Glyceryl Trinitrate Versus Misoprostol for Termination of First Trimester Missed Miscarriage

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ABSTRACT:

BACKGROUND:

Missed abortion refers to a pregnancy that can manifest as an anembryonic gestation or fetal demise prior to 20 weeks' gestation. Medical management has been used as a treatment options.A common medical regimen used to evacuate the uterus is vaginal misoprostol (Cytotec) in single or multiple doses.

OBJECTIVE:

To compare the therapeutic efficacy and adverse effects of intravaginal administration of a nitric oxide donor (glyceryl trinitrate) with that of a prostaglandin (misoprostol) to induce cervical changes in women with missed miscarriages to terminate their pregnancies.

METHODS:

A prospective, randomized comparative trial conducted at Al-Yarmouk Teaching Hospital, Department of Obstetrics & Gynaecology/ Baghdad-Iraq, enrolled Sixty women with first trimester missed miscarriages that requested pregnancy termination. They were randomly selected to receive either two tablets of 500 µg glyceryl trinitrate vaginally (n = 30) or 200 µg misoprostol tablet vaginally (n = 30), every 3 hours to a maximum of four doses or until reaching desirable cervical changes. Baseline vital signs were recorded and repeated with monitoring for adverse side effects every 3 hours until finishing therapy.

RESULT:

The difference in cervical changes between the two groups was statistically not significant ($p > 0.05$). The successful outcome taken as cervical dilatation ≥ 10 mm, incomplete, or complete miscarriage was achieved in 30% of women in the glyceryl trinitrate and in 53% of women in the misoprostol group which was statistically not significant ($p>0.05$).

Systolic & diastolic blood pressure, temperature & heart rate were lower with glyceryl trinitrate than misoprostol, but the differences were not significant ($p>0.05$).The most frequent side effect associated with glyceryl trinitrate administration was headache, which occurred in 27/30 women, compared with only 5/30 women in misoprostol group; relative risk 5.42 ($p <0.05$). Women treated with misoprostol reported mainly lower abdominal pain; relative risk 4.2 ($p <0.05$).

CONCLUSION:

Although glyceryl trinitrate was less effective than misoprostol when used prior to termination of missed miscarriage, the difference was statistically not significant. Moreover glyceryl trinitrate caused less adverse effects than misoprostol and it could have a role in the management of this obstetrical problem.

KEY WORDS: glyceryl trinitrate, misoprostol, missed miscarriage

INTRODUCTION:

Missed miscarriage is defined as a gestational sac containing a dead embryo (fetus) before 20 weeks gestation without clinical symptoms of expulsion. [1]. It is diagnosed mainly by ultrasound examination showing a fetal pole with crown-rump length > 6 mm and no heart beat, or a crown-rump length < 6 mm with no change on rescan 7 days later.[2]

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The three management options mostly available for missed miscarriage are; expectant, surgical, and medical management. [3 , 4]

Medical management by prostoglandins (PGs) orally or vaginally[3,5,6], antiprogesterones[2,3,5], or various combinations of the two[3] has the advantages of being non invasive, used without anaesthesia.[7], can be available at all gestations[6] and can be used as an outpatient method for termination of early pregnancy, with subsequently less cost.[8,9] Misoprostol, a PGE1 analogue, is the most interesting drug to be used recently because it is effective, inexpensive (when compared with

PGE2) & marketed for its ulcer-healing properties.[10,11,12] Misoprostol softens the cervix, and can increase the frequency of uterine contractions.[5,13] It has the side effects of diarrhea, abdominal pain, nausea, flatulence, dyspepsia, vomiting and rarely constipation. These side effects are more common with oral than other routes.[14,15,16] Other adverse events may include skin rash, dizziness, headache , breast pain, & chills. [15]

Nitric oxide donors, like glyceryl trinitrate have been used therapeutically for over a century. They cause marked venorelaxation & many other smooth muscles relaxation[17]. The nitric oxide donor isosorbide mononitrate administered vaginally has been found to produce cervical ripening and may be alternative to PGs for the purpose of first trimester termination of pregnancy[18] . Side effects to glyceryl trinitrate are generally dose related and almost all are due to vasodilation: headache, which may be so sever, is the most commonly reported side effect[21], flushing, dizziness, and postural hypotension[17]. Allergic reaction to nitroglycerine is uncommon[19].

METHODS:

This prospective, randomized comparative trial was conducted at Al-Yarmouk teaching hospital through the period from January 2006 to January 2007.

Sixty women from out-patient department who were diagnosed to have first trimester missed miscarriage by ultrasound examination were included in this trial and admitted for termination of their pregnancies by medical methods and informed written consent for the intervention was obtained from all of them. The following exclusion criteria were used: women with any contraindication to PGs or nitric oxide donors like asthma, heart disease, severe hypotension or allergy to these drugs, patient with prior uterine or cervical surgery, Patient with active vaginal bleeding, Patients with clinical signs of septic miscarriage, and patients with abnormal coagulation profiles.

Patients were randomly selected to receive either glyceryl trinitrate in the form of angesid tablet 1 mg vaginally (30 women) or 200 micrograms of PGE1 misoprostol tablet vaginally (30 women). History and clinical examination were done, including vaginal examination to assess baseline cervical state and then every 3 hours for 12 hours to look for any change in cervical width and length. Weight and height were measured.

All women had their Hb%, PCV, blood group & Rh status, and coagulation profile tested and cross matched blood prepared.

If the cervical dilatation remained below 10 mm after 3 hours of drug administration, the participant received another dose, up to a total of four doses.

Successful outcome was taken as a cervical dilatation of ≥ 10 mm, incomplete miscarriage or complete miscarriage . Failure was considered when only cervical softening occurred without dilatation, dilatation < 10 mm or no cervical changes at all 3 hours after the 4th dose of the drug.

Statistical Analysis

Patients data were tabulated and processed using Microsoft technology which include unpaired t-test for continuous variables, and Z-test for difference in proportion. Qualitative data were expressed as frequency and percent , quantitative data as mean and median.

Relative risk was estimated for determining the strength of association between different treatment groups and side effects.

RESULTS:

Table 1 shows the matched demographic characteristics of both groups. There was no statistically significant difference in maternal age, weight, height, gestational age, parity and uterine size between the two groups.

Table 1: Maternal demographic characteristics of the studied groups

Character	Nitric oxide group (1) (n = 30)	PG E1 group (2) (n = 30)	P value
Maternal age (years):			
Mean	30.533	31	> 0.05
SD	7.75	5.93	
Range	18-42	23-41	
Maternal weight (Kg):			
Mean	64.4	65.1	> 0.05
SD	6.63	5.85	
Range	50-78	53-74	
Maternal height (cm):			
Mean	160.66	160.1	> 0.05
SD	6.64	4.37	
Range	150-170	155-168	
Gestational age(week):			
Mean	10.7	10.73	> 0.05
SD	1.51	1.95	
Range	7-13	9-13	
parity:			> 0.05
Nulliparous (n):	12	9	
Multiparous (n):	18	21	
uterine size(cm=week)			
Mean	10.6	10.6	> 0.05
SD	2.04	2.1	

As shown in *table 2*, the proportion of women with cervical dilatation ≥ 10 mm after 12 hours or those who aborted their fetuses within this period was less in the glyceryl trinitrate group compared with misoprostol group. Although, about 53% of the patients treated by misoprostol had responded successfully compared to only 30% among patients treated by glyceryl trinitrate, the difference was not significant statistically (p> 0.05).

In the glyceryl trinitrate group 40% had no change in their initial cervical state, 30% showed softening of the cervix only, 16.66% had incomplete miscarriage, 6.67% had cervical dilatation ≥ 10 mm, and 6.67% had complete miscarriage. In the misoprostol group 36.7% had no change in their initial cervical state, 10% showed only softening of the cervix, 33.3% had incomplete miscarriage, 16.7% had cervical dilatation ≥ 10 mm, and 3.31% had complete miscarriage.

Table 2: The type of response in the two groups

Type of response	Glyceryl Trinitrate		Misoprostol		Total		P value
	N	%	N	%	N	%	
* Success of Method	9	30%	16	53.3%	25	41.6%	> 0.05
1- Opened cervical os (≥ 10 mm dilatation)	2	6.67%	5	16.7%	7	11.66%	
2- 2- Incomplete miscarriage	5	16.66%	10	33.3%	15	25%	
3- Complete miscarriage	2	6.67%	1	3.31%	3	5%	
* Failure of Method	21	70%	14	46.7%	35	58.3%	
1- Soft cervix only	9	30%	3	10%	12	20%	
2- No cervical changes	12	40%	11	36.7%	23	38.3%	

As shown in figure 3, few patients in both groups had cervical dilatation ≥ 10 mm after the first two doses, but after the third and fourth doses the cumulative number of patients was higher in the misoprostol group than in the glyceryl trinitrate group. The difference did not reach statistical significance.

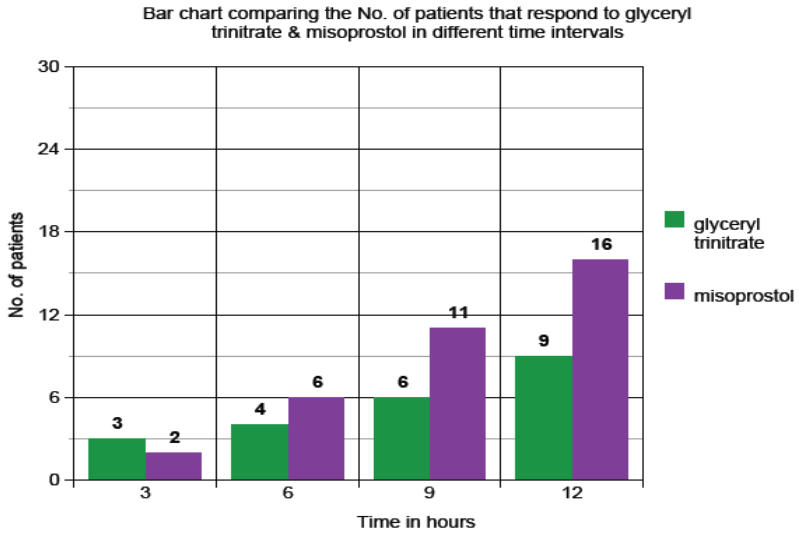

Figure 3:

Although the mean and median number of doses required to achieve a successful outcome was higher in the misoprostol group than in the glyceryl trinitrate group, it did not reach statistical difference as shown in table 4.

Table 4 : The mean & median number of doses required to achieve a successful outcome for the two groups

Patient group	Mean	Median	SD	P value
Glyceryl trinitrate group (G1)	2.5	3	1.414	> 0.05
Misoprostol group (G2)	2.8	3.5	1.08	

The time interval between the first dose and achievement of a successful outcome did not show a statistical difference between the two groups as illustrated in table 5.

Table 5: Time-interval to a successful outcome (hours)

Patient group	Mean	Median	SD	P value
Glyceryl trinitrate group (G1)	7.6	9	4.2	> 0.05
Misoprostol group (G2)	8.4	9	3.2	

As shown in table 6 the administration of glyceryl trinitrate was associated with a lower systolic & diastolic blood pressure but the difference in the mean systolic & diastolic blood pressure between both treatment groups was not significant, being not more than 3.2 mmHg and 1.6 mmHg respectively .

There was a small non-significant difference in mean body temperature between the two groups, with misoprostol being associated with a rise of approximately 0.3°C. Furthermore there was a lower heart rate in the group treated with glyceryl trinitrate that did not reach statistical significance P > 0.05.

Table 6 : Mean vital signs with time intervals (hours)

Vital signs (mean)	Patient Groups	Time interval (hours)			
		Baseline	[3]	[6]	[9]
Heart rate (b/min)	G1	86.2	82.5	81.5	85.6
	G2	75.8	83.2	86.5	87.2
Systolic blood pressure(mmHg)	G1	115.5	111.5	114.7	113
	G2	113.3	114.6	117.9	114
Diastolic blood pressure(mmHg)	G1	72	71	70.5	71.8
	G2	73.3	72.6	71.1	73
Body temperature (C°)	G1	37.02	37	37.1	37.03
	G2	36.9	37.1	37.2	37.3

G1 : Glyceryl trinitrate group
G2: Misoprostol group

The most frequent adverse effect associated with glyceryl trinitrate administration was headache, which occurred in 27 out of 30 patients (90%) , compared with only 5 out of 30 women (16.6%) in the misoprostol treated group ($p<0.05$). Dizziness occurred in 2 patients only & no patient experienced significant hypotension . Other adverse effects were higher in misoprostol group, namely abdominal pain (21 vs. 5), nausea and vomiting (9 vs. 2), high fever (2 vs. 0) & severe bleeding (3 vs. 0), as shown in table 7.

Table 7 : Adverse effects experienced by participants

Adverse effects	No. of affected patients				RR
	G1 N	n=30 %	G2 n	n=30 %	
Headache	27	(90%)	5	(16.6%)	5.42
Abdominal pain	5	(16.6%)	21	(70%)	4.2
Backache	3	(10%)	4	(13.3%)	1.3
Nausea	2	(6.6%)	6	(20%)	3
Vomiting	0		3	(10%)	3
Dizziness	2	(6.6%)	0		2
High fever > 37.7	0		2	(6.6%)	2
Severe bleeding	0		3	(10%)	3
Diarrhoea	0		0		1

G1: gyceryl trinitrate group
G2: misoprostol group

DISCUSSION:

Missed miscarriage is a common obstetrical problem and the presence of non-continuing pregnancy is upsetting to patients and there is a small risk of coagulation defect if missed miscarriage continues for many weeks[20].

Nitric oxide donors have been tried prior to surgical termination of pregnancy [18]. In 2005 a randomized trial by Gabriel et al[16], found that intracervical application of isosorbide dinitrate in women with missed miscarriages appeared to be

more effective for cervical ripening prior to surgical evacuation of the uterus than misoprostol.

In our study, we used glyceryl trinitrate (angised tab) as an alternative to isosorbide dinitrate. and a smaller dose of misoprostol. The efficacy of glyceryl trinitrate for cervical ripening was less than misoprostol (30% vs. 53.3%). Makhlouf et al 2003 [21], showed that glyceryl trinitrate was effective for cervical softening only and was less effective in second trimester termination than misoprostol (0% VS 100%).

The adverse effects of abdominal pain, backache, nausea, vomiting, fever and bleeding were less with glyceryl trinitrate compared with misoprostol. The only non-serious side effect that occurred more frequently in the glyceryl trinitrate group was headache that affected 90% of these patients in our study compared with 60% reported by Gabriel et al[16] . However this side effect was more tolerable than those caused by misoprostol.

The changes in vital signs in our study, were somewhat different from that shown by other studies. There was a fall in maternal pulse rate of no more than 5 b/min in glyceryl trinitrate group compared with misoprostol group. In Gabriel et al study[16] there was a similar difference in body temperature but they showed significant increase in pulse rate in nitric oxide group.

Systolic and diastolic blood pressure were lower in glyceryl trinitrate group compared with misoprostol group but the difference was not significant, whereas in Gabriel et al study[16] the fall in blood pressure was significant in the glyceryl trinitrate group with symptomatic hypotension affecting some patients that required discontinuation of treatment. A study done by Antony et al in 2000 [22], showed that maternal systolic and diastolic blood pressures were greater with the isosorbide mononitrate group compared with the vaginal examination–only group.

Fabio et al 2000 [23], have used sodium nitroprusside as a nitric oxide donor and found that using this agent is effective prior to evacuation of first trimester pregnant uterus and there was no significant change in blood pressure.

We found that mean number of doses of glyceryl trinitrate was less than that of misoprostol (2.5 vs. 2.8) but the difference was statistically not significant. In Gabriel et al study[16], although the mean number of doses of nitric oxide was less than misoprostol but the difference was significant ($p<0.001$) and with their first dose application, 20 patients out of 30 responded to isordil vs. 3 patients only in the misoprostol group.

Boonsri et al 2000[11], compared glyceryl trinitrate tablet with PGE2 tablet vaginally and found that the former was less effective than PG although it had no significant changes in maternal pulse and blood pressure, and they attributed these results to the low dose they used and reported that increasing the dose might cause more adverse effects.

CONCLUSION :

Although it was found to be less effective than misoprostol for termination of missed miscarriage, glyceryl trinitrate caused less side effects. Moreover the difference in effectiveness between the two groups was not significant. Cervical softening without significant dilatation, though regarded as failure of method, has been achieved by a considerable number of patients (30%) treated with glyceryl trinitrate which can make surgical evacuation easier and less traumatic.

REFERENCES:

1. Gary F. Cunningham, Paul C. MacDonald, et al. In Abortion.Williams obstetrics 20th edition. Appleton & Lange, USA 1997;26,579-605.
2. Hayman R. Induction of labour. Lawrence J.Mascarenhas. Problem in early pregnancy. In David M. Lensley, Philip N Barker (ed). An evidence based text for MRCOG, Obstetric & Gynecology. London Harcourt publisher 1st edition Arnold 2004,327-324 & 606-615.
3. Jurkovic D, Ross JA, Nicolaides KH. Expectant management of missed miscarriage. Br J Obstat Gynaecol 1998;105,670-671.
4. John Howkins , Christopher N. Hudson (ed). Oreration on the cavity of the uterus (including termination of pregnancy). Shaw´s textbook of operative gynaecology 5th edition, Churchill Livingstone, Edinburgh, UK, 1983;8,111-125.
5. J.G.GRUDZINSKAS. Miscarriage , ectopic pregnancy & trophoblastic disease, A.A.Calder; Normal labour . In D Keith Edmonds (ed). Dewhurst`s textbook of Obstetric & Gynecology for postgraduates 6th edition blackwell London 1999;7,61-75 & Ch. 20:242-251 .
6. Hernandez-valencia M. Cervical ripening with PGE1: how an ambulatory method decrease the hospital stay in abortus with intrauterine fetal demise. Fetal Diagn Ther. 2003; 18, 54-58.

7. Haitham H, Premila W, Ashok MD Gillian M Flett B & Allan T. Medical abortion at 64-91 days of gestation; A review of 483 consecutive cases Am J Obstet Gynecol,2003; 188:1315-1319.
8. Buster . Jordan A Carson & Harold J. Miller. Outpatient management of missed abortion with vaginal misoprostol , Obstet Gynaecol. 2002 ; 99 ,520-521.
9. Gillian Flett & Allan Templeton. Termination of pregnancy. In D. Keith Edmonds (ed), Dewhurst`s textbook of obstetrics & gynaecology for postgraduate 7th edition, Blackwell, London. 2007;33,318-326.
10. Searle . cytotec (misoprostol) product information from american hospital service. Shokie; IL ; 1988 Dec.
11. I.Z.Mackenzie ; Labour induction. In David K. Games, Philip J. Steer, Carl P. Weiner, Bernard Gonik (ed). High risk pregnancy management options 2nd edition, London, Harcourt publisher 1999;62,1079-1101.
12. Gary W. Faik , Diseases of the stomach & duodenum. In Thomas E. Andreoli , Charles E. Carpenter , Roobert C. Griggs , Joseph Loscalzo (ed) . CECIL essential of medicine 5th edition W.B.Saunders company, Philadelphia 2001;35,339-340 .
13. Senior J , Marshall k , Sangha JK. In vetro characterization of prostanoid receptors on human myometrium at term pregnancy. Br J Pharm , 1993;108,501-506 .
14. Embery MP . Induction of abortion by prostaglandin E1 & E2 Br. Med. J., 1970; ii, 258-260.
15. Gabriel Arteaga - Troncosa. et al. Intracervical application of the nitric oxide donor isosorbid dinitrate for induction of cervical ripening. Br. J. Obstet Gynaecol 2005;112,1615-1619.
16. Sciscione AC , Ngnyen L , manley J , et al. A randomized comparison of transcervical foley´s catheter to intravaginal misoprostol for preinduction cervical ripening . Obstet Gynecol 2001; 97, 603-607 .
17. Dinesh K , Jonn M .IanCotell O , et al. Nitrate. In British Medical Association Royal Pharmaceutical Society of Great British.2004 , 98-100.
18. Thomson AJ , Lunan CB, caerron AD, et al. nitric oxide donors induce ripening of human uterine cervix : a randomized controlled trial Br. J. Obstet gynaecol 1997 ; 104 ,1054-1057 .
19. Mosby´s Drug Consult 2002 , www.mosbys drug consult.com. Nitroglycerin . P 2066-2071.
20. Mordechai Hallak ; Hypertention in pregnancy. In David K. Games , Philip J. Steer , Carl P. Weiner , Bernard Gonic (ed). High risk pregnancy management options 2nd edition, London, Harcourt publisher 1999; 37,639-663.
21. Makhlouf AM, Al-Hussaini TK, Habib DM, Makarem MH. Second trimester pregnancy termination, comparison of three different methods. J Obstet Gynaecol. 2003; 23,407-11.
22. Nicoll AE, Machenzie F, Gree IA, Norman JE. Vaginal application of the nitric oxide donor isosorbide mononitrate for preinduction cervical ripening: a randomized controlled trial to determine effects on maternal & fetal hemodynamics. Am J Obstet Gynecol.2001; 184, 958-964.
23. Fabio Facchinetti, Federico Piccinini, Annibole Volpe. Chemical ripening of the cervix with intracervical application of sodium nitroprusside: a randomized controlled trial. Hum Reprod 2000;15 ,2224-27.