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Is methylergometrine more effective than other uterotonic agents for the active management of the third stage of labor?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not methylergometrine is more effective than other uterotonic agents in preventing postpartum hemorrhage during the third stage of labor.

Study Design: Review of two randomized controlled trials (RCTs) published in 2004 and 2009, and one prospective study published in 2006.

Data Sources: Each article used was published in English and found using PubMed and Medline. The studies compared the efficacy of methylergometrine against uterotonic agents, specifically oxytocin and misoprostol.

Outcomes Measured: The efficacy of methylergometrine was measured via the incidence of postpartum hemorrhage despite the use of prophylactic medication and adverse effects of medications.

Results: Vimala et al (2004) found that methylergometrine and misoprostol were equally effective at decreasing the amount of blood loss [170±42ml vs. 185±56ml; $p > 0.05$], as well as in terms of adverse side effects, specifically nausea [13.3% vs. 6.6%; $p > 0.05$]. Singh et al (2009) found that methylergometrine was less effective compared to oxytocin in reducing the mean blood loss during the third stage of labor [223.48ml vs. 154.73ml; $p < 0.01$]. While Fujimoto et al (2006) also noted that methylergometrine was more likely increase incidences of postpartum hemorrhage than oxytocin [18.6% vs. 7.3%; OR = 0.31], no differences in resultant adverse side effects were found [2.8% vs. 1.2%].

Conclusions: Due to the limitations of the studies with regards to the use of methylergometrine compared to other uterotonic agents, its efficacy over these drugs remains inconclusive. However, methylergometrine was not shown to produce more adverse side effects than standard of care uterotonic agents oxytocin and misoprostol.

Key Words: Methylergometrine, oxytocin, misoprostol, postpartum hemorrhage, third stage labor.

INTRODUCTION

Postpartum hemorrhage, defined as when a vaginal delivery results in greater than 500ml of blood loss, is a major cause of maternal death. While it can be attributed to lacerations sustained during childbirth, retention of products of conception or placental tissue, or defects in blood coagulation, uterine atony is the preeminent cause of hemorrhage after delivery. Following the vaginal birth of an infant, the myometrium is responsible for contracting in order to reduce uterine size and help clamp the vasculature where the placenta implants. However, if the uterus becomes atonic, the myometrial fibers fail to constrict and continued bleeding from uterine vessels occurs, which can result in excessive blood loss. Postpartum hemorrhage is the foremost cause of pregnancy-related mortality in developing countries and is ranked third in the United States[1], with 11.8% of maternal deaths in the US from 2006-2010 resulting from hemorrhage.[2]

Considering the potentially life-threatening consequences of labor complications, the appropriate treatment with regards to postpartum hemorrhage is important to both practitioners and patients. Since physician assistants are involved in the delivery of infants, knowledge of the management of labor complications is essential. In all but four states, the extent of obstetrical care a PA can provide is determined by the supervising physician and hospital regulations. This means that PAs can be involved in labor and delivery,[3] where recognizing and appropriately treating postpartum hemorrhage is vital.

In 2012, there were 3,952,841 live births in the US.[4] Though data on the national expenditure in cases of maternal hemorrhage are not available, a study limited to California hospitals performed by UCLA calculated that there is an increased cost of $3,000 per patient. If severe hemorrhage necessitates hysterectomy, there is an increased cost of $6,403.[5] Statistics are

not available for the number of health care visits attributed to postpartum hemorrhage each year, but another study based in California found that 2.4% of live births were associated with postpartum hemorrhage.[6]

In spite of identifying the cause and risk factors for most postpartum hemorrhage, it is still difficult to determine which patient will develop hemorrhage. Uterine atony can be attributed to prolonged labor, undue manipulation or dysfunction of the uterus, uterine fibroids, augmented labor via oxytocin, or use of general anesthesia. Women whose uterus has undergone greater distention due to multiple gestation or polyhydramnios are also prone to atony.[1] Prophylactic administration of uterotonic agents has been implemented to prevent hemorrhage, but this method is not infallible, as evidenced by maternal mortality rates. Uterotonic agents are responsible for stimulating contractions of the uterus, namely in the form of oxytocin, methylergometrine, or misoprostol.[7] These medications are generally administered during the third stage of labor, or following delivery of the anterior shoulder.[8,9,10]

Currently, oxytocin and misoprostol are uterotonic agents used for the prevention of postpartum hemorrhage during the third stage of labor. The gold standard treatment for postpartum hemorrhage is administration of intravenous oxytocin. Oxytocin has been found to most effectively minimize the amount of blood loss with the least amount of side effects. Another option for treatment also includes sublingual administration of misoprostol, which is effective but associated with more side effects. Although misoprostol is not first line in the United States, its use has been noted specifically in low resource areas where skilled practitioners and high tech equipment is not as readily available. Due to these factors, it has been noted to be a standard of care medication in prevention of postpartum hemorrhage. Since it

is provided as a sublingual tablet, it does not require training to administer. Additionally, unlike oxytocin, it does not require refrigeration to maintain its potency.[1,7]

In the past, methylergometrine has been used as an adjunct therapy if oxytocin has not been effective in stopping bleeding in cases of postpartum hemorrhage.[1] Methylergometrine, also known as methylergonovine, is an ergot derivative that presents as another one option for the active management due to its uterotonic properties. It is available as an injection (IV or IM) as well as an oral tablet.[11] The effects of this drug also last for approximately 2-4 hours, which is longer than oxytocin that lasts about 15-30 minutes, and misoprostol that lasts about 75 minutes.[7]

OBJECTIVE

The objective of this systematic review is to determine whether or not methylergometrine is more effective than other uterotonic agents for the active management of the third stage of labor.

METHODS

This review examined two randomized controlled trials and one prospective study, all of which examined pregnant women at full term with a single uterine pregnancy who were in labor. The intervention used was methylergometrine, which was compared to the experimental group who received either oxytocin or misoprostol. Though the studies used different outcomes, the intention was to determine the efficacy of methylergometrine compared to other uterotonic agents. These outcomes were measured by mean amount of blood loss, incidence of postpartum hemorrhage, and incidence of adverse side effects.

In order to find articles for this review, key words utilized include methylergometrine, oxytocin, misoprostol, postpartum hemorrhage, and third stage of labor. All articles used were published in English and found via searches on Medline and PubMed. These articles were then

selected by the author based upon their relevance to the stated clinical question and whether or not outcomes were applicable to patients. The inclusion criteria included randomized controlled trials and one prospective study published after the year 2000 that studied full term pregnant females with a single uterine pregnancy in the third stage of labor. Pregnant women who had to undergo a cesarean section, induced labor, preterm labor, or multiple gestation were excluded. Summary statistics used were means, standard deviations, p-values, and odds ratios.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (Years)	Inclusion Criteria	Exclusion Criteria	W/D	Inter-ventions
Fuji-moto[8] (2006)	Prosp-ective Study	438	Not specified	Pregnant women in spontaneous onset of labor, healthy, single gestation	Previous c-section, history of antepartum hemorrhage or postpartum hemorrhage in a previous pregnancy, or contraindication for receiving uterotonic drugs.	0	Methylerg-ometrine 200 μg (IV)
Singh[9] (2009)	RCT	300	Not specified	Pregnant women ≥37 weeks of gestation in spontaneous or induced onset of labor with healthy, single gestation	Known hyper-sensitivity/ contraindication to prostaglandins, intrauterine fetal demise, antepartum hemorrhage, multiple pregnancy, malpresentation, cardiac disease, Rh^- mother, hypersensitive disorders, hemoglobin < 7g/dl, or use of oxytoxics until the second stage of labor.	0	Methylerg-ometrine 200 μg (IV)
Vima-la[10] (2004)	RCT	120	Not specified	Pregnant women ≥37 weeks of gestation with spontaneous onset of labor	Use of oxytoxin to augment or induce labor, c-section deliveries, grand multipara (parity >5), gestation <37 weeks, multiple gestation, pregnancy-induced hypertension, hemoglobin concentration <8 gm/dl, or known hyper-sensitivity to prostaglandins	0	Methylerg-ometrine 200 μg (IV)

OUTCOMES MEASURED

The outcomes measured were the incidence of postpartum hemorrhage despite the use of prophylactic uterotonic agents as well as adverse effects of medication use. This was determined by the difference of mean blood loss and whether or not the values were significant, as well as clinical cases of postpartum hemorrhage. This allowed for determination as to whether or not each agent was better at preventing significant amounts of blood lost. There was also analysis regarding the adverse side effects of the medications. Patients reported several side effects, including nausea, vomiting, and headache, though this review focused specifically on incidence of subsequent nausea experienced by patients.[8,9,10]

RESULTS

The two randomized controlled trials and one prospective study used in this review all compare the effectiveness of methylergometrine compared to another uterotonic agent, either oxytocin or misoprostol. Efficacy of these medications was evaluated through incidence of postpartum hemorrhage and adverse side effects of medication. The inclusion and exclusion criteria were all comparable in these studies (Table 1), and all patients that entered the trial were accounted for at the conclusion.[8,9,10]

In the randomized controlled trial performed by Vimala et al, 120 pregnant women were randomized into two treatment groups. Use of IV methylergometrine was compared to sublingual misoprostol during the third stage of labor. Both treatment groups had similar results with regards to estimated blood loss and incidence of post partum hemorrhage, and the differences in the data were not found to be statistically significant. With methylergometrine, there were no cases of postpartum hemorrhage, whereas there were two cases after administration of misoprostol amounting to 3.3% ($p > 0.05$, CI = 90%) (Table 2).[10]

Table 2: Methylergometrine vs. misoprostol during the third stage of labor (Vimala et al, 2004)[10]

	Methylergometrine	Misoprostol	P value
Estimated Blood Loss (ml)	170 ± 42	185 ± 56	$p > 0.05$
Blood Loss ≥500ml	0%	3.3%	$p > 0.05$
Nausea	13.3%	6.6%	$p > 0.05$

In terms of adverse side effects, methylergometrine and misoprostol were once again comparable with 13.3% and 6.6% incidences, respectively ($p > 0.05$, CI = 90%) (Table 2). This study showed that overall, there were no noteworthy differences between using methylergometrine and misoprostol in terms of drug efficacy, and the discrepancies can be attributed to random variance (Table 2). This suggests that the two are equally effective in the management of postpartum hemorrhage during the third stage of labor. As seen in Tables 3, for every 30 participants who were administered methylergometrine, there was one fewer incidence of postpartum hemorrhage compared to those who were given misoprostol. However, for every 15 patients treated with methylergometrine, one additional would experience nausea (Table 4).[10]

Table 3: Methylergometrine vs. misoprostol comparison of incidence of postpartum hemorrhage (Vimala et al, 2004)[10]

More episodes of postpartum hemorrhage		Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT)
Misoprostol: Control Event Rate (CER)	Methylergometrine: Experimental Event Rate (EER)	$\frac{EER - CER}{CER}$	EER – CER	1/ARR
0.033	0	-1	-0.033	-30

Table 4: Methylergometrine vs. misoprostol comparison of incidence of nausea (Vimala et al, 2004)[10]

More episodes of nausea due to medication		Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Misoprostol: Control Event Rate (CER)	Methylergometrine: Experimental Event Rate (EER)	$\frac{EER - CER}{CER}$	EER – CER	1/ARI
0.066	0.133	1.015	0.067	15

Singh et al performed a randomized controlled trial that evaluated IV methylergometrine against IV oxytocin, with 75 women recruited for each group. This study showed that oxytocin

was more effective than methylergometrine at minimizing blood loss by measuring the mean amount of blood loss after delivery. For those given oxytocin, blood loss was about 154.73ml, compared to methylergometrine where blood loss was about 223.48ml ($p < 0.01$; CI = 0.95) (Table 5).[9]

Table 5: Methylergometrine vs. oxytocin during the third stage of labor (Singh et al, 2009)[9]

	Methylergometrine	Oxytocin	P value
Mean Blood Loss (ml)	223.48	154.73	$p < 0.01$

Although the study performed by the Singh et al did not include an analysis as to whether or not incidences of postpartum hemorrhage were statistically significant, the data indicated that for every 38 patients who were given prophylactic methylergometrine, there was one more incidence of postpartum hemorrhage than those who were given prophylactic oxytocin (Table 6). It was found that the only cases of blood loss exceeding 500ml were in those given methylergometrine, with no incidence of postpartum hemorrhage in the group given oxytocin.[9]

Table 6: Methylergometrine vs. oxytocin comparison of incidence of postpartum hemorrhage (Singh et al, 2009)[9]

More episodes of postpartum hemorrhage due to medication		Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Oxytocin: Control Event Rate (CER)	Methylergometrine: Experimental Event Rate (EER)	$\frac{EER - CER}{CER}$	EER – CER	1/ARI
0	0.027	N/A	0.027	38

In the prospective study carried out by Fujimoto et al, use of prophylactic IV methylergometrine and IV oxytocin were examined. Although there were reported incidences of postpartum hemorrhage with use of both drugs, methylergometrine administration resulted in more cases. There was noted to be a statistically significant increase in incidence of postpartum hemorrhage when methylergometrine was used compared to oxytocin at 18.6% and 7.3%, respectively (OR 0.31, CI = 95%) (Table 7).[8]

Table 7: Methylergometrine vs. oxytocin during the third stage of labor (Fujimoto et al, 2006)[8]

	Methylergometrine	Oxytocin	Odds Ratio
Blood Loss ≥500ml	18.6%%	7.3%	0.31
Nausea	2.8%	1.2%	--

Considering the results from the Fujimoto et al study, it can be established that for every 8 participants who was administered methylergometrine, there was one more incidence of postpartum hemorrhage compared to those given oxytocin (Table 8). Furthermore, for every 63 patients treated with methylergometrine, one additional patient would also experience nausea (Table 9). Though there is not a prominent difference in adverse side effects, the ability of oxytocin to minimizing postpartum hemorrhage was shown to be greater.[9]

Table 8: Methylergometrine vs. oxytocin comparison of incidence of postpartum hemorrhage (Fujimoto et al, 2006)[8]

More episodes of postpartum hemorrhage		Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Oxytocin: Control Event Rate (CER)	Methylergometrine: Experimental Event Rate (EER)	$\frac{EER - CER}{CER}$	EER – CER	1/ARI
0.073	0.186	1.55	0.133	8

Table 9: Methylergometrine vs. oxytocin comparison of incidence of nausea (Fujimoto et al, 2006)[8]

More episodes of nausea due to medication		Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Oxytocin: Control Event Rate (CER)	Methylergometrine: Experimental Event Rate (EER)	$\frac{EER - CER}{CER}$	EER – CER	1/ARI
0.012	0.028	1.33	0.016	63

DISCUSSION

Though studies by Singh et al and Fujimoto et al came to the conclusion that oxytocin was more effective than methylergometrine in preventing postpartum hemorrhage, the contrast in the numbers needed to harm indicates that there is an issue with consistency in the underlying data.

While the availability of methylergometrine is not an issue in the United States, it can be in low resource countries. Much like oxytocin, methylergometrine is given intravenously, which means that training is required for those who are tasked with administering it during labor.[1] Though the studies utilized in this review did not address intramuscular or oral methylergometrine, these are also options that are available. While injectable forms must be refrigerated and shield against light, the oral tablet can be stored at room temperature, potentially making it more accessible.[11]

This drug is used specifically for managing issues related to postpartum hemorrhage, such as uterine atony and failure of the uterus to return to its normal size after the placenta is delivered. As an ergot derivative, it works by increasing and sustaining smooth muscle contraction in the uterus.[11] The use of methylergometrine is contraindicated in patients with hypertension,[1] and consequently preeclampsia and eclampsia.[7] It also should not be used in those with coronary heart disease, as it increases the risk of vasospasm and thus myocardial ischemia. Such vasoconstriction can also occur in the peripheral vascular system and lead to ischemia and gangrene, known as ergotism where there is an overdose or chronic use of the drug. This ergot toxicity is possible if methylergometrine is used in conjunction with potent CYP3A4 inhibitors as well, so it is not recommended if a patient is also taking macrolides, azole antifungals, or protease inhibitors.[11]

There were limitations with this review due to inadequate randomized controlled trials performed with regards to the clinical question. While standard of care uterotonic agents were compared to methylergometrine, another randomized controlled trial would have provided more valuable information than a prospective study. Moreover, all of the studies used had small sample sizes. The treatment groups ranged from 60-82 patients, which does not provide a great

deal of information. Due to this, there was quite a bit of variation in the data from one study to the next.[8,9,10]

CONCLUSION

After reviewing the data from the three studies, it is inconclusive as to whether or not methylergometrine is more effective than other uterotonic agents. Though both studies that compared methylergometrine to oxytocin showed that its use resulted in more incidence of postpartum hemorrhage, the underlying numbers showed quite a bit of discrepancy. The numbers needed to harm in the Fujimoto study were far more drastic at one in every eight patients resulting in postpartum hemorrhage (Table 8), as opposed to the Singh study where one in every thirty eight had that outcome (Table 6).[8,9] When comparing methylergometrine to misoprostol in a randomized controlled study, the two appeared to be equivalent, but since it was only one study, more evidence would be necessary to definitively come to such a conclusion.[10]

Future studies are indicated in order to determine whether or not methylergometrine is a viable option for prevention of postpartum hemorrhage. Comparing oral methylergometrine with other uterotonic agents may be a more valuable study, especially since it can be more easily used and stored in countries with low resources where the gold standard treatment is not a viable option.

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