SYSTEMATIC REVIEW

Effectiveness of Uterotonic Drugs in Preventing Postpartum Hemorrhage: A Systematic Review

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ABSTRACT

Introduction: Postpartum haemorrhage is one of the major causes of maternal mortality in developing countries, including Indonesia. One method to prevent postpartum haemorrhage is the administration of uterotonic drugs. This review examines various alternatives of uterotonic medicines administered as part of management to prevent postpartum haemorrhage. **Methods:** The study method used a systematic review. The articles were searched from two databases, including PubMed and CINAHL. The databases obtained 190 articles, and then it was screened using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) approach. The screening found five full-text articles that match the study aim. **Results:** Administering uterotonic drugs were adequate to prevent postpartum haemorrhage. Uterotonic drugs stimulate the contraction of uterine, promote the hemostasis, and compress the uterine blood vessels. However, combining uterotonics and tranexamic or inhaled oxygen was more effective in preventing postpartum haemorrhage than single uterotonic administration. **Conclusion:** Maternity Nurses would develop new evidence-based combinations of uterotonic medications and non-pharmacological interventions, especially nursing interventions that are part of Indonesian culture, traditions, and beliefs.

Keywords: Maternal mortality, Nursing interventions, Post-Partum Hemorrhage, Pregnancy

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INTRODUCTION

Indonesia's maternal mortality rate is still high and has not reached the SDGs target (1). Maternal death is caused by proximate determinants directly such as bleeding, preeclampsia/eclampsia, and infections or women's diseases history, such as heart disease, malaria, tuberculosis, kidney, and acquired immunodeficiency syndrome (2). Proximate determinants are directly influenced by the distant determinants, such as maternal health status, reproductive status, access to health services, and use of health care facilities (3). Demographic and sociocultural factors are associated with the lack of public awareness about pregnant women's health (4). Women's empowerment, educational background, socioeconomic status, community, and policies indirectly play a role in increasing maternal mortality (2–4). The causes of maternal mortality in Indonesia are dominated by direct causes such as bleeding, preeclampsia, and infection (5).

Postpartum haemorrhage (PPH) is one of the major causes of maternal mortality in developing countries; about 14 million obstetric bleeding cases and 127,000 deaths (6). According to the Data and Information Center of the Indonesian Ministry of Health (7), in 2013, maternal bleeding was the most significant cause of maternal death, amounting to 30.3% of the total causes of maternal death (7). PPH can be caused by uterine atony, birth canal injury, detachment of part of the placenta from the uterus, and the loss of part of the placenta in the uterus (8).

Postpartum haemorrhage can occur during labour, especially in the third stage. Placental separation generally lasts between 5-10 minutes, generally up to 30 minutes (9). The risk of bleeding will increase if the third stage of labour is over 30 minutes. The duration of the third stage is important documentation because the prolonged third stage can increases PPH risk (9). Leaving the placenta in the uterus also causes ineffective uterus contraction and causes bleeding. Therefore, the longer the third stage treatment, the more bleeding risk will be released (9).

Haemorrhage effects on the mother cause various

complications, such as hemorrhagic shock that may lead to death (10). Other complications are anaemia, fatigue, orthostatic hypotension, dilutional coagulopathy, myocardial ischemia, and anterior pituitary ischemia (5). Interventions for postpartum bleeding include stoping bleeding from the source, giving blood transfusions, and administering fluids such as Ringer's Laktate and Sodium Chloride (10). Modifying of patient position, for example elevating the leg that increase venous return would reduce the bleeding (10). Furthermore, blood transfusions should be given if the bleeding continues and is expected to exceed 2000 ml or the patient's clinical condition shows signs of shock (10). In addition to solve PPH, health professionals administer medication, for example uterotonic drugs; oxytocin, methylergonovine, misoprostol, and carbetocin. Uterotonic drugs stimulates the contraction of uterine that effect in compressing uterine blood vessels and compressing it. Administering uterotonic drugs in PPH have approved from multiple studies, but there is a limited comprehensive analysis that viewed the used of uterotonic drugs to treat the bleeding. The aim of this study was to analyse the effectiveness of uterotonics to treat PPH.

METHODS

Researchers searched articles about the use of uterotonic drugs to prevent and treat PPH from two international databases including PubMed and CINAHL plus. These databases were chosen because the researchers have access full-text articles. The full-text articles is needed to analysis process in this review. Keywords used were intervention OR management; AND bleeding OR hemorrhage; AND uterotonic drugs; AND giving birth OR delivery OR labour. The inclusion criteria of the selected articles were published from 2016 to 2020 or the last five years, design research using a Randomized Control Trial (RCT) approach, and articles written in English. The articles were limited in the last five years in order to get more update results related to uterotonic drugs research. The article selection stage used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guide, which includes five steps: determining acceptability criteria, defining sources of information, literature selection, data collection, and items selection. This selection method was applied in other study (11–13).

The article search results obtained 190 articles from two databases: PubMed (187 papers) and CINAHL (three documents). Next, the articles were saved in the Endnote reference manager to check for duplicate papers. After reading the title and abstract, 11 articles met the inclusion criteria. Next, the critical appraisal was carried out on 11 articles using The JBI tool (The Checklist for Randomized Controlled Trial) and shown in Table I. Five papers were further analysed by reading full-text and have JBI Score with range 10-12 (0,7% - 0,9%). A summary of the analysis of each article is shown in Table II. Selecting articles process using the PRISMA approach can be read in (Fig.1).

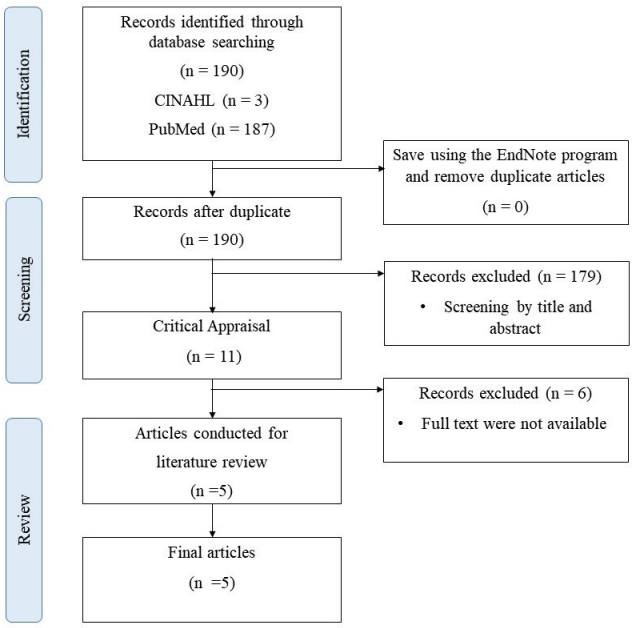

Figure 1: Selecting Article Process (PRISMA)

RESULT

The five articles assessed uterotonics effectiveness in preventing PPH. The studies were carried out in four different countries: India, Iran, Mali, and Bangladesh. Samples were pregnant women in the third trimester (38-42 weeks of gestation). Pregnant women observed from the third trimester until delivering the baby. Each article had a different number of samples with a range of 51-120 pregnant women. The majority of articles divided samples into two groups (intervention group and control group). The findings showed that they were three uterotonics drugs tested, including misoprostol, oxytocin, and carbetocin. The uterotonic drugs administered intravenously, intramuscularly, sublingually, and buccally. The drug doses were different, intravenous carbetocin doses with amount 100 mcg, intramuscular oxytocin 10 IU, and sublingual misoprostol with amount 400 mcg. Several studies in this review combined the uterotonic drugs with other intervention, for example oxygen administration, balloon tamponade, and tranexamic acid administration. The combination was proven to reduce the amount of bleeding significantly rather than to a single intervention (only uterotonic administration). The uterotonic drugs stimulate uterine muscle contractions, increase the hemostasis, and press the uterine blood vessels, so stop the bleeding.

DISCUSSION

Postpartum haemorrhage (PPH) is bleeding loses more than 500 ml after expected vaginal give birth (14). The PPH would be prevented by uterotonics treatment. Uterotonic

Table I: RCT Research Design JBI Score

No	JBI Components	Articles Number										
		1	2	3	4	5	6	7	8	9	10	11
1.	Was true randomization used for assignment of participants to treatment groups?	✓	-	✓	✓	✓	✓	✓	✓	✓	-	✓
2.	Was allocation to treatment groups concealed?	✓	-	✓	✓	-	✓	✓	-	✓	✓	✓
3.	Were treatment groups similar at the baseline?	-	-	-	✓	-	-	-	-	-	-	-
4.	Were participants blind to treatment assignment?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5.	Were those delivering treatment blind to treatment assignment?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
6.	Were outcomes assessors blind to treatment assignment?	✓	-	✓	✓	-	-	✓	-	-	-	✓
7.	Were treatment groups treated identically other than the intervention of interest?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	-	-	✓	-	-	-	✓	-	-	-	-
9.	Were participants analyzed in the groups to which they were randomized?	✓	-	✓	✓	-	-	✓	-	-	-	✓
10.	Were outcomes measured in the same way for treatment groups?	✓	-	-	✓	-	-	✓	-	-	-	-
11.	Were outcomes measured in a reliable way?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12.	Was appropriate statistical analysis used?	✓	-	✓	✓	-	-	✓	-	-	-	✓
13	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	✓	✓	-	-	✓	✓	✓	✓	✓	✓	✓
	Total Score	**11**	**5**	**10**	**11**	**6**	**7**	**12**	**6**	**7**	**6**	**10**

Table II: Article Analysis

Authors	Objectives	Setting	Samples	Data Collection Method	Result
Dumont, A., Bodin, C., Hounkpatin, B., Popowski, T., Traorй, M., Perrin, R., & Rozenberg, P. (2017). (23)	Assess the effectiveness of low-cost uterine balloon tamponade as an adjunct to misoprostol for the treatment of uncontrolled PPH.	Mali	51 woman	The condom is placed over the foley catheter and secured with sutures. The catheter inserted into the uterus, and the condom is filled with misoprostol and 250 mL of solute without exceeding 1000 mL	Balloon tamponade, misoprostol, and PPH management can reduce the morbidity and mortality of postpartum hemorrhage.
Kabir, N., Akter, D., Daisy, T. A., Jesmin, S., Razzak, M., Tasnim, S., & Islam, G. M. R. (2015). (16)	Evaluate the efficacy and safety of carbetocin compared to oxytocin in the active management of the 3rd stage of labor after vaginal delivery.	Bangladesh	94 woman	One group received intravenous 100 mcg of carbetocin, and the other group received 10 IU intramuscular oxytocin in the 3rd stage of labor.	Carbetocin can be considered as a good alternative to oxytocin in the active management of 3rd stage labor in vaginal delivery.
Priya, G. P., Veena, P., Chaturvedula, L., & Subitha, L. (2015). (18)	Evaluate misoprostol as non-parenteral drugs are safe, effective, and easily administered to prevent postpartum hemorrhage.	India	500 woman	Divided into 2 groups containing 250 women in each group. One group received 400 mcg of sublingual misoprostol, and the other group received 10 IU of intramuscular oxytocin.	Sublingual misoprostol is as effective as intramuscular oxytocin and prophylactic oxytocin in managing the third stage of labor to prevent postpartum hemorrhage.
Shady, N. W., Sallam, H. F., Elsayed, A. H., Abdelkader, A. M., Ali, S. S., Alanwar, A., & Abbas, A. M. (2019). (19)	Evaluate the effect of prophylactic oral tranexamic acid (TA) plus buccal misoprostol on the amount of blood loss after vaginal delivery.	Tertiary university hospital	Women (aged 20-35 years) with a singleton pregnancy in a cephalic presentation between 38 and 42 weeks of gestation.	Group I (oxytocin group): received 10 IU oxytocin IV Group II (misoprostol group): received 600 mg buccal misoprostol Group III (TA and misoprostol group)	There was a significant difference in low HB and high blood loss in the misoprostol group compared to the TA and misoprostol group. There was a significant difference in high HB and low blood loss in the TA and misoprostol groups compared to the oxytocin group.
Suhrabi, Z., Taghinejad, H., Direkvand-Moghadam, A., & Akbari, M. (2016). (15)	This study aims to assess the effect of Inhaled Oxygen Plus Oxytocin Compared with Oxytocin only on a postpartum hemorrhage.	Iran	120 woman	For both groups, the management of the third stage of labor was carried out using 1000 cc of Ringer's Lactate and 20 IU of Oxytocin. In addition to routine administration, the intervention group was also given 8 liters of oxygen through a face mask.	The results showed that the mean blood loss was (256.16 ± 97) ml in two hours after delivery in the control group and (149.5 ± 46.49) ml in the intervention group. There was a significant difference between the PPH of the two groups (p<0.006).

drugs stimulate the contraction of uterine, promote the hemostasis, and compress blood vessels. The uterotonic drugs include oxytocin, methylergonovine, misoprostol, and carbetocin (14). This systematic analysis reviewed several studies that tested the usage of uterotonic drugs in preventing postpartum haemorrhage, including oxytocin (15), carbetocin (16), and misoprostol (17–19). Oxytocin is a polypeptide hormone naturally synthesized by the mother's body in the posterior pituitary and increases during pregnancy. In addition, oxytocin is a potent uterotonic in plasma and induces labour to work for the cervical maturation process (20). Oxytocin can also be obtained outside the body from being naturally synthesized in the mother's body. Oxytocin can be administered parenteral, oral, buccal, or intramuscular injection with a half-life of about 12-17 minutes (20). A study conducted by Suhrabi et al. (15) stated that oxytocin helps improve uterine involution and can be a way to treat bleeding. From the statistical tests of characteristics for both groups that involved in his study, the management of the third and fourth stage of labour was carried out using 1000 cc Ringer Lactate and 20 IU Oxytocin (15). The intervention group showed that the mean blood loss was 149.5 ml, and the control group was 256 ml after two hours delivery. In addition, it found that a differences between control and intervention groups in PPH cases (15).

Carbetocin has a similar characteristics with oxytocin, it has prolonged duration of action (about one hour), ensuring more contraction time and minimal adverse effects. Carbetocin ties to oxytocin receptors that exist on the smooth muscle of uterine, resulting in rhythmic uterine contractions, increasing frequency of the contractions, and increasing uterine tone (16). In addition, carbetocin ensures more effective contractions and minimal side effects such as headache, tremor, low blood pressure, queasiness, stomachache, and pruritus (16). The study of Kabir et al. (16) showed that carbetocin had effectivity in reducing loss blood more than oxytocin. Extensive blood loss has not happened in the carbetocin patients group. However massive 8.5% of women in the oxytocin group had occurred massive blood loss. Patients in the carbetocin group did not require the uterine fundal massage, blood transfusion, and other uterotonic drugs (16). The mean amount of blood loss was 64 ml less in the carbetocin group, and the side effects of the drug were almost similar in the two groups (16). From the study results, it can be concluded that carbetocin seem to be an effective uterotonic drug to prevent bleeding in the third stage of labour.

Misoprostol is a new uterotonic drug that has the same function as oxytocin to prevent PPH (21). Most misoprostol is administered orally after delivery of the baby, with the time to reach peak levels is 9-15 minutes, and the half-life is 20-30 minutes (22). Study Ononge et al. (17) found that misoprostol can be given to postpartum mothers if oxytocin was not available. Thus, misoprostol can be an alternative because its effectiveness is not much different from giving oxytocin. Misoprostol was given as much as 600 mcg orally postpartum (17). However, the administration of misoprostol cannot be given to patients who have decreased consciousness (21). Priya et al. (18) chose sublingual administration for misoprostol administration. The results found that sublingual misoprostol had a pharmacokinetic advantage in achieving the shortest time to peak concentration (18). Blood loss in postpartum mothers was less in mothers given misoprostol than oxytocin, although misoprostol had more side effects than oxytocin. The side effects are short-lived and self-limiting, and the peak plasma level of misoprostol is longer than oxytocin (18). In that study, sublingual misoprostol had lower efficacy than the uterine injection, achieving peak plasma levels with oral misoprostol was 30 minutes compared to IM/IV oxytocin administration of 1-2 minutes (18). However, sublingual misoprostol is effective as oxytocin, so it can be applied when oxytocin is not available.

Misoprostol can also be combined to increase its effectiveness with oral tranexamic to prevent worsening conditions in postpartum hemorrhage patients. Study conducted by Shady et al. (19) showed that administration of misoprostol and tranexamic can reduce bleeding and increase hemoglobin values and pulse rate in mothers postpartum hemorrhaging. This certainly improves the condition of mothers who experience postpartum hemorrhage and even prevents bleeding in postpartum mothers (19). Misoprostol and tranexamic can be alternatives because their effectiveness is not much different from oxytocin. However, this intervention cannot be applied to mothers with decreased consciousness because misoprostol and tranexamic are given orally (19). Dumont et al. (23) designed a study in Benin and Mali to evaluates the uterine balloon tamponade (UBT) effectiveness combined with misoprostol to manage uncontrolled PPH. Using UBT as a complementary uterotonic is easy to apply, non-invasive, and priceless rather than other products in high-income countries. This study hypothesized that the combination between UBT and misoprostol was more effective than misoprostol only in stopping bleeding and preventing severe maternal morbidity (23). The results of this trial showed that no beneficial effect of UBT usage in condom catheter device rather than misoprostol treatment in uterine with no contraction (23). In addition, the combination of uterotonic drugs with other measures such as balloon tamponade, oxygen administration, and TA is more effective in preventing postpartum hemorrhage than uterotonic drugs alone.

This review provide new inside that combining uterotonic drugs with other interventions reduce the PPH significantly. However, the discussion of this study may not describe the current condition of the usage uterotonic drugs in hospitals because the use of

uterotonic drugs in Indonesia, especially in hospitals, has not been published by academics at universities, so informations were limited. Researchers need to consult and discuss more with clinicians in hospitals.

CONCLUSION

It can be concluded from this review that uterotonics (oxytocin, carbetocin, and misoprostol) prevent postpartum hemorrhage effectively. However, their effectiveness increases when combined with other measures, such as concurrent administration of oxygen or insertion of balloon tampons. Thus, combining pharmacological and non-pharmacological approaches increases the efficacy of postpartum hemorrhage prevention. Nurses are expected to develop collaborative studies that research combinations of pharmacological and non-pharmacological interventions, especially with approaches to Indonesian's culture, traditions, and beliefs.

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