL blood loss in comparison to the oxytocin group ($p = 0.005$), and they reported that rectal misoprostol could be used to reduce the incidence of PPH. Nagasree and Smitha (2015) found that there was no difference between the 800 μg rectal misoprostol and 5 IU intravenous oxytocin groups in terms of PPH, and they had recommended the use of misoprostol in low-income areas because it is inexpensive and easy to use. Priya et al. (2015) reported that more women in their oxytocin group than women in the misoprostol group stated more blood loss ($p = 0.04$). It was concluded that sublingual misoprostol is as effective as prophylactic intramuscular oxytocin in active management of the third stage of labor [14,17,22].

Atukunda et al. (2014) reported more blood loss (0.00500 mL) in the misoprostol group than the oxytocin group (≥500 mL) ($p = 0.001$). Al-Sawaf et al. (2013) stated that the amount of bleeding was lower in the oxytocin group in comparison to the misoprostol and control groups. They recommended prophylactic administration of 5 IU of intramuscular oxytocin in low-risk vaginal deliveries and use of sublingual misoprostol in areas with limited medical facilities [21,23].

Rajaei et al. (2014) reported that bleeding was lower in the misoprostol group than the oxytocin group ($p = 0.007$), and misoprostol was more effective in reducing blood loss and should be used in low-income areas (Table 1) [19].

Chaudhuri et al. (2012) reported postpartum blood levels of ≥500 mL in terms of incidence of bleeding ($p = 0.85$) [24]. Badejoko et al. (2012) and Firouzbakht et al. (2013) they found no difference between their groups in terms of postpartum blood loss values [15,16]. In order to determine the efficacy and potential benefits of sublingual misoprostol in low-risk vaginal deliveries, studies involving a larger population should be performed.

When the results were compared in terms of blood loss of ≥1000 mL *in the postpartum period*: Chaudhuri et al. (2012), in their 400 μg sublingual misoprostol group, stated that blood loss was higher than the 10 IU intramuscular oxytocin group. Badejoko et al. (2012) found that blood loss was lower in the 20 IU oxytocin infusion group in comparison to the 600 μg rectal misoprostol group. Atukunda et al. (2014) compared the 10 IU intramuscular oxytocin + sublingual placebo group and 600 μg sublingual misoprostol + 1 mL group, while they found that blood loss was higher in the placebo injection group. In reducing postpartum hemorrhage, it was thought that the type of uterotonic drugs, the amount of the drug and the way of administration of the drug could be effective (Table 1) [16,21,24].

When the results were compared in terms of postpartum hemoglobin (Hb) and hematocrit (Hct) changes: Uthman et al. (2011) showed that there was a difference between the groups in terms of the mean hemoglobin decline levels ($p < 0.001$). Mirteimouri et al. (2013) observed a difference in the postpartum Hb mean values ($p < 0.001$), while Badejoko et al. (2012) showed that the decrease in postpartum hematocrit levels was lower in the misoprostol group in comparison to the oxytocin group ($p < 0.001$). No significant differences were found between the groups in the study by Shrestha et al. (2011) in terms of hematocrit decline, Al-Sawaf et al. (2013) in terms of postpartum hemoglobin and hematocrit values, Firouzbakht et al. (2013) in terms of hematocrit values and Atukunda et al. (2014) and Nagasree and Smitha (2015) in terms of postpartum hemoglobin changes ($p > 0.05$) (Table 1) [13–18,21,23].

There were significant differences between the groups in terms of Hb and Htc values in three studies, while the groups in four studies showed similarity in terms of their Hb and Htc values. Although the amount of blood loss had a direct effect on postpartum Hb and Htc values, the individual and obstetric characteristics of women were effective in this change.

In this systematic review, additional uterotonic requirements were compared in the case of PPH: Three studies in this review used more uterotonic agents in the oxytocin group than the misoprostol group, the need for uterotonia in the remaining studies showed similarity in the groups (Table 1) [14,18,19]. Additional uterotonic requirements are associated with increased bleeding, but the use of different clinical protocols (interventions, methods, and techniques) in management of bleeding affected the need for additional uterotonics (Table 1) [15,16,21–23].

When the routes of administration of the uterotonics and side effects were compared: Shivering and fever were the most commonly seen side effects. When the incidence of shivering in the misoprostol and oxytocin groups were examined, the highest shivering rate was seen in the 600 mg sublingual misoprostol (56.4%) and the lowest was in 3 IU intravenous oxytocin (0%) groups. Studies that compared the effects of misoprostol and oxytocin have shown that high-dose misoprostol (1000 gg) was effective in reducing PPH but had more side effects. It was considered that the route of administration of the drug up to the dose was very significantly effective in the formation of side effects.

When the route of administration of the uterotonics and other interventions were compared: Badejoko et al. (2012) reported that a woman in their misoprostol group underwent bilateral uterine artery ligation due to atony, whereas another woman in the oxytocin group underwent hysterectomy [16]. Mirteimouri et al. (2013) and Rajaei et al. (2014) reported that their groups were similar in terms of blood transfusion [14]. Firouzbakht et al. (2016)

observed that no women required surgical intervention (manual removal of placenta, dilatation/abortion, laparotomy or hysterectomy), and blood loss did not reach 1000 ml [15].

Bellad et al. (2012) reported that blood transfusions were given to one woman from each group, whereas Al-Sawaf et al. (2013) reported that a woman in the control group had a blood transfusion (500 mL). Atukunda et al. (2014) showed that blood transfusion frequencies were similar in the groups, while Priya et al. (2015) reported that no woman had blood transfusion [20–23].

The route and dose of administration of uterotonics affected the frequency of their side effects. Because rectal misoprostol is easily applicable and inexpensive, it is stated that it will be a simple treatment option that can be used in prevention of PPH, especially in developing countries.

Conclusions

In this systematic review analysis, misoprostol was found to be more effective than oxytocin in the 10 of 12 studies.

Although rectal misoprostol showed similar effect to oxytocin, less side effects were detected. On the other hand, while misoprostol reduced the risk of maternal blood loss, misoprostol, especially given sublingually, caused various serious side effects. Increased body temperature, nausea and vomiting, as well as shivering were the most commonly observed side effects.

Nurses and midwives have the responsibility of administering prescribed uterotonic drugs, monitoring the effects and side effects, planning and administering the necessary care when undesirable effects occur.

In conclusion, it is very important to determine and prevent the factors that affect and increase the frequency of side effects of uterotonic drugs in order to provide mothers with postpartum comfort. For this reason, nursing-midwife care guides should be developed to know and monitor the side effects of uterotonic drugs administered in the postpartum period, and evidence-based investigations specific to this topic should be conducted.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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