



UTEROTONIC USE IN THE ACTIVE MANAGEMENT OF THIRD STAGE OF LABOR (AMTSL): SYSTEMATIC REVIEW

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ABSTRACT

Background: Maternal mortality rate in Indonesia has decreased from 184/100,000 live birth (LB) (2016) to 177/100,000 LB (2017), but this number is still high enough than SDGs target of 70/100,000 LB. The one of direct cause of maternal death is hemorrhage, especially postpartum hemorrhage (PPH). Causes of PPH are uterine atony, laceration of birth canal, resistant placenta and uterine inversion. PPH prevention method is Active Management of Third Stage of Labor (AMTSL). The objective of this systematic review is to analyze the use of uterotonics in AMTSL.

Methods: This systematic review used the PRISMA protocol, articles taken from Google Scholar, Science Direct, and Pub Med. The time span of the research article was 2010 to 2021.

Result: The results of the study describe that the use of uterotonics in single use or combination in third stage of labor can reduce the risk of PPH and shorten the time of the stage. The side effects were reported in misoprostol and methyl ergometrine than oxytocin. In addition, combination therapy with oxytocin and misoprostol can reduce the length of the third stage and the potential for a decrease in hemoglobin within 24 hours of delivery. In Indonesia, if oxytocin is not available, maternal nipple stimulation is performed as nonpharmacological therapy or ergometrine 0.2 mg is given to patients without complications of high blood pressure.

Conclusion: The use of uterotonics is adjusted to its cost-effectiveness, ability to store and refrigerate also the benefits compare to the side effects to the patients.

Keywords: active management of the third stage, uterotonics, postpartum, hemorrhage

INTRODUCTION

Maternal Mortality Rate (MMR) is one of health status's indicator in Indonesia. There is a downward trend in MMR in the

world and in Indonesia. In 2017, the world's MMR decreases from 214 (in 2016) to 211/100,000 live birth (LB). In Indonesia, the MMR reached 184 down to 177/100,000 LB in the same year period^[1]. However, the decline of MMR is

still much higher when compared to Sustainable Development Goals's target (SDGs) in 2030 which is less than 70/100,000 LB^[2].

The direct causes of MMR globally and in Indonesia are hemorrhage, especially PPH, pre-eclampsia and eclampsia, infections, complications caused by comorbidities disease during childbirth and unsafe abortion. These direct causes contribute 75% of the causes of MMR^[3,4].

Postpartum hemorrhage is defined as vaginal bleeding of more than 500 ml immediately after delivery of the placenta or 1,000 ml in operative delivery which has the potential to affect the mother's hemodynamics^[5]. The American College of Obstetrics and Gynecology in 2017 updated the definition of postpartum hemorrhage as vaginal bleeding of more than 1,000 ml or immediately after delivery of the placenta or that has the potential to affect maternal hemodynamics either during vaginal or operative delivery^[6].

Some causes of PPH are uterine atony, laceration of the birth canal, placenta resistant and uterine inversion^[6]. The prevention of postpartum hemorrhage is active management of third stage of labor (AMTSL). AMTSL is a prophylactic intervention recommended by World Health Organization (WHO) since 2007 which consists of: 1) Giving uterotonic immediately after baby is born preferably oxytocin; 2) Controlled cord tension; and 3) uterine massage. The main aspect of the three procedures combined in one step of care is the administration of uterotonics^[7].

Uterotonic in AMTSL is a therapy that can increase uterine contraction immediately after the baby's born. Several uterotonics are oxytocin, ergometrine, misoprostol^[8]. Oxytocin 10 in intramuscular route is first line therapy recommendations of WHO^[7,9]. Alternatives therapy when oxytocin is unavailable are ergometrine 0.2 mg

intramuscularly, misoprostol 600 – 900 mg orally, sub lingually or rectally^[9].

Several studies abroad and in Indonesia have begun to compare the effectiveness of each uterotonic in the third stage of labor to present the best results in third stage of labor. This study mainly explored the effectiveness of each uterotonic in single-dose such as oxytocin, methyl ergometrine, misoprostol and the combination of the therapies. Several related systematic reviews also analyzed the use of uterotonics in the third stage of labor, but in this systematic review analyzed the use of uterotonics and the combination on labor outcomes both on bleeding and side effects in mother.

Based on this background, the authors compiled a systematic review to analyze the use of uterotonics in AMSTL.

METHODS

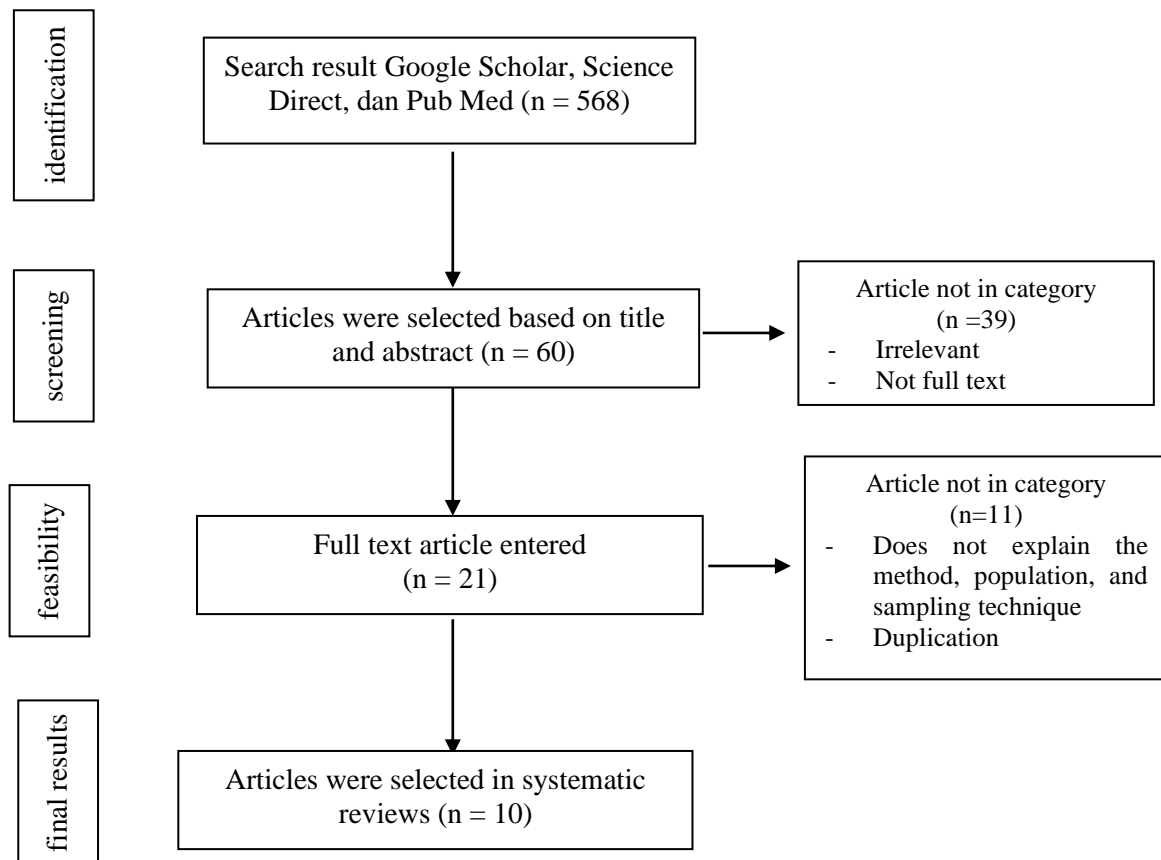
This systematic review uses the PRISMA protocol (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols). The articles taken from Google Scholar, Science Direct, and Pub Med. The time span of this articles is latest 10 years; 2011 to 2021. In addition, relevant text books and guidelines were used to add further information or additional reports that were not identified in the electronic search.

The keywords taken from the PICOS technique (Population Intervention Compare Outcome Study design). The keywords of this study are uterotonic or oxytocin or ergometrine or misoprostol and active management of third stage of labor (AMTSL).

The inclusion criteria for those articles are: (1) target group: mothers giving birth, (2) intervention: uterotonics (3) outcome: bleeding or placental detachment or side effect (4) research method: experimental design (5) articles written in English and Indonesian.

Articles were excluded according to the exclusion criteria, namely (1) incomplete documents, (2) irrelevant (3) not explaining the research method, population, and sampling technique, (4) document duplication (5) articles written in another language of English and Indonesian.

Figure 1 is a prism protocol for determining the number of articles for data extraction. This protocol consists of identification, screening, feasibility and final results.



Picture 1. PRISMA Protocol

RESULT

There are 10 articles which appropriate with inclusion and exclusion criteria. This article will be explained in data extraction table. There are 3 articles compare between AMTSL and expectant

management. There are 6 articles describe comparison of the effectiveness of single use doses uterotonics. Uterotonic therapy include oxytocin, methyl ergometrine, misoprostol and carboprost. While 1 article describe the combination of uterotonic therapy in AMTSL. Several

dependent variables are the average of blood loss during labor, the duration of the third stage, changes in hematocrit, the risk of postpartum hemorrhage and a

description of the side effects. The results of the extraction of research articles are presented in table 1.

Table 1 Extraction of The Articles

No	Main Author Name, Title	Study design	Population	Intervention and comparison	Result Study
1.	Puti Lenggo Geni, Irwan Taufiqur Rachman, Heru Pradjatmo The Administration of Misoprostol in Active Management of the Third Stage of Labor in Reducing Postpartum Hemorrhage. 2017 ^[10]	Blinding randomized controlled trial	Total of 104 mothers during the third stage of labor, divided into 2 groups, namely: 1. Intervention group: 52 mothers given misoprostol 600 mcg orally 2. Control group: 52 mothers were not given misoprostol 600 mcg orally	The intervention was administration of misoprostol 600 mcg orally in the third stage of labor combine with AMTSL. The independent variables were the average of blood loss during labor, decreased hemoglobin levels and hematocrit levels in 24 hours postpartum.	Misoprostol administration in AMTSL method affected in the amount of blood loss during labor and decreased hemoglobin levels (OR 2.45; ρ value = 0.04), (OR 2.99; ρ value = 0.01). Misoprostol administration had no effect on decreasing hematocrit levels (ρ value = 0.75).
2.	Revinel, Comparative Effectiveness of the Third Stage of Labor Between Administration of Rectally Misoprostol and Oxytocin Intramuscular. 2014 ^[11]	Randomized controlled clinical trial study	Total of 60 mothers during the third stage of labor, divided into 2 groups, namely; 1. Intervention group: 30 mothers given misoprostol 600 mg per rectal 2. Control group: 30 mothers with 10 iu of intramuscular oxytocin.	The intervention was the administration of misoprostol 600 mg per rectal in the third stage of labor. The independent variables were the duration of third stage of labor and the amount of bleeding up to 2 hours postpartum.	There is an effect of administration misoprostol rectally on the duration of third stage of labor and the amount blood loss during labor above 150 ml. The average of duration of third stage of labor misoprostol 600 mgr rectally vs. oxytocin 10 iu intramuscularly are 5.7 minutes vs. 9.7 minutes. Mean amount of bleeding 2 hours postpartum with misoprostol 600 mgr rectally vs oxytocin 10 iu intramuscularly; 153.3cc vs 187.7cc.
3.	Yusran Antonius, Eddy Hartono, Umar Malinta. Comparison of Bleeding Amount and Length of Third Stage of Labor Using Sublingual Misoprostol with Intramuscular Oxytocin in Grandemultipara. 2011 ^[12]	Randomized clinical trial	Total of 70 mothers during the third stage of labor, divided into 2 groups: 1. Intervention group: 35 mothers given misoprostol 400 mcg sublingual 2. Control group: 35 mothers given oxytocin 10 iu intramuscularly.	The intervention was the administration of misoprostol 400 mcg sublingually in the third stage of labor. The independent variables were the duration of third stage of labor and the amount of blood loss during labor.	There was a significant difference in the duration of third stage of labor. The misoprostol 400 mcg sublingual group had a shorter duration of third stage of labor with a mean \pm SD; 9.09 \pm 2.15 minute compared to oxytocin group of 10.45 \pm 2.26 minute (ρ value = 0.012). The amount of blood loss was less in the sublingual 400 mcg misoprostol group with a mean \pm SD; 190.73 \pm 18.91 ml compared to oxytocin group

					220.24±39.27 ml, ρ value = 0.000). There was no relationship between the use of both therapies with side effects (ρ value = 0.098).
4.	Mukta Mani, Sahay Priti Bala Role of Misoprostol 600 mcg Oral in Active Management of Third Stage of Labor: A Comparative Study with Oxytocin 10 IU im.2013 ^[13]	Randomized clinical trial	Total of 200 mothers during the third stage of labor, divided into 2 groups: 1. Intervention group: 100 mothers given misoprostol 600 mcg orally 2. Control group: 100 mothers given oxytocin 10 iu intramuscularly.	The intervention was the administration of misoprostol 600 mcg orally in the third stage of labor. The independent variables were the duration of third stage of labor, the amount of blood loss during labor and the decrease in hemoglobin levels.	There was no difference in the effect of misoprostol 600 mcg orally and oxytocin 10 iu intramuscularly. In the intervention group; the mean the amount of blood loss during labor was 145 ml, the mean duration of third stage of labor 3.76 minutes and the decrease in hemoglobin was 0.55 g/dl. In the control group; the mean the amount of blood loss during labor was 125.6 ml, the mean duration of third stage of labor 3.50 minutes and the decrease in hemoglobin was 0.48 g/dl.
5.	Thibaud Quibel, Idir Ghout, François Goffinet, Laurent J. Salomon, Julie Fort, Sophie Javoise, Laurence Bussieres, Philippe Aegerter, and Patrick Rozenberg. Active Management of the Third Stage of Labor with a Combination of Oxytocin and Misoprostol to Prevent Postpartum Hemorrhage. 2016 ^[14]	Randomized controlled trial	Total of 1,605 mothers during the third stage of labor, divided into 2 groups: 1. The intervention group: 806 mothers with oxytocin 10 iu intravenously plus misoprostol 400 mcg orally 2. The control group: 799 mothers with 10 iu intravenous oxytocin plus a placebo.	The intervention was the administration of misoprostol 400 mcg orally and oxytocin 10 iu intravenously. The independent variables were the amount of blood loss during labor and secondary postpartum hemorrhage (24 hours).	There was no effect due to administration misoprostol 400 mcg orally and oxytocin 10 iu intravenously compared to placebo and oxytocin 10 iu intravenously on AMTSL on blood loss during labor and secondary postpartum hemorrhage (24 hours).
6.	Olkamien, Comparison of active vs expectant management at Sinar Kasih Hospital Tentena. 2014 ^[15]	Randomized controlled trial	Total of 128 mothers during the third stage of labor, divided into 2 groups: 1. The intervention group: 64 mothers with active management of third stage of labor.	The intervention was Active Management of Third Stage of Labor (AMTSL). The independent variable was the duration of third stage of labor.	Active Management of Third Stage of Labor (AMTSL) shortens the third stage of labor; 11.6±3.5 minutes compared to expectant management; 18.7±3.7 minutes with ρ value < 0,05.

			2. The control group: 64 mothers with expectant management of third stage of labor.		
7.	Kavita A. Chandnani, Deepti D Sharma. Third stage of labour: expectant versus active management – a comparative study in local low risk population.2019 ^[16]	Prospective comparative study	Total of 200 mothers during the third stage of labor, divided into 2 groups: 1. Group A: 100 mothers with expectant management of third stage of labor. 2. Group B: 100 mothers with active management of third stage of labor.	Group A is the group with expectant management of third stage of labor intervention and group B is the group with active management of third stage of labor. The independent variable was the duration of the third stage of labor and the amount of blood loss.	The average volume of blood loss in group A was 360.5ml and group B was 290.6ml. In group A: 12 patients have a blood loss more than 500 ml of blood. In group B, 66% of patient had the duration of the third stage of labor less than 5 minutes compared to group A, which was only 22%. The average duration of the third stage of labor in group A was 13.46±8.3 minutes and group B 5.32±3.05 minutes. Active management of the third stage of labor can reduce the amount of blood loss and shorten the duration of the third stage also can reduce the potential for postpartum hemorrhage.
8.	Ajantha Boopathi, Sujir Radhakrishnan Nayak, Arun Rao, Bharathi Rao. Oxytocin versus Methylergometrine in the Active Management of Third Stage of Labour.2014 ^[17]	Prospective comparative study	Total of 300 mothers during labor, divided into 2 groups: 1. Group A: 150 mothers given 10 iu intramuscular oxytocin 1 minute after birth. 2. Group B: 150 mothers given intravenous injection of methyl ergometrine 0.5 mg in the delivery of the baby's anterior shoulder.	The independent variables were the duration of the third stage of labor, blood loss, decreased incidence of postpartum hemorrhage, effects on hematocrit, blood pressure and side effects.	The duration of the third stage of labor was shorter in group B (2.31±1.06 minutes) than in group A (3.45 + 2.75). The mean blood loss of labor in group B was less (149.33±145.47 ml) than group A (196.57±192.30), with ρ value <0.0001. The risk of primary postpartum hemorrhage (PPH) was lower in group B than group A. The perceived side effects; nausea and vomiting were significant in group B who received intravenous injection of 0.5 mg methyl ergometrine with ρ value < 0.001.
9.	Pradnya A. Supe, Shailesh J. Kore, Y. S. Nandanwar.	Prospective comparative study	Total of 200 mothers during the delivery of the baby's anterior	This study compared 3 interventions; 800 mcg of	There was no difference between four groups in this study, but the mean

	A Comparative Study of Efficacy of Misoprostol With Methyl Ergometrine and Carboprost In Active Management of Third Stage of Labour.2016 ^[18]		<p>shoulder, divided into 4 groups:</p> <ol style="list-style-type: none"> 1. Group A: 25 mothers given 800 mcg misoprostol rectally. 2. Group B: 25 mothers given intravenous injection of methyl ergometrine 0.5 mg 3. Group C: 25 mothers given 125 mcg carboprost 4. Group D: 25 mothers as control group. 	<p>misoprostol rectally, injection of methyl ergometrine 0.2 mg intravenously and 125 mcg of carboprost.</p> <p>The independent variables were duration of the third stage of labor and the amount of blood loss.</p>	<p>duration of the third stage of labor was the shortest in group A (misoprostol 800 mcg);8.88 ± 5.0 minutes. Group B 8.96 ± 3.6 minutes, group C 8.90 ± 3.59 minutes and group D 9.56 ± 4.63 minutes.</p> <p>There was a difference in the mean blood loss during delivery with value < 0.001 where group A had the least amount of 124.40 ± 34.7 ml, compared to group B 152.20 ± 49.3 ml, group C 153.80 ± 43.7 ml and group C. D 167.40 ± 52.9ml.</p> <p>Descriptions of side effects are shivering cause of misoprostol, pain in the abdomen cause of methyl ergometrine and vomiting and diarrhea cause of carboprost.</p>
10.	Abubaker Y. H. Abdel Rahim, Mohamed A. A Gadir E. Ounsa, Rayan G. Albarakati, Elsadig Y. Mohamed, Sawsan M. Abdalla. Comparison Between Oxytocin, Ergometrine And Misoprostol In Active Management of The Third Stage of Labour: A Randomized Controlled Trial.2019 ^[19]	Randomized controlled trial	<p>Total of 150 mothers during the delivery of the baby's anterior shoulder, divided into 3 groups:</p> <ol style="list-style-type: none"> 1. Group A: 50 mothers given 400 mcg of sublingual misoprostol. 2. Group B: 50 mothers given 10 iu intravenous infusion of oxytocin. 3. Group C: 50 mothers given intravenous infusion of methyl ergometrine. 	<p>This study compared 3 intervention: 400 mcg of sublingual misoprostol, 10 iu of intravenous infusion oxytocin dan 0.5 mg of intravenous infusion of methyl ergometrine 0,5mg.</p> <p>The independent variables were duration of the third stage of labor and the amount of blood loss.</p>	<p>The shortest duration of third stage of labor: group A who received misoprostol 400 mcg sublingually (3.89 ± 0.37 minutes), group B oxytocin (4.6 ± 0.9 minutes) and group C Methyl Ergometrine (5.45 ± 0.9 minutes).</p> <p>The average of blood loss in labor were group A (168.36 ± 24.83ml), group B (205.56 ± 34.82ml) and group C (214.49 ± 35.97ml).</p>

DISCUSSION

During the third stage of labor, the uterine muscles contract downwards which causes vasoconstriction of the blood vessels that pass through the uterine and placenta, thereby stopping blood flow to the placenta. The cessation of blood flow to the placenta causes detachment of the placenta^[20].

Since 2007, the World Health Organization (WHO) has recommended Active Management of Third Stage of Labor (AMTSL) as a method to prevent the risk of PPH. (AMTSL) is one of the innovation to replace expectant management. Expectant management is a delivery assistance step which waiting for the natural signs of placental separation, clamping the umbilical cord after it does not beat and giving uterotonics when uterine atony occurs^[7].

AMTSL consists of administration of uterotonic as the main component, controlled tension of the umbilical cord and uterine massage^[7]. Uterotonic in AMTSL intends the increase of uterine contractions to prevent incidence of uterine atony. The first line uterotonic administration is oxytocin 10 iu intra muscular within 1 minute after birth.

Several studies have concluded that AMTSL can reduce the amount of blood loss and duration of third stage of labor less than 5 minutes compared with expectant management^[16]. Study in Indonesia concluded that AMTSL proven shorten the duration of the third stage of labor: 11.6 ± 3.5 minutes compared to expectant management: 18.7 ± 3.7 minutes^[15].

Research study also conclude that the AMTSL has side effects, including; increase in diastolic blood pressure, nausea and vomiting after childbirth, abdominal pain and an increase used of analgesics^[20]. But the benefits of uterotonics are more important than side

effects so that every pregnant woman is communicated about the side effects that will be felt by the mother due to the administration of uterotonics^[21].

However, in the context of preventing PPH, which is mostly caused by uterine atony, AMTSL is a recommended procedure by the WHO. Uterotonic expected to stimulate uterine contractions so as to shorten the duration of third stage of labor and reduce blood loss^[7,20]. Uterotonic in AMTSL included:

1. Oxytocin

Oxytocin is one of the most widely used uterotonic types^[8]. The oxytocin injection is unstable at room temperature and require cold transport in distribution. However, storage is not in frozen conditions^[8,22].

Oxytocin can increase the frequency, amplitude, and duration of uterine contractions. The mechanism of oxytocin as a uterotonic is stimulate inositol triphosphate and an increasing of intracellular calcium in the myometrium. Calcium ions in myometrium stimulate bind calmodulin and activate myosin light chain kinase which is the core mechanism of uterine smooth muscle contraction^[23].

At low doses, oxytocin can stimulate rhythmic uterine contractions and prevent bleeding. However, at high doses it will cause a persistent tetanic uterine contractions. Intravenous administration by infusion can be used to maintain uterine contractions with a response time of 3-5 minutes after administration. Through the intramuscular route, oxytocin can maintain uterine contraction activity for up to 2 – 3 hours with a response time of 2 – 5 minutes after the initial administration^[8]. Administration of intravenous oxytocin cause major side

effects including severe hypotension, tachycardia and dysrhythmias^[23].

Administration of oxytocin 10 iu in intramuscular route is one of the main recommendations of WHO^[7,9]. Administration of oxytocin as first line therapy in AMTSL because it proven have no any side effects compared to other types of uterotonic^[17].

2. Methyl Ergometrine

Methyl ergometrine is a uterotonic that can increase uterine muscle tone at low doses, while at high doses this therapy causes uterine tetany contraction. The ergot alkaloids in methyl ergometrine increase vasoconstriction and stimulation of central dopamine receptors. These compounds interact with alpha adrenergic receptors in the myometrium. This stimulates the entry of calcium into the myometrial cells causing contraction^[24].

Ergot alkaloids in methyl ergometrine stimulates acute coronary vasospasm or myocardial infarction so it is not recommended to hypertension, pre-eclampsia and cardiac malfunction. The administration should be assessed that the benefits outweigh the possible risks^[25].

As an uterotonic, methyl ergometry can be an alternative to shorten the third stage of labor, reducing the risk of blood loss and postpartum hemorrhage. Research in India described the use of methyl ergometrine to be more effective in AMTSL than oxytocin. However, the study also noted that there were significant side effects in the group receiving methyl ergometrine^[17].

3. Misoprostol

Misoprostol is a prostaglandin E1 analogue licensed for the treatment of peptic ulcers. However, the benefits of "off label" misoprostol are used in obstetrics as a uterotonic^[8,26].

Misoprostol wrapped in aluminum oil packaging, soluble in water, stable in heat and do not require cold temperatures and affordable prices. This performance placing misoprostol as a uterotonic alternative in areas with low resources^[8,13]. Recommendation doses of misoprostol is 600 mcg orally^[22].

Misoprostol can be given orally, sublingually, vaginally and rectally. The oral and sublingual pathways have a rapid onset of time, while the vaginal and rectal routes produce the longest therapeutic activity^[8].

Several studies compared the effectiveness of oxytocin 10 iu intramuscularly with misoprostol in AMTSL with the main indicators the duration of the third stage of labor, the amount of blood loss and a decrease in hemoglobin levels^[11-13,19]. In addition, the side effects of therapy are also concluded by several studies as one way to obtain effective and efficient therapy but is safe for patients^[11,12]. A study with a larger sample size in India involving 200 mothers in the third stage of labor concluded that there was no statistically significant difference in the duration of the third stage of labor and a decrease in hemoglobin 24 hours postpartum in misoprostol 600 mcg orally group and oxytocin 10 iu intramuscular group. The third stage duration was reduced only 20 seconds and bleeding was reduced by about 20 cc in misoprostol group^[13].

A systematic review that focused on the effectiveness of preventing postpartum hemorrhage concluded that the misoprostol group had PPH incident lower than the oxytocin group. However, the incidence of misoprostol side effects was felt by more patients compared to the oxytocin group. Commonly side

effects are nausea, vomiting and shivering^[28].

Based on recommendations from WHO and the Ministry of Health in Indonesia, first line uterotonic prophylaxis in AMTSL is oxytocin 10 iu intramuscularly^[5,7]. In the Ministry of Health of Indonesia's guidelines (2013), if there is no oxytocin, The mother's nipple stimulation used to produce natural oxytocin. Furthermore, methyl ergometrine 0.2 mg intramuscularly can be given to patients who do not have preeclampsia, eclampsia and hypertension^[5]. The use of uterotonics is adjusted to its cost-effectiveness, ability to store and refrigerate also the benefits vs side effects to the patients.

CONCLUSION

Several uterotonics that can be used in AMTSL are oxytocin, ergometrin, misoprostol, carbetocin and carboprost. The first line uterotonic in Indonesia is oxytocin 10 iu intramuscularly. The study concluded that the administration of uterotonics can reduce the duration of third stage of labor and prevent PPH. In addition, side effects after administration of methyl ergometrine and misoprostol were described more than those of oxytocin. Several studies concluded the effectiveness of combination therapy, but also reported the side effects experienced by patients on combination therapy. The use of uterotonics is adjusted to its cost-effectiveness, ability to store and the benefits and side effects felt by the mother in labor.

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