Original Paper

Comparison of Oral Misoprostol with Conventional Uterotonics in the Management of Third Stage of Labor

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Abstract

Background: Randomized prospective control study it is objective to compare effect of oral misoprostol with conventional uterotonics in the management of the third stage of labor.
Aim of study: The incidence of Hemorrhage and the decrease in hemoglobin concentration is the main out comes of the trial. Secondary outcomes included the occurrences of sever postpartum hemorrhage.
Patient and method: This study was done in Department of obstetrics and gynecology at Baghdad Teaching Hospital. In controlled trials a pregnant women total number 280 were randomized into four groups, as followed: Group I: received oral misoprostol 400 Mg, followed by two doses of oral misoprostol 100 Mg 4hours a part. (n=72), group 2: received intravenous infusion of oxytocin10 IU plus oral misoprostol 400 Mg followed by two doses of 100Mg oral misoprostol 4 hours apart group 3: received intravenous infusion of oxytocin 10 IU. (n=69), group 4: received intravenous infusion of 10 IU oxytocin plus intramuscular administration of methylergometrine (methergine) 0.2 mg. (n=77). The data of 40 women were excluded from the study because of loss to follow up, previous cesarean deliveries performed after randomization n=25, pre delivery hemoglobin was unavailable n= 10, postpartum percentage of hematocrit unavailable n=5. Main measures, the incidences of postpartum hemorrhage and the changes in hematocrit concentration from before delivery to 24 hours postpartum, in those women used oral misoprostol in management of third stage of labor with or without the use of other uterotonics
Result: Shows, Mean blood loss in misoprostol group was not significantly higher than blood loss in oxytocin group and oxytocin misoprostol group, but there was statistically significant difference when compared with oxytocin-methylergometrine group.
Conclusion: Oral administrated misoprostol is as effective as conventional oxytocic in prevention of postpartum hemorrhage.

Keywords: Misoprostol, uterotonics, postpartum hemorrhage, labor

Introduction

The third stage of labor carries the highest risk of mortality and morbidity for the mother because of the potential postpartum hemorrhage (PPH), which account for about one quarter of maternal death worldwide. [(1)]Hemorrhage requires prompt treatment in order to avoid blood transfusion and for major surgical intervention. Post-partum hemorrhage was defined as measured blood loss of 500ml or more, whereas sever postpartum hemorrhage was defined as measured of blood loss of 1000ml or more [(2)].

Misoprostol is a synthetic analogue of prostaglandin El used for reducing the incidence of postpartum hemorrhage so reducing maternal mortality which is an essential health objective in many of the developing worlds.[(3)]

The prostaglandins were first used clinically by intravenous infusion to induce labor in 1968 [(4)] and to induce

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abortion in 1970 [7,8,23]. As it became apparent that I.V administration in high concentration needed for abortion caused unpleasant side effects (notably vomiting and diarrhea), this route had been largely superseded with varying degree of success by alternatives including oral. Intrauterine (extra amniotic or intra-amniotic) and vaginal administration. [5,6]

In 1988, the US food and drug administration approved misoprostol under brand name cytotec for prevention of gastric ulcer among long term users of non-steroidal anti-innarnmatory drug .[7,8]

In July 2003, Gynuity Health project and family care international launched an initiative to evaluate misoprostol as altemative therapy tor postpartum hemorrhage prevention and bringing misoprostol to market; assist in registering the drug for these indications.[9]

Patients and Methods

This study was conducted as prospective, controlled trial carried out between 1st of March to 31st of December 2006 in the matemity unit and department of obstetrics and gynecology of Baghdad Teaching Hospital. The study involves320 pregnant women those women either attended the hospital directly or they were referred from antenatal care centers, primary health centers and private clinics.

Forty women were excluded from the study because of loss to follow up. A random allocation was generated without any blocking or stratification.

A total Of 280 women were eligible. Immediately after cord clamping, they received one or the following four treatments.

l- Two tablets of oral misoprostol (400Mg) ,cytotec (Ali Raif co., Turkey) followed by two doses of misoprostol 100 Mg (half tablet) orally at 4 and 8 hours postpartum (misoprostol group n=72

2-Intravenous infusion of oxytocin 10 IU in 500 ml saline over 30 minutes (oxytocin group).n=69

3-Intravenous infusion of oxytocin 10 IU in 500mL saline over 30 minutes and two tablets oral misoprcystol (400Mg) cytotec, followed by two doses of misoprostol 100 Mg (half tablet) orally at 4 and 8 hours postpartum (misoprostol -oxytocin group) .n=62

4-Intravenous infusion of oxytocin 10 1.U in 500) ml saline over 30 minute and dose of intramuscular 0.2mg methylergometrine maleate (oxytocin methylergometrine maleate group). "n=77

If oxytocin was during labor, we were stopped at the end of the second stage, to compare the effect of misoprostol alone with or without use of others utertonics drugs. The management of third stage of labor includes active management. If the placenta was not delivered within 30 minutes of delivery, it was removed manually under general anesthesia. If bleeding despite oxytocin infusion or if atonic uterus was palpated, an additional dose of intramuscular methylergometrine maleate 0.2mg was given. Blood transfusion were performed to women whenever the blood loss more than 500 ml and low hemoglobin.

The data contained information was matched in characteristics, such as age, parity, body mass index, gestational age at delivery, and obstetric history.

Throughout the study period. Frequency Of postpartum blood transfusion, need for additional oxytocic length of third Stage or labor. Manual removal of placenta, and subsequent evacuation of the uterus were also recorded.

All patients were evaluated, and specific side effect with oral misoprostol was sought. A blood sample was obtained before delivery' for determination percentage of hematocrit. A second blood sample for estimation percentage of hematocrit was obtained 24 hours postpartum.

Statistical analysis

Statistical analysis of the data was performed using the statistical package for social sciences for window SPSS Inc.

Results was reported as mean ±2 standard deviation and percentages .Difference between the groups were assessed used X^2 test or fisher exact test for categorical data whenever appropriate. P>0.01 was statistically significant.

Results

Total number including in study was 280 women were eligible and randomized to one of four study groups
0xytocin group n=69. Misoprostol-oxytocin group=62, misoprostol group n=72, oxytocin - methylergometrine maleate group=77

There was obvious in table.1 that largest percentage of primigravida was located in oxytocin-methylergometrine group 55(71.42) as compared with 47(65.27), 45(65.21), 41(66.12) in misoprostl group, oxytocin group, oxytocin-misoprostol group respectively, While the largest percentage of multipara was situated in misoprostol group 25(34.72) compared with 24(34.78), 21(33.87), 22(28.75) in oxytocin group. Misoprostol- oxytocin group, oxytocin-methylergometrine group respectively. Although there was difference in percentages among the studies group, but these differences was not significant statistically. (P< 0.01 x^2 test)
As shown in table.2, the largest percentage of multifetal in oxytocin group2 (2.89%) as compared with 0 (0%), 1(1.61%), 1(1.29%) in misoprostol, oxytocin-misoprostol, oxytocin-methylergometrine groups respectively. The hydrarnnios was similar among groups.
The largest percentage of preterm deliveries ≤34 weeks was found in oxytocin -methylergometrine group 8 (10.38%) compared with (6.94%) 4(5.79%), in misoprostol, oxytocin, misoprostol oxytocin group respectively. The percentage of IUD is similar in both misoprostol and groups respectively, but less than 2 (3.22%).
Misoprostol-oxytocin and oxytocin methy lergometrine group respectively. The largest percentage of birth weight>4000gm was shown in misoprostol oxytocin group as compared with in misoprostol, oxytocin - methylergometrine group respectively. Although there is different in the percentage of variables but there were no statistical significant difference among studied druys (p<0.01) test.

Table.3 shows that there were significant differences among groups in terms of predelivery and post-delivery hematocrit (%). When compared misoprostol group in terms of pre-delivery hematocrit with oxytocin group, we shows that there were no statistical significant difference between them, but when we compared it with rest groups (misoprostol- oxytocin group and oxytocin- methylergometrine group) the result shows that the difference was statistically significant, that mean amount of blood loss was comparable in misoprostol, oxytoein groups fisher test. The table.3 also shows that there were no significant difference among the groups in percentage of anemia, and anti- partum blood transfusion. p<0.01

Although the table.4 shows the number of women with blood loss ≥500ml was more in the misoprostol group 6(8.33) when compared with oxytocin misoprostol-oxytocin and oxytocin methylergometrine groups 5(7.24) 1(1.29) respectively, but statistically does not shows significant difference. There were more drops in hematocrit in misoprostol group as comparable with oxytocin group, misoprostol-oxytocin group, but the difference was statistically not significant, but when compared with oxytocin methylergometrine group, there was statistical significant difference.

Table. 5 shows the incidence Of blood loss >1000m was greater in oxytocin group (5.79) as compared with other groups misoprostol, misoprostol- oxytocin, oxytocin- methylergometrine 83.129 respectively, but the result of sever blood loss was not statistically significant.

P<O.OI, x2 test. The table also shows that the mean blood loss (334±190) ml in misoprostol group was found to be greater than oxytocin group (289±202) ml, and misoprostol- oxytocin group (344±210) ml but statistically not significant, but when we compared with oxytocin methylergometrine maleate group (265±125) ml the difference was statistically significant. Also shown in the table.5 the need for additional oxytocin and methylergometrine was higher in misoprostol group as compared with oxytocin, oxytocin- misoprostol, misoprostol- methylergometrine groups but the difference was not reach statistically significant ,in general there were no significant difference were detected among the studies groups.

The mean length of third stage of labor was greater in misoprostol group (22.34±4.09), when compared with (16.59±1.39, 20.71 5.75, 13.70±2.55) in oxytocin, misoprostol-oxytocin, oxytocin and methylergometrine groups respectively, but the difference was not statistically significant.

As shown in table.6 the percentage of women with fever was higher in misoprostol group 5(6.94%) as compare with other groups which were not significant statistically. Gastrointestinal side effects also more in misoprostol group as compared with other groups These side effects include nausea which observed in in misoprostol group as compared with 2(2.89%), 4(6.45%), 3(3.89%) in oxytocin group, oxytocin misoprostol group, oxytocin -methylergometrine group respectively Vomiting reported in 6(8.33%) in misoprostol group as compared with 2(3.22%), in oxytocin group, misoprostol oxytocin group, oxytocin- methylergometrine group respectively.

There were more women experiencing shivering in misoprostol group 13(18%)when compared with other groups and the difference was Statistically significant, These gastrointestinal side effects shows no statistically significant difference among the groups -These side effects was mild and self-limiting some of them like fever relieve with simple analgesia like paracetomol.[10]

Table1. Characteristics of parity of women in 4 studies groups

	Misoprositol n=72	**Oxytocin n=69**	**Misoprositol Oxytocin n=62**	**Oxytocin-Methylergometrine n=77**
Primigravida	47(65.27)	45(65.21)	41(66.12)	55(71.42)
Multipara	25(34.72)	24(34.78)	21(33.87)	22(28.75)
Parity 1-4	21(29.16)	19(27.53)	17(27.41)	20(25.96)
Parity >4	4 (5.55)	4(7.24)	4 (6.45)	2 (2.59)

The data presented as n (%)

† No statistical significant differences among groups (p< 0.01), x^2 test.

Table 2. Intrapartium data of women in 4 studies groups.

	Misoprositol n=72	**Oxytocin n=69**	**Misoprositol-Oxytocin n=62**	**Oxytocin-Methylergometrine n=77**
Multifetal gestation†	0(0)	2(2.89)	1(1.61)	1(1.29)
Hydramnios†	1(1.38)	1(1.44)	1(1.61)	1(1.29)
Preterm delivery≤34weeks†	5(6.94)	4(5.79)	4(6.45)	8(10.38)
Intrauterine fetal demise (IUD)†	1(1.38)	1(1.44)	2(3.22)	1(1.29)
Birth weight >4.000 kg†	6(8.33)	4(5.79)	7(11.29)	6(7.79)

The data presented as n (%)

† No statistical significant differences among groups (p< 0.01), x^2 test

Table 3. Pre and post-delivery hematological variables of women in 4 studies groups

	Misoprositol n=72	**Oxytocin n=69**	**Misoprositol-Oxytocin n=62**	**Oxytocin-Methylergometrine n=77**
Pre-delivery hematocrit %*	32.0±2.4	32.0±2.7	33.0±2.0	33.0±2.7
Post-delivery hematocrit %*	31.0±2.6	31.6±2.7	32.2±2.8	32.3±2.8
Maternal anemia hemoglobin <10†	11(15.27)	11(15.94)	8(12.90)	13(16.88)
Ante partum blood transfusions†	1 (1.3)	1 (1.4)	0 (0)	0 (0)

Data presented as mean ± standard deviation or n (%)
* Statistical significant differences among groups (p> 0.05), analysis of variance Fisher test
† No statistical significant differences among groups (p< 0.01), x^2 test

Table 4. Primary outcome variable of women in 4 studies groups

	Misoprositol n=72	Oxytocin n=69	Misoprositol-Oxytocin n=62	Oxytocin-Methylergometrine n=77
Blood loss ≥ †500ml	6(8.33)	5(7.24)	2(3.2)	1(1.29)
Drop in hemoglobin gm/dl†	0.34±0.19	0.29±0.20	0.34±0.17	0.26±0.12
Drop in hematocrit(%)†	1.0±0.75	0.78±0.60	1.03±0.65	0.78±0.30

Data presented as mean± standard deviation or n(%)
† No statistical significant differences among groups (p< 0.01), x2 test

Table 5. Secondary outcomes variables of women in 4 studies groups

	Misoprositol n=72	Oxytocin n=69	Misoprositol-Oxytocin n=62	Oxytocin-Methylergometrine n=77
Blood loss ≥1000ml	4(5.55)	4(5.79)	3(4.83)	1(1.29)
Mean blood loss (ml)	333 ±190	289± 202	344 ± 177	265±125
Additional oxytocin†	4 (5.55)	3(4.34)	2(3.2)	0(0)
Additional methylergometrine maleate†	4 (5.55)	3 (4.34)	2 (3.2)	0(0)
Length of 3rd stage (min) †	22.34±4.09	16.59±1.39	20.71± 5.75	13.70± 2.55
3rd stage ≥ 30 min†	3 (4.16)	1(1.44)	2(3.2)	0(0)
Post partum blood transfusion†	2 (2.77)	2 (2.89)	1 (1.61)	0 (0)
Manual removal of placenta†	1(1.38)	1(1.44)	0(0)	1 (1.29)

The data presented as mean ±stander deviation, and n (%) p>0.01 .ANOVA , fisher test and x^2 test
† No statistical significant differences among groups (p< 0.01), x^2 test

Table 6. Side effects As a result Of treatment of women in 4 studies Groups

	Misoprositol n=72	Oxytocin n=69	Misoprositol-Oxytocin n=62	Oxytocin-Methylergometrine n=77
Shivering*	13 (18)	3 (4.34)	9 (14.5)	0 (0)
Body temperature ≥ 38C^O†	5 (6.94)	0 (0)	4 (6.45)	0 (0)
Nausea†	3(4.16)	2 (2.89)	4 (6.45)	3 (3.89)
Vomiting†	6(8.33)	0 (0)	2 (3.22)	3 (3.89)
Diarrhoea†	3(4.16)	0 (0)	3 (4.83)	0 (0)
Abdominal pain†	1 (1.38)	0 (0)	2 (3.22)	3 (3.89)

The data presented as n (%), p >0.01 ANOVA X^2 TEST
* Statistical significant differences among groups (p> 0.01),
† No statistical significant differences among groups (p< 0.01), x^2 test

Discussion

The leading cause of postpartum hemorrhage is uterine a tony[11]; most often preventable by conventional uterotonics, among which oxytocin is usually preferred'[12] However the use of oxytocin is not yet feasible in many of developing world where deliveries still take place in rural areas with birth attendants who do not practice active management or third stage of labor [13] .Also, injectable uterotonics, such as oxytocin are unstable in high temperature and require cold — chain storage[14]. Regarding the oral route administration, most women preferred to take the misoprostol tablets by mouth to avoid the uncomfortable vaginal or rectal examination and provide more privacy[2].

Our study shows that oral misoprostol is effective in similar way to oxytocin in reducing postpartum hemorrhage ;However, it is probably less effective than methylergometrine maleate-oxytocin in combination, this obvious by result of blood loss 500ml in misoprostol was 6(8.33) as compared with 5(7.24), 2(3.2), 1(1.29) in oxytocin , oxytoein — misoprostol, oxytocin methylergometrine (table,4) the table shows there was no statistical significant difference in amount of blood loss and drop of hemoglobin and hematoerit among the studied groups.

This result agrees with Chan ASM, NgPS *et al* (2001) who compared oral misoprostol and I.M syntometrine in the management of the third stage of labor. Who found that the amount of blood loss >500ml is 5.8% in misoprostol group and 4.3% in syntometrine group and blood loss>1000 is 0.5% in misoprostol group and 0.4% in syntometrine group. There was no statistical significant difference between them[15]'

The study that misoprostol may be used as alternative to I.M syntometrine in the management of third stage of labor, especially in situation in which syntometrine is contraindicated or where storage and parenteral administration of is potential problem[15].

The study also agrees with Walley RL *et al*., [16]" who compared oral misoprostol with oxytocin in the management of third stage of labor. The result shows there was no significant difference the 2 groups in drop in hemoglobin concentration from mean 1 1.lto 10.5 in the misoprostol group and 10.9 to 10.4 in the oxytocin group and incidence of PPH.

The table.5 also shows that the mean blood loss (334±190) ml in misoprostol group which was found to be greater than oxytocin group (289 ± 202) ml, statistically not significant, but when we compared with oxytocin methylergometrine maleate group (265±125) ml the difference was statistically significant.[17]

While this results are disagree with Hofmeyr GJ.*et al* (2005)[18] which the studies reveal no significant difference of PPH compared misoprostol group with syntometrine .This may be explained by the small sample size in our study and because the visual estimation of blood loss during the postpartum period has been shown to be under estimate. The method of clinical estimation of blood loss has been found to be an acceptable method. Change in laboratory criteria such as hematocrit or hemoglobin concentration, is a more objective measure than estimated blood loss[19].

Also our study reveal that need for additional oxytoeics was higher in misoprostol group as compared with other four groups and the mean Length of third stage or labor longer in misoprostol group compared With other groups although the study fail to reach statistical Significant difference among studies groups.

The study also agree with Oladapo OT, *et al*.[19].Who found that need for Additional oxytocic drugs was 12.8%after misprostol and 4.4% after methylergometrione group

and there is no significant difference also in length or third Stage between the two groups' [20] Other study also found the length of third stage and uses of additional oxytocic's were similar between misoprostol and oxytocin groups as in our study[21]. Also we found combining oxytocin and misoprostol not only decreases the amount of postpartum hemorrhage ,but also decrease the length of third stage and additional need of oxytocics ,compared with the used or either drug alone. This finding is not surprising ' because absorption of misoprostol probably only in the stomach[22]. Addition of oxytocin compensated the critical period for orally administrated misoprostol to reach therapeutics plasma concentration in the third stage of labor [13,23].

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