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Calcium in the Management of Atonic Postpartum Hemorrhage

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ABSTRACT
Objective: was to compare the role of methergine, misoprostol and calcium in the management of atonic postpartum hemorrhage. **Design**: Randomized Controlled Trial. **Setting**: This study was conducted in obstetrics and gynecology department of Al-azhar University Hospital, Assiut.
Patients: 300 women with PPH were included in the study.
Intervention: 300 women, each received 5 IU of oxytocin as prophylaxis then divided into three groups:
Group A (N=100): women with atonic PPH took methergine, **Group B (N=100):** women with atonic PPH took misoprostol and **Group C (N=100):** women with atonic PPH took calcium.
Outcome measures: The primary outcome was change in hemoglobin concentration before and after intervention.
Results: There was no significant difference between the three study groups as regard mean hemoglobin level before and after treatment. However, a significant difference was present as regard mean change (drop) in hemoglobin level after treatment, with misoprostol group showing the highest drop in Hb% (2.07 ±0.8) compared to calcium group (1.7 ±0.8) and methergine group (1.3 ±0.5).
Conclusion: Methergine is more effective in controlling the amount of blood loss during delivery giving a better chance in treatment of atonic postpartum hemorrhage followed with calcium then misoprostol. Although of that calcium is good alternative to methergine with low side effects so can be used safely and effectively when methergine is contriandicated.
Keywords: postpartum hemorrage, hemoglobin, calcium.

INTRODUCTION

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality. In the developed world, the incidence of PPH overall, and that of severe cases resulting in transfusion and/or hysterectomy, have increased significantly over the first decade of the new millennium (2001-2010). These increases appear to be directly linked to a concomitant increase in the incidence of uterine atony [1]. PPH can be prevented by using a uterotonic immediately after birth of the baby, and this intervention is recommended for all women. The preferred uterotonic is oxytocin, which is available in injectable form and requires refrigeration, making it impractical in settings where births still occur at home under the care of unskilled birth attendants, or where refrigeration is not possible [2].

For prophylaxis against uterine atony, oxytocin is routinely used during the third stage of labor. If the uterus fails to adequately contract in response to oxytocin administration, second-line uterotonics including methylergonovine maleate, prostaglandin F2α (carboprost), calcium and prostaglandin E1-analogue (misoprostol) are recommended. While commonly used, these drugs have important side effects and complications including (depending on the drug) hypertension, nausea/ vomiting, bronchospasm, pyrexia, and gastrointestinal disturbance [3].

AIM OF THE WORK

The aim of this study is to compare the role of methergine, misoprostol and calcium in the management of atonic postpartum hemorrhage.

Methodology

All participants were subjected to the following:

A) Detailed medical history including:

- Personal history.
- Menstrual history.
- Past and obstetric history (parity, methods of previous deliveries, gestational age of previous miscarriage)

B) Physical examination:

After history taking and fulfilling both inclusion and exclusion criteria, clinical examination was done including: general abdominal and pelvic examination.

C) Ultrasound examination:

To ensure date of pregnancy, viability and any abnormalities.

D) Laboratory investigations:

- Before intervention: Routine investigations including: kidney function, liver function, fasting and postprandial blood sugar and complete blood picture.
- After intervention: Hb% estimation.

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E) All patients were given 5 IU syntocinone in the third stage of labor after normal delivery of the baby.

F) Intervention:

We give the first group of PPH methergine, the second group misoprostol and the third group calcium.

How to asses PPH:

1- Uterine tone has been assessed before drug administration; immediately after delivery of the placenta and then every 5 minutes.
2- Uterine tone has been rated according to the extent of indentation by finger pressure using a 5 point scale with 0 indicate soft boggy uterus and 4 indicate rock hard tetanic uterus.
3- Complete blood count has been done twice, just before and 24 hours after delivery.
4- Estimation of blood loss began after suction of amniotic fluid and discarding it.
5- After delivery of the placenta, the volume of blood loss was assessed by weight by subtracting the dry weight of absorbing materials (pads, sponges, etc) from the weight of blood-containing materials and using the conversion 1 gm weight = 1 ml to quantify the blood volume contained in the materials.

Sample size justifications:

The required sample size has been calculated using the IBM© Sample Power© Software (IBM© Corp., Armonk, NY, USA).

The primary outcome measure is PPH defined as blood loss ≥500 mL after normal delivery or a drop in maternal hemoglobin by 2g/dl or more lower than the prenatal Hb.

It is estimated that a sample size of 300 women with PPH would achieve a power of 98% (beta-error <0.02) with a confidence level of 99.9%.

Inclusion criteria included women who give written consent to participate in this study:

- Gestational age 37-41 weeks.
- Singleton pregnancy.
- Normal delivery route.

Exclusion criteria included women who refused to give written informed consent:

- Women who require general anesthesia.
- Women with any condition predisposing to uterine atony and postpartum hemorrhage, such as abnormal placentation, multiple gestation, preeclampsia, macrosomia, polyhydramnios, uterine fibroids, bleeding diathesis, chorioamnionitis, or a previous history of postpartum bleeding, emergency CS in labor, women on medications that could affect myometrium contractility, such as nifedipine, labetalol or magnesium sulphate.
- **The study was approved by the Ethics Board of Al-Azhar University.**

Data management and statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC using **the IBM© Sample Power© Software (IBM© Corp., Armonk, NY, USA).** Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

i. Descriptive statistics:

1. Mean, standard deviation (± SD) and range for parametric numerical data.
2. Frequency and percentage of non-numerical data**.**

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

ii. Analytical statistics:

1. **Student** *t* test was used to assess the statistical significance of the difference between three study group means.
2. **Chi-Square test** was used to examine the relationship between three qualitative variables

P value: level of significance:

- *P* >0.05: Not significant (NS).
- *P* < 0.05: Significant (S).

RESULTS

Table 1: Comparison between three groups as regard personal and medical data

		Group						P	Sig
		methergine		Misoprostol		calcium			
		Mean	±SD	Mean	±SD	Mean	±SD		
Age		29.25	2.84	28.75	1.94	28.75	2.90	0.782‡	NS
Parity	PG	35	35.0%	20	20.0%	30	30.0%	0.571*	NS
	P0-P2	40	40.0%	45	45.0%	55	55.0%		
	=>P3	25	25.0%	35	35.0%	15	15.0%		
Abortion	Yes	20	20.0%	15	15.0%	15	15.0%	1.0**	NS
	No	80	80.0%	85	85.0%	85	85.0%		

‡ANOVA, *Chi-square, **Fisher exact test

There was no significant difference between the three study groups as regard patients' age, parity or history of previous abortions. The mean age among methergine cases, misoprostol cases and calcium cases was 29.2 ±2.8, 28.8 ±1.9 years and 28.7±2.9 respectively.

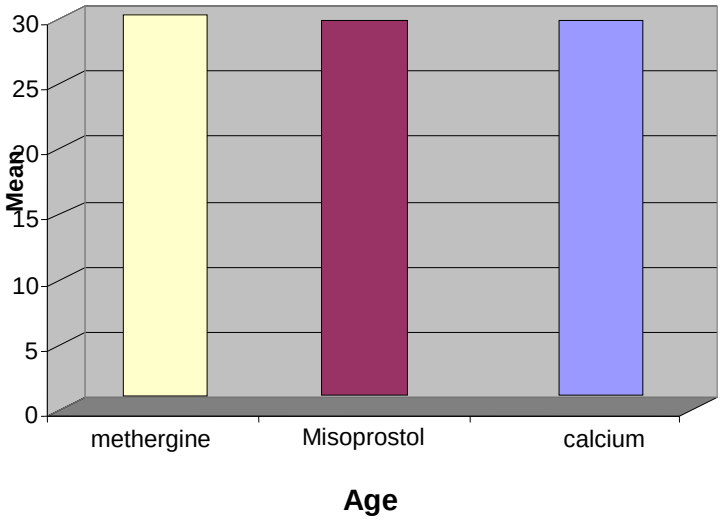


Table 2: Comparison between the three groups as regard hemoglobin level before and after treatment and its change

	Group						P*	Sig	Post hoc test
	methergine		Misoprostol		calcium				
	Mean	±SD	Mean	±SD	Mean	±SD			
Hb% before: (g/dL)	10.85	0.81	10.95	1.16	10.77	1.01	0.859*	NS	
Hb% 24Hrs after: (g/dL)	9.51	0.96	8.88	1.52	9.03	1.19	0.252*	NS	
Hb Change	1.34	0.54	2.07	0.80	1.74	.84	0.011*	S	Misoprostol Vs calcium[a] Misoprostol Vs methergine[b] calcium Vs methergine[a]

*ANOVA
a NS
b HS

There was no significant difference between three study groups as regard mean hemoglobin level before and after treatment. However, a significant difference was present as regard mean change (drop) in hemoglobin level after treatment with misoprostol showing the highest drop in Hb% (2.07 ±0.8) compared to calcium (1.7 ±0.8) and methergine (1.3 ±0.5). By using post hoc test, the significant difference was shown to be between misoprostol group and methergine group only.

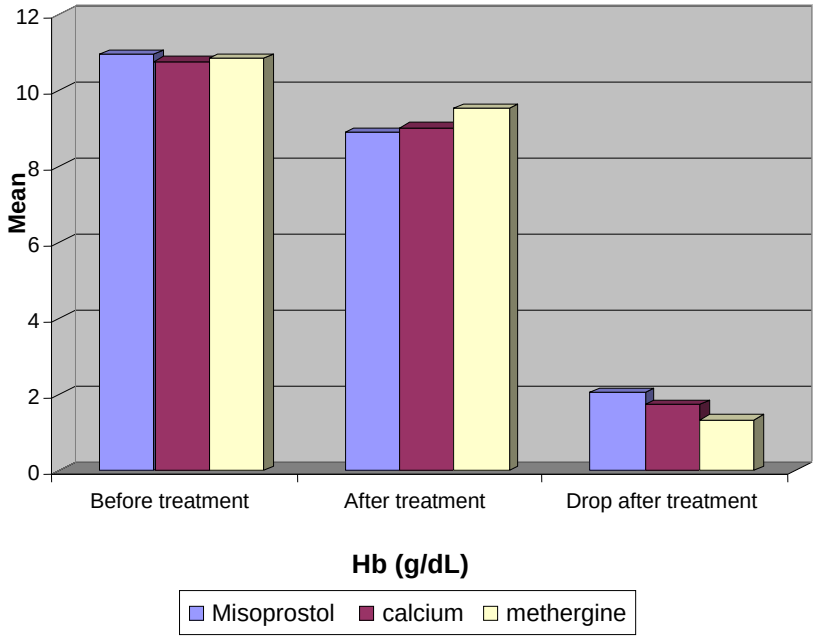
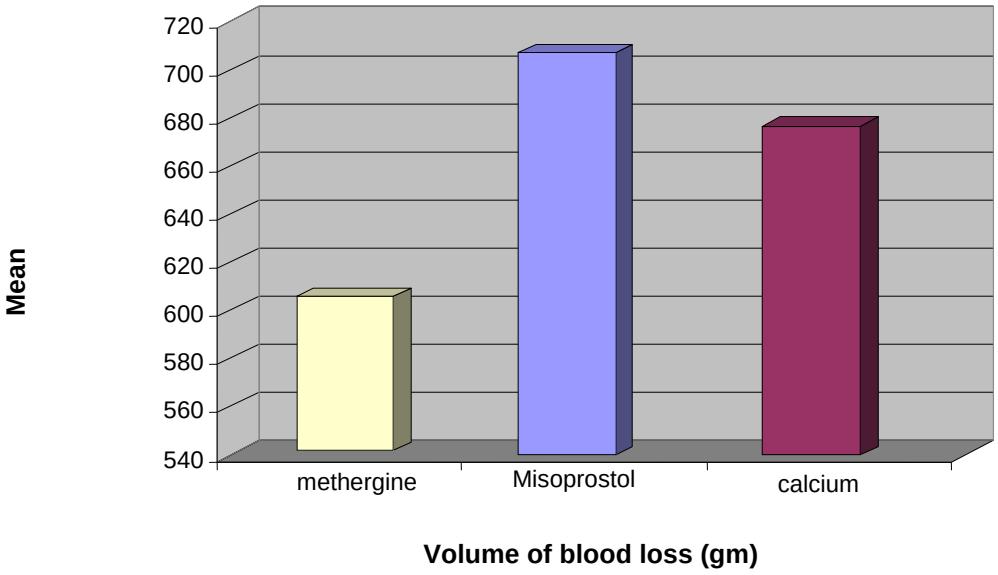


Table 3: Comparison between the three groups as regard volume of post partum blood loss, uterine tone before and after treatment

	Group						P	Sig	Post hoc test
	methergine		Mesoprestol		calcium				
	Mean	±SD	Mean	±SD	Mean	±SD			
Volume of blood loss	604	79.5	707.5	80.7	677	98.20	0.001*	HS	Misoprostol Vs calcium[a] Misoprostol Vs methergine[b] calcium Vs methergine[b]
Uterine tone before	1	0.0	1.0	0.0	1	0.00	---	---	
Uterine tone after	4	0.0	2.5	0.51	2.7	0.47	0.001*	HS	Misoprostol Vs calcium[a] Misoprostol Vs methergine[b] calcium Vs methergine[b]

*ANOVA
a NS
b HS

There was a highly significant difference between three study groups as regard mean volume of blood loss and mean uterine tone after treatment. Methergine group showed the lowest volume of blood loss (604 ±79.5) compared to calcium (677 ±98.2) and misoprostol (707.5 ±89.7). By using post hoc test, the significant difference was shown to be between methergine and misoprostol groups, and between methergine and calcium group. As regard uterine tone after treatment, methergine group showed the highest tone compared to calcium and misoprostol groups. By using post hoc test, the significant difference was shown to be between methergine and misoprostol groups, and between methergine and calcium group.



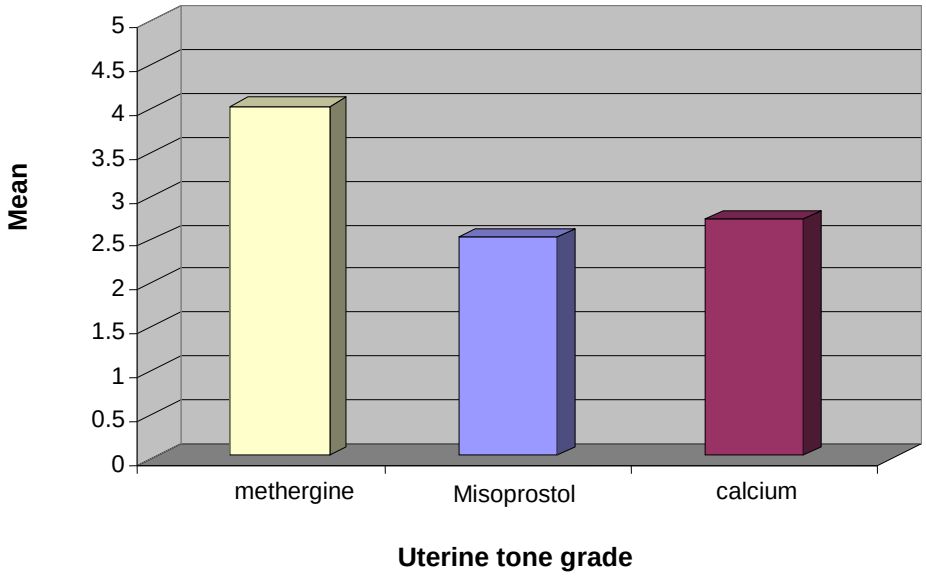


Table 4: Comparison between the three groups as regard need for additional uterotonics or need for blood transfusion.

		Group						P	Sig
		methergine		Misoprostol		calcium			
		N	%	N	%	N	%		
Need for additional uterotonics	No	100	100.0%	70	70.0%	70	70.0%	0.015	S
	Yes	0	0%	30	30.0%	30	30.0%		
Need for blood transfusion	No	100	100.0%	100	100.0%	100	100.0%	??	NS
	Yes	0	0%	0	0%	0	0%		

*Fisher exact test

There was significant difference between three study groups as regard the need for additional uterotonics, but no significant difference was found between the three study groups as regard the need for blood transfusion.

In case of failure of these drugs to treat PPH we can shift to medical agents like carbetocin and carboprost or surgical methods as laparotomy with Uterine artery ligation, Ovarian artery ligation ,Internal iliac (hypogastric) artery ligation ,Hysterectomy ,Selective arterial embolization, B-Lynch and Cho sutures.

-we use 2-4 packed RBCs with one unit of fresh frozen plasma in average.

DISCUSSION

Postpartum hemorrhage is a potentially life thereatening complication of both vaginal and cesarean delivery, the prevalence of PPH is approximately 6% of all deliveries **[4].**

The most frequent cause of PPH is uterine atony, therefore active management of the third stage of labor rather than expectant management is recommended **[5].**

During the second half of the 20th century, a package of interventions performed during the third stage of labor become the cornerstone for the prevention of PPH. This approach become known as the "active management of the third stage of labor" and consisted initially of the following components: the administration of a prophylactic uterotonic after delivery of a baby, early cord clamping and cutting and the controlled traction of the umbilical cord. Uterine massage is also frequently included as a part of the active management of the third stage of labor **[6].**

In our study the aim is to compare between the effect of methergine , calcium and misoprostol on decreasing blood loss for high-risk parturient.

The study included 300 women and the following was done:

Group 1 (100 cases) received 0.2 mg /1 ml methergine IV slowly .

Group 2 (100 cases) received calcium gluconate 100 mg/mL injection slowly IV single ampules.

Group 3 (100 cases) received 400 ug misoprostol (rectal) .

The results showed a significant difference as regard mean change in Hb level after treatment with misoprostol showing the highest drop: Hb (2.07 ±0.8) compared to calcium (1.7 ±0.8) and methergine (1.3 ±0.5). By using post hoc test, the significant difference was shown to be between misoprostol group and methergine group only.

In a study done by **Attilakos *et al.*** [2], comparing methergine and calcium: there was no significant difference in the mean hemoglobin fall after the delivery. This is in agreement with our study.

Another study done by **Fazel *et al.*** [9] comparing rectal misoprostol to IV calcium, the decrease in Hb level in the two groups wasn't statistically significant (P = 0.55). This is in agreement with our study.

As regard volume of blood loss, in our study there was highly significant difference between the 3 groups as regard mean volume of blood loss.

Methergine showed the lowest volume of blood loss (604 ±79.5) compared to calcium (677 ±98.2) and misoprostol (707.5 ±89.7). By using post hoc test, the significant difference was shown to be between methergine and misoprostol groups and between methergine and calcium groups.

In a study done by **Chong *et al.*** [6] comparing methergine and calcium, the mean blood loss was observed to be greater in the calcium group compared to the methergine group but the difference wasn't statistically significant. This disagrees with our study.

In another study done by **Larciprete *et al.*** [10] comparing methergine and calcium, there was no significant difference in the amount of estimated blood loss between the 2 groups. This disagrees with our study. In the study done by Larciprete et al., (2013): blood loss was estimated by the surgeon in the usual way (visual estimation, number of the used swabs and amount of aspirated blood) and this could be the cause of difference in results between their study and our study.

In the study done by **Fazel *et al.*** [9] comparing rectal misoprostol to IV calcium, there was no difference in the amount of blood loss between the two groups. This disagrees with our study.

Duthie *et al.* [8] studied intraoperative blood loss during elective lower segment Cesarean section by using alkaline hematin method in forty women with singleton pregnancies delivered under general anethesia with mean birth weight 3177 gm.

In the study done by **Larciprete *et al.*** [10] comparing methergine and calcium: there was

significant difference in the uterine tone and in the fundal height. The uterine contractility was better in methergine group at 2.12 and 24 hours after delivery and the difference was statistically significant at 24 hours (P <0.05). This is in agreement with our study.

Concerning the need for additional uterotonics: In our study, there was significant difference between the three study groups as regard need for additional uterotonics. The results demonstrated an increased use of additional oxytocin (20 IU) in the calcium group (30% of cases) and in the mesoprostol group (30% of cases) VS (0% of cases) in methergine group.

In the study done by **Larciprete *et al*.**[10], the main result of the study is that methergine is associated with reduced use of additional oxytocics. This is in agreement with our study.

All the previous studies of methergine [7,4] demonstrated a lower rate of additional oxytocin usage, but no study has demonstrated a significant difference in the rate of PPH, which is arguably a more important outcome. The reason for this is that only a very large study with many thousands of women would have adequate power to demonstrate a significant difference in this relatively rare outcome. Perhaps large retrospective studies from countries or institutions where methergine is used routinely may provide interesting data, although such studies would be prone to bias.

Nevertheless, the lower use of additional oxytocics is an important outcome with possible financial savings if the additional oxytocics require prolonged administration in the labor ward or in the recovery area. However, this may be offset by the higher cost of methergine in comparison to oxytocin. The UK cost of a methergine ampoule is GBP 17.64 (although a reduced price may be available), whereas the cost of a 10 IU ampoule of oxytocin is LE 0.86 [2].

CONCLUSION

According to the results of this study, it's found that there's good overall agreement that methergine is more effective in controlling the amount of blood loss during delivery and giving a better chance in prevention of atonic postpartum hemorrhage. Although of that calcium is good alternative to methergine with low side effects so can be used safely and effectively when methergine is contriandicated.

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