Different Doses of Sublingual Misoprostol versus Methylergometrine for the Prevention of Atonic Postpartum Haemorrhage.

Soltan, M.H., El-Gendi, E., Imam, H. H. and Fathi, O
Department of Obstetrics and Gynaecology, El-Menia Faculty of Medicine, El-Menia University, Egypt.

Abstract:

Objective: In the poor underdeveloped countries, anaemia is very common in pregnant women. Maternal mortality is four times higher in severely anaemic women than non-anaemic ones and postpartum haemorrhage (PPH) is the most common cause of death. Its main cause is uterine atony, which accounts for more than 70%**.** The objective of this study is to evaluate the use of sublingual misoprostol in different doses of 600, 800 and1000µg in management of the third stage of labor, with regards to blood loss and incidence of atonic postpartum haemorrhag (APPH).

Study Design: Double blind randomized controlled study

Methods : One thousand and two hundred parturient were studied in a control and three study groups, each composed of 300 women. Methylergometrine 0.2 mg IM injection and sublingual misoprostol 600, 800 and 1000 µg tablets were given to women in control and the three study groups respectively, immediately after delivery.
Outcome Measures:
Duration of the third stage of labour, Blood loss in the third stage of labour, Outcomes in anaemic compared to non-anaemic women , Incidance of atonic postpartum haemorrhage in different groups,
Haemoglobin deficit after 24 hrs of delivery, Changes in the women's blood pressure during the study,
Side effects of the drug, and, Women's acceptability of sublingual misoprostol administration.

Results : Only significant reduction in blood loss and haemoglobin deficits were seen in the third stage of labour and after delivery in women used misoprostol doses of 800 µg and 1000 µg. The incidences of PPH in studied women and controls were almost similar, ranging between 2 and 3%. Similar results were seen in anaemic and non-anaemic women with a higher incidence of APPH in the non-misoprostol user anaemic women. Side effects of the drug were dose related.

Conclusion : Misoprostol in high dose may be used for managing third stage of labour to reduce maternal morbidity and mortality due to APPH particularly, in the poor underdeveloped countries where, facilities to deliver in health centers, purchase and store the oxytocic ampoules or medically trained persons are not readily available in all places. Benefits of large dose misoprostol outweigh its side effects.

Corrospondance :
Prof. Mohamed H. Soltan
Director General
Suzan Mubarak Maternity University Hospital
El-menia, Egypt
email: mohamedsoltan552@hotmail.com

Introduction

In the poor underdeveloped countries, anaemia is very common in pregnant women. [1] Maternal mortality is four times higher in severely anaemic women than non-anaemic ones [2] and postpartum haemorrhage (PPH) is the most common cause of death. [3] Its main cause is uterine atony, which accounts for more than 70%. [4] Active management of the third stage of labor is recommended for all parturient women. It is the most effective mean of preventing atonic postpartum hemorrhage (APPH). It reduces more than 50% of the PPH risk, and routine prophylaxis reduces 70% of the need for therapeutic oxitocics to treat excessive postpartum bleeding. [5]

Several drugs reduce PPH by stimulating the uterus to contract. Ergot derivatives have been used for decades, although oxytocin is the drug of choice in some centers, methylergometrine is still been used in some places. Several prostaglandins are used as second or third line agents. These drugs, however, must be refrigerated to remain effective. Moreover, most uterotonics must be administered by injection, which requires sterile equipment and training in safe administration, prerequisites which are unavailable for most women delivering in poor undeveloped countries. [6]

Misoprostol, a prostaglandin E1 analogue, is heat stable and can be administered orally, rectally, or sublingually. A multicentre study found that misoprostol was less effective for prophylaxis than intravenous or intramuscular injections of oxytocin but did not investigate the possible benefit of misoprostol to the large number of women who give birth outside health facilities. [7] Distribution of misoprostol in Indonesia in certain areas reduced the frequency of excessive bleeding and the need for emergency referral to hospitals for PPH compared with the data from a control area where misoprostol was not available. [8]

Most of the randomized studies of prophylactic misoprostol have used oral and rectal administration, though a recent pharmacokinetic study showed that sublingual administration secures the highest peak concentration and the best bioavailability. [9] A recent pilot study found that sublingual misoprostol and intravenous syntometrine have comparable effects on blood loss in the third stage of labour. [10] All studies tried misoprostol doses from 200 to 600 µg and the reported results were either less effective or similar to the results of standard oxytocics in reducing third stage blood loss and PPH incidences. Therefore, it was necessary to study higher doses of misoprostol and to compare them with the oxytocic drug that still been used in some poor undeveloped countries, methylergometrine. [11]

The aim of the study was to evaluate the efficacy and safety of various doses of sublingual misoprostol 600, 800 and 1000 µg and compare them to methylergometrine for management of the third stage of labor, with special emphasis on PPH prevention.

Methods

A prospective randomized controlled study was carried out on 1200 parturient delivered in Mallawy general hospital, El-Menia, Egypt, in the period from April 2002 to Feb. 2003. The study was approved by the ethical committee of the faculty of medicine, El-Menia University, Egypt. The husband's of all women signed an informed consent before admission of their wives into the study.

Inclusion criteria were

Full term single living fetus, no medical disorders associated with pregnancy, spontaneous and instrumental vaginal deliveries with or without episiotomy.

Exclusion criteria were

Traumatic postpartum haemorrage, Cesarean section delivery, blood diseases, women with chorioamnionities, placenta previa and abruptio placenta.

Multiple gestation and previous history of PPH were not excluded.

Cases and controls were subjected to thorough history taking, physical examination and routine investigations such as complete blood count and abdominal ultrasound examination.

Randomization and allocation of women to study groups and controls were done through a computer generation; the study officer handled out an opaque closed envelope containing the orders to manage the women according to planned protocol.

Each of control and the three study groups was composed of 300 women. The women in control group were given 0.2 mg IM methylergometrine, which has been used routinely in the hospital as part of active management of the

third stage of labour. While women in the study groups I, II, III were given 600, 800 and 1000 µg of sublingual misoprostol respectively. The above medications were given to the mothers immediately after delivery of the baby.

The outcome measures in the study were

- Duration of the third stage.
- Estimation of blood loss, collected by graduated plastic bag [7], as well as weighing the towels, linens, and gauzes.
- Incidence of PPH in different groups.
- Effect of misoprostol on the women's blood pressure.
- Haemoglobin deficit after 24 hrs of delivery.
- Outcome in anaemic compared to non-anaemic women.
- Side effects of misoprostol
- Acceptability of the drug sublingually by the women.

Placentas were delivered by Brandt's Andrew technique. Retained placentas for more than 30 minutes were removed manually under general anesthesia. Excess bleeding before and after placental expulsions was evaluated and treated according to WHO recommendation [8]. Blood samples were taken on admission and after 24 hours of delivery for haemoglobin estimation. Side effects observed or complained of by studied women and controls were reported to the nurses and recorded. Women in the study were asked, if they had any difficulties or problems tolerating the drug with the sublingual route.

Calculation and analysis

The average blood loss in the third stage of labour is 250-350 ml, and 12% of women will loose > 500 ml [10]. Use of uterotonics should reduce this proportion to 5 %. [10]. According to our calculations we needed 300 women in each group to have a power of 80% (1 - β) with a risk of type 2 error (α) of 5%.

Data were collected and analyzed using SPSS program version 11 for windows using relative risk (RR), t and chi square tests for statistical significance.

Results

One hundred and forty four women were excluded from analysis because they were exposed to trauma to the perineum, vagina or cervix during labour and had traumatic excessive bleeding. Blood loss in these women hardly exceeded 500 ml and treated by dealing with the cause. Table (1) shows that the age and parity of women in studied and control groups are not statistically significantly different. There was no significant difference among study groups and controls with regards to women with previous history of PPH, Chi square P = 0.09.

The duration of the third stage of labour was not significantly different in studied women compared to control group (Table 2), there were five cases of retained placenta required manual removal under general anesthesia. These cases were distributed as follow: one in control group, one in studied group I (RR 0.9), one in studied group II (RR 0.98) and two cases were in study group III (RR 2.05).

Table (1). Comparison of age and parity between studied groups and controls.

GROUPS	AGE Mean ±SD	T	P	Parity Mean ±SD	T	P
Controls	25±5.9	-	-	1.7±1.9	-	-
group I	26±6.4	1.64	0.1	1.7±1.76	0.29	0.77
Group II	26.4±5.9	1.29	0.197	1.7±1.78	0.07	0.94
Group II	26±5.6	0.521	0.603	1.8±2.02	0.66	0.504

Table (2). Comparison between the duration of the third stage in minutes in the four groups.

Groups	Mean ± SD	T	P
Controls	8.6±3.1	-	-
Group I	8.3±3.3	1.3	0.19
Group II	8.5±3.36	0,302	0.76
Group III	8.4±3.16	0.68	0.32

Table (3) shows that third stage blood loss in women of study group I is not statistically different from women in control group, while, blood loss in women of studied groups II and III are significantly reduced in comparison to women of the control group. Cases of atonic PPH in the whole study were 29, an incidence of 2.7%, they were distributed as follow: seven cases in control group, in one case, the PPH was severe with blood loss exceeding 1000 ml and the women had blood transfusion. The other six cases had average blood loss between 500 – 1000 ml. In studied group I, there were seven cases, their blood losses were average amount between 500 – 1000 ml.

In studied group II there were nine cases of APPH; in one case the PPH was severe and intractable required total abdominal hysterectomy. She received 3000 ml of blood transfusion, and the remaining eight cases had an average blood loss. In group III, APPH occurred in six cases with average blood loss, without need for blood transfusion. Extra oxytocic drugs particularly, intravenous oxytocin infusion was used in all 29 cases developed APPH.

Table (4), shows the haemoglobin deficit between the admission and the 24 hrs post-delivery levels. It can be seen that there are no significant differences between studied group I and control group; however, this deficit is statistically significantly reduced when studied groups II, III are compared with controls.

Table (3). comparison between amounts of blood loss in ml among the four groups.

Groups	Mean ± SD	T	P
Controls	149.3±104	-	-
Group I	143±111.1	0.66	0.508
Group II	131.2±92	2.11	0.03
Group III	128±67	2.7	0.006

Table (4). Comparison between haemoglobin deficit in g/dL among the four groups.

Groups	Hb deficit Mean ± SD	T	P
Controls	O.46±0.4	-	-
Group I	0.4±0.42	1.8	0.06
Group II	0.38±0.4	2.2	0.02
Group III	0.3±0.4	2.3	0.01

Table (5), shows the third stage outcome in anaemic and non-anaemic subgroups. The incidence of anaemia (haemoglobin less than 10.5 g/ ml) in the studied population was 28.5%. It can bee seen from this table that the third stage blood loss is non-significantly higher in the anaemic than the non-anaemic women. The incidence of APPH in control group (misoprostol non-user) is higher in anaemic than non-anaemic women (4.5% Vs 2%), while these incidences are similar in the three studied groups.

Table (6), shows the side effects of both methylergometrine and misoprostol used in the study. It can be seen that the differences between side effects in studied women and controls is highly statistically significant and they are dose related. The incidence of shivering in the 600µg, 800µg, 1000µg and control groups are29%, 33% 35% and 10.6% respectively. Similarly, fever incidences follow the same pattern, it is 8%, 9.6%, 13.6 and 2% respectively. None of the studied women complained of headache or chest pain.

Table (5). The outcome in anemic and non-anemic women of the study. G=group ,M=mean,* Chi 2 =6.3 P=0.09.

Anemic status	Controls N=266	Study G (I) N=271	Study G(II) N=269	Study G (III) N=278
Anemic:				
Number	66 (24.8%)	75 (27.6%)	82 (30.4%)	97 (30.3%0
M. blood loss	152.5±97.2	154.9±99.3	149.5±101.3	158.5±100.5*
PPH cases	3 (4.5%)	2 (2.6%)	3 (3.6%)	2 (2.5%)
Non-anemic:				
Number	200(75.2%)	196(72.4%)	187 (69.6%)	181 (69.7%)
M. blood loss	139.6±105	122.7±102.1	123.6±150	119.4±102.1
PPH cases	4 (2%)	5 (2.5%)	6 (3.5%)	4 (2.5%)

Table (6). Side effects of sublingual misoprostol among study groups and control. *Chi 2= 63.1, P=0.0001, G=group.

Side effect	Control G.	Study G.(I)	Study G. (II)	Study G.(III)
Shivering	32 (12.1%)	88 (32.5%) RR= 3.57	100 (37.1%) RR= 4.3	121 (46.5%)* RR= 6.3
Fever	6 (2.3%)	25 (9.2%) RR= 4.4	29 (10.7%) RR= 5.2	41 (15.7%)* RR= 8.1
Vomiting	12(4.6%)	10 (3.6%)	21 (7.8%)	41 (15.7%)*
Diarrhea	4 (1.5%)	2 (0.8%)	5 (1.9%)	3 (1.2%)*

Table (7) shows statistically significant drop in systolic and diastolic blood pressure in the studied group III in comparison to control group, while the other two studied groups do not show such change. This drop in blood pressure was commonly associated with shivering and fever and did not require treatment.

Twenty eight women (4.6%) in studied groups II and III (11 {3.6%} in group II and 17 {5.6%} in group III) reported unpleasant sensation of having too many tablets under the tongue, this had made them nauseated and sometime they swallowed some particles of the tablets, however, none of these women spitted the tablets out of their mouth nor requested discontinuation of the trial.

Discussion

Reduction of postpartum blood loss at primary care level, in rural areas and first line health care units has been thought of for decades. Because the misoprostol drug is cheap, stable at room temperature, rapidly absorbed after oral, rectal and sublingual routes; and has strong uterotonic effect, it was thought to be ideal for this purpose especially in poor underdeveloped countries.

Multiple controlled trials investigating misoprostol as a prophylactic agent to prevent postpartum bleeding have been reported [14 – 20]. A systematic review of randomized controlled trials of oral or rectal misoprostol to prevent postpartum hemorrhage concluded that the traditional injectable preparations were more effective than misoprostol as part of active management of the third stage of labor. [21] The results of this study showed that sublingual misoprostol in a dose of 600 µg was as good as methylergometrine and higher doses (800 and 1000 µg) were significantly better than the injectable methylergometrine in reducing third stage blood loss and haemoglobin deficit. Therefore, it is possible that the effect of misoprostol is a dose related one.

High doses of misoprostol have been used to treat the established postpartum haemorrhage without serious side effects. [12, 16] As well as the reported results of using low or average doses of misoprostol, which produced an effect either less or similar in reducing third stage blood loss and PPH incidence compared to injectable oxytocics, this has encouraged us to take the initiative to try high doses of misoprostol for management of the third stage of labour. [22]

The results of this study show that third stage blood loss, haemoglobin deficit were significantly reduced in women used high doses of misoprostol. This has not been reported with 600µg or less neither in this study nore in previous other studies. [22] The PPH incidence in our study population is 2.7% which is remarkably less than the reported incidences in general obstetric population 5 – 15% [23], therefore, the sublingual route of high dose misoprostol may have more potential for both prophylactic and active postpartum hemorrhage treatment.

Anaemia is prevalent in pregnant women worldwide, particularly, in the poor underdeveloped countries; it was interesting to look at the performance of anaemic women receiving misoprostol in the study. It is not surprising to see that there was no significant difference between anaemic and non-anaemic women with regards to third stage blood loss, as misoprostol acts to stimulate uterine muscle contractions after reaching its peak concentration. However, the incidence of APPH in anaemic control group (women not using misoprostol) in this study was higher than non-anaemic women, which suggests that misoprostol may have a protective effect against APPH in third stage in anaemic pregnant women.

Table (7). Comparison of the changes in mean blood pressure in mmHg among the four groups.

Groups	Mean change in systolic BP	T	P	Mean change in diastolic BP	T	P
Controls	1.4±6.5	-	-	0.67±9.2	-	-
Group I	0.8±8.4	0.53	.53	0.2±9.5	0.88	0.3
Group II	0.69±9.2	1.02	0.3	0.32±6.2	1.2	0.2
Group III	0.67±9.2	2.3	0.01	0.67±7.4	3.4	0.001

Duration of the third stage of labour was not statistically different between study and control groups. This is in agreement with results of all previous misoprostol studies. Because the cease of bleeding in uncomplicated third stage of labour normally occurs within 10 min after delivery, and the peak concentration of sublingual misoprostol is usually reached after 26 min [9] , Therefore one would not expect that the drug effect the third stage duration. [24]

It is difficult to explain the drop in blood pressure that occurred in the 1000µg group, especially, the majority of these women had simultaneous shivering and fever. However, the blood pressure of these women had returned to normal within short time without treatment.

Adverse effects of misoprostol are dose related this fact has been supported by the results of our study. Lumbiganon et al [25] reported that of 843 women treated with 600 µg of oral misoprostol, 13% had shivering within 1 hour of delivery and more than 11% had pyrexia between 2 and 6 hours postpartum. Another study investigating 600 µg of oral misoprostol given in the third stage of labor reported an incidence of shivering of 22%. [17] A more recent study reported the incidence of shivering and fever decreased to 11% and 4%, respectively with 400 µg of misoprostol given orally at cord clamping. [26] One small study evaluating 70 women who received either 400 µg or 200 µg of rectal misoprostol in the postpartum period reported an overall incidence of shivering in 7%, but whether the patient received 400 or 200 µg was not clearly noted. [27] The incidences of shivering and fever reported in our study are higher than other studies. However, these adverse effects of misoprostol were of temporary nature lasting only for short time, they neither cause serious or permanent damage nor require a specific treatment; therefore, the mother should be informed that she would expect a temporarily shivering and fever after delivery. And higher doses of misoprostol should not be dismissed from the routine evaluation to prevent PPH.

The problem of unpleasant feeling of having too many tablets under the tongue, observed in our study may be overcome by manufacturing the 800 and 1000µg in a single tablet for comfortable easy use.

Conclusion

The benefits of using large dose misoprostol to prevent maternal morbidity and mortality due to APPH outweigh the temporary side effects, especially in the poor underdeveloped countries, where giving birth in health facilities is not available at all places for more than half of obstetric population.

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