ORIGINAL ARTICLE

MISOPROSTOL FOR THE PURPOSE OF MID-TRIMESTER TERMINATION OF PREGNANCY: A COMPARATIVE STUDY WITH PROSTAGLANDIN F_2 ALPHA

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Objective: To compare the efficacy of misoprostol verses prostaglandin $F_2\alpha$ ($PGF_2\alpha$) in the medical management of termination of mid-trimester pregnancy due to medical reasons. **Methods:** This experimental study was conducted in Obstetrics and Gynaecology Department, Bahawal Victoria Hospital, Bahawalpur for a period of 6 months from April 2005 to September 2005. Time interval between induction with misoprostol or $PGF_2\alpha$ and expulsion of foetus, number of tablets of misoprostol used and total dose of injection $PGF_2\alpha$ used for termination of pregnancy as well as the complications experienced with both drugs. Fifty patients of 18–35 years of age were randomly selected who presented to Gynaecology and Obstetrics outdoor with mid-trimester foetal loss or congenitally malformed foetus incompatible to life, confirmed on ultrasonography. These women were randomised to receive either intravaginal misoprostol or extra-amniotic $PGF_2\alpha$. **Results:** Ninety-six percent of cases were managed successfully with Misoprostol as compared to 92% where $PGF_2\alpha$ was tried ($p>0.5$). Mean induction to expulsion duration for misoprostol and $PGF_2\alpha$ were 9.02±4.57 and 16.04±6.22 hours respectively ($p<0.5$). Complications profile was low especially in cases of $PGF_2\alpha$ and only one case experienced significant haemorrhage. **Conclusion:** Misoprostol and $PGF_2\alpha$ were found to be of same success rate but former was found to be more efficacious in terms of induction to expulsion duration.

Keywords: Misoprostol, Mid-trimester foetal death, $PGF_2\alpha$, Abortion, Pregnancy, Outcome, Second trimester termination of pregnancy

INTRODUCTION

Pioneer of prostaglandins (E_2 and F_2 alpha) research for obstetrics and gynaecological purposes was Karim, who noticed appearance of prostaglandin F_2 alpha ($PGF_2\alpha$) in the blood and amniotic fluid during labour.[1] When they used this substance intravenously during parturition, it was easy for them to deduce about $PGF_2\alpha$ as a drug for induction. In another study at Oxford, Embrey tried prostaglandin E_2 intravenously having the same properties but more efficacious to a factor multiple of five.[2]

It was 8th decade of the last century when McKenzie found vaginal prostaglandin preparations fruitful for ripening the cervix.[3] Now-a-days prostaglandin (natural as well as synthetic) preparations in the form of pessaries, tablets, gels and solutions are in vogue for cervical ripening and induction of labour.

Dimensions of problems with either elective or therapeutic second trimester termination of pregnancy take medico-legal, social and medical areas into account. As far as the option of surgical evacuation of uterine contents during the second trimester is concerned, one cannot be benefited through simple means, e.g., dilatation and curettage or vacuum extraction.[4]

Pharmacological cervical ripening for induction of second trimester miscarriage and intrauterine death with a prostaglandin analogue is becoming more and more popular, after its first use in 1993 by Sanchez Ramos.

Direct administration of prostaglandins inside uterus to achieve optimal stimulation is not only an effective way of induction but also with less systemic side effects.[5] Therefore gynaecologists are now accustomed to extra amniotic use of such agents with intention to interrupt the pregnancies; thus having low plasma level of the drugs with minimal systemic effects.[6]

Despite of the high cost of $PGF_2\alpha$ in the form of pessaries or gel and huge requirements regarding temperature control for storage and transportation, it is still the drug of choice. On the other hand prostaglandins E_1 analogue, (Misoprostol) can be purchased on reasonable price as well as its shelf life is tremendously better.

Misoprostol is the synthetic prostaglandin of choice for medical termination as it is cheap, easily available, and stable at room temperature and found to be quite effective with little or no gastrointestinal side-effects especially in the form of vaginal pessary. Most of the trials conducted on misoprostol for induction of labour have been performed in combination with other agents like RU486 and gemeprost. RU486 is not available in our local market whereas use of expensive agents like gemeprost will be a big financial burden on our patients. When misoprostol used alone, there are

less chances of uterine hyper stimulation and scarred uterus is not a contraindication to its use in second trimester.[7]

Misoprostol can be used via oral, vaginal or rectal route but when used *per vaginum* there are fewer chances of gastrointestinal side effects like abdominal pain, and vaginal bleeding.[7] In Bulgaho study there were no side effects of misoprostol at vaginal dose of 50–200 μg.[1]

We conducted this study in the department of Obstetrics and Gynaecology, Bahawal Victoria Hospital, Bahawalpur. For our population that mostly belongs to lower socio-economic class, misoprostol has gained much recognition as the effective agent for cervical ripening. Besides being cost-effective, it has decreased induction-abortion interval, with consequent less analgesic requirement and early discharge from hospital. Our study evaluated the efficacy of misoprostol usage verses use of $PGF_2\alpha$ in induction during second trimester of pregnancy.

MATERIAL AND METHODS

This interventional study was carried out in Obstetrics and Gynaecology Department, Bahawal Victoria Hospital, Bahawalpur. Simple random sampling was used in the formation of treatment groups. According to time and resources fifty newly diagnosed patients (18–35 years of age) were selected to receive either intravaginal misoprostol or extra amniotic $PGF_2\alpha$ for mid-trimester termination of pregnancy due to foetal loss between 14–28 weeks, or congenitally malformed foetus incompatible to life (singleton pregnancy), confirmed on ultrasonography. All patients with history of allergic disorders, uncontrolled hypertension, and deranged liver function tests and with previous more than one caesarean section were excluded from the study. Informed consent was taken from every patient with proper counselling prior to induction.

One group consisted of patients receiving intravaginal misoprostol. Each case received misoprostol 200 μg per vagina with 2.5 mg hydroxyethyl gel. The misoprostol was obtained as white powder by crushing one 200 μg tablet of Misoprostol. The white powder was mixed with re-packed sterile 2.5 mg hydroxyethyl gel and the mixture was drawn into a sterile 5 ml disposable syringe without a needle. This was then squirted into posterior vaginal fornix and the time was noted. The dose was repeated at 6-hour interval until cervical ripening or dilatation started. Maximum of 800 μg total dose (i.e., four tablets) was placed in the vagina, each tablet repeated at an interval of 6 hours.

Second group comprised of women that were induced with extra amniotic $PGF_2\alpha$ injection. The patient was put in lithotomy position. Vulva, vagina and perineum were cleaned with pyodine solution and draped. The posterior vaginal wall was retracted with Sim's Speculum, anterior lip of cervix held with sponge holding forceps. A Foley's catheter (14–16 Fr) was introduced through the cervical canal with the help of sponge forceps and passed just beneath the internal os and retained in the extramniotic space by inflating the balloon of Foley's catheter with 40 ml of distilled water.

One injection of Prostaglandin $F_2\alpha$ (5 mg) was diluted with 19 ml of normal saline such that 2 ml of the solution contained 0.50 mg (500 μg) of $PGF_2\alpha$. Four millilitre of this solution was injected with the help of catheter tip syringe, 2 ml to fill the dead space and 2 ml into the extramniotic space, 2 ml of the diluted injection (0.50 mg) was administered one hourly.

Median, mode and mean were calculated in both groups for all the variables. Percentages of complications and analgesia requirements during labour were also calculated. All data will be analysed through SPSS-14. The induction to expulsion duration of the two groups was analysed with reference to variables like gravidity, parity, menstrual age, dose repetition. Chi-square test was applied and $p<0.05$ was taken as significant.

RESULTS

Fifty cases were randomly selected who were all in their second trimester of pregnancy (i.e., between 14–28 weeks), presenting either with missed abortion (before 24 weeks), intrauterine death (between 24–28 weeks) or with congenital foetal anomalies incompatible to life.

Misoprostol group consisted of 7 primigravidae and 18 multigravidae among which 4 women had missed abortion, 16 had intrauterine death while 3 had anencephalic foetuses and 2 had gross hydrocephalic foetuses. Among 18 multigravidae only 2 had history of previous caesarean section while the rest had vaginal deliveries without any complications.

Extramniotic $PGF_2\alpha$ group consisted of 6 primgravida and 19 multigravidae among which 5 had missed abortion, 8 had intrauterine death, 7 had anencephalic foetuses and 3 had hydrocephalic foetuses, while 1 woman each had a foetus with big omphelocoele and microcephaly respectively. Out of 19 multigravidae, 2 had obstetrical history of previous 1 caesarean section while the rest had vaginal deliveries.

Table-1 summarises the demographic characteristics of the 50 women who underwent medical termination of pregnancy due to foetal demise. The mean gestational age was 23.68 weeks in misoprostol group and 22.8 weeks in the $PGF_2\alpha$ group. The same holds true for the variables like gravida (range= 1–8 in both groups) and parity (range= 0–6 in misoprostol and 0–7 in $PGF_2\alpha$ group).

Table-2 shows there was no clinically significant difference between vaginal examination of two groups but the efficacy (duration that the drug takes from the time of administration till the expulsion of foetus) of the two drugs was remarkably different when calculated statistically.

Both drugs proved to be successful in termination of pregnancy and there was no significant difference (Table-3). The Table-4 compared both drugs in terms of their complications.

Table-1: Demographic characteristics of study groups. [Mean (range)]

Characteristics	Misoprostol Group (n=25)	$PGF_2\alpha$ Group (n=25)
Weight (Kg)	64 (52–85)	64 (52–81)
Height (Cm)	160 (150–176)	160 (154–170)
Married for (Years)	3.8 (0.08–12)	3.95 (0.10–13)
Period of gestation	23.68 (18–28)	22.8 (18–28)

Table-2: Findings of medical termination of pregnancy using prostaglandins

Characteristics	Misoprostol		$PGF_2\alpha$	
	Mode	Median	Mode	Median
Bishop score	6	6	6	6
Duration between first dose till expulsion (hours)	6	7.50	8	15

Table-3: Outcome of termination of pregnancy

Outcome	Misoprostol n (%)	$PGF_2\alpha$ n (%)
Complete expulsion of foetus	20 (80)	12 (48)
Evacuation needed	5 (20)	13 (52)
Total	25 (100)	25 (100)

$p<0.05$, χ^2 value= 5.5554

Table-4: Complications after termination of pregnancy

	Misoprostol n (%)	$PGF_2\alpha$ n (%)
No complications	24 (96)	19 (76)
Complications	1 (4)	6 (24)
Total	25 (100)	25 (100)

$p<0.05$, χ^2 value= 4.1526

DISCUSSION

The inclusion of prostaglandins in the management of termination of second trimester foetal demise has changed the conventional way of surgical evacuation of the uterus. This alternative approach for such problems is based on the uterotonic properties of the agents. One such agent is the cheap, safe and orally active prostaglandin analogue, misoprostol. The other agent is $PGF_2\alpha$ when used, is the drug of choice, though it's high cost and reduced shelf life in the hot climate renders it a second option in our setup. However, experience with these agents should be compared in the same settings and designs to further define their efficacy and their possible therapeutic role in this condition.

Carbonell studied the women with 800 µg of vaginal misoprostol every 24–48 hours up to a maximum of 3 doses. Carbonell regimen yielded the highest overall success rates (87–94%).[8] When 50 µg misoprostol was administered vaginally 4 hourly, it was found as an effective and safe agent for ripening of cervix and convenient way of inducing abortion during 2nd trimester of pregnancy.[9] Kooper Smith study is one of the examples regarding misoprostol which completed within a day and with the success rate of 60–70% respectively.[10]

In our study both misoprostol and $PGF_2\alpha$ were successful but with misoprostol termination of pregnancy in 96% of cases while $PGF_2\alpha$ lagged slightly behind (success rate is 92% of the cases). These results were comparable and the differences in the success rate between the two regimens were not clinically significant ($p>0.5$). There was no significant difference in efficacy in relation to gestation, weight, height, gravida and parity. However this could be a result of the increasing experience in our unit with this protocol rather than a true difference between the agents.

Aston found 40% of women treated with misoprostol required surgical evacuation, which represents a large saving and a worthwhile benefit. The results with $PGF_2\alpha$ appears inferior to those obtained with misoprostol, emptying the uterus in 45% women.[11]

The use of $PGF_2\alpha$ by Roztocil resulted in a success rate of induction with prostaglandins up to 95.5% while in another study Chohan tried extramniotic $PGF_2\alpha$ for mid-trimester induction of labour with success rate of 85%.[12,13] The success rate is high and the abortion time is less in dead foetus than those in live foetus pregnancy.[14]

Egyptians compared extra amniotic $PGF_2\alpha$ and intravaginal misoprostol and found that all women in misoprostol group aborted within 20 hours of which 90% within 13 hours. In this way misoprostol was found to be more efficacious, cheap, safe and well tolerated because $PGF_2\alpha$ was associated with more incidences of pyrexia, vomiting and diarrhea.[15]

In our study mean induction to expulsion duration with misoprostol was 9.02±4.57 while 16.04±6.22 hours with $PGF_2\alpha$. Moreover about 76% cases expelled within 10 hours when treated with misoprostol and only 20% cases with $PGF_2\alpha$ proved to be successful in 10 hours. This result was clinically significant ($p<0.5$) with reduced hospital stay and total expenditure. The least time taken by a patient (4.5 hours only) was also from the misoprostol group. On the other hand, the maximum duration (28 hours) from induction to expulsion was for cases treated with $PGF_2\alpha$ group.

According to study conducted by Fariha at Rawalpindi, average induction-abortion interval was 16.09±9.38 hours when misoprostol was used. Achievement of successful abortions was in 79.41%, and total failures were 7 of 34 cases. In the $PGF_2\alpha$ group, all women aborted within 20.24±11.57 hours,

76.47% of which aborted within one day.[16] Comparing vaginal misoprostol versus oxytocin plus $PGF_2\alpha$ for second trimester miscarriage in 126 patients Ramsey used concurrent extra-amniotic normal saline infusion for cervical ripening. Median induction to expulsion duration was significantly less in misoprostol group while success rate was 95% versus 85% respectively.[17]

Perry results favour $PGF_2\alpha$ over misoprostol, both used vaginally. As the complete abortion rates and the incidence of adverse effects were similar in both groups but mean time for initiation to termination and evacuation of uterine contents was less (17.5±8.6 vs 22.3±12.5 hours) in $PGF_2\alpha$ treated group. Moreover $PGF_2\alpha$ was associated with greater number of successful uterine evacuation within 24 hours.[18] In a series studied by Samina, Dinoprostone, intracervical Foleys catheter and misoprostol were equally effective in terms of cervical ripening, induction-delivery interval, mode of delivery and maternal complications in labour induction.[19]

In another study on 217 women, 15–24 weeks gestation, oral and vaginal misoprostol groups were compared with intra-amniotic $PGF_2\alpha$ (IAPG) followed by oxytocin infusion. The induction to expulsion time was longer for oral misoprostol group (30.5±14.4 hr) compared with vaginal misoprostol group (18.3±8.2 hr) and IAPG group (21.1±10.2 hr). Women in the vaginal group reported being more willing to repeat the termination method in future and reported fewer side effects than those in other groups.[20]

The incidence of complications was low whichever course of treatment was followed. Blood loss in the termination of second trimester foetal demise is always a concern, but in agreement with latest experiences, this is rarely significant clinically in the protocol using misoprostol. On the other hand one case of $PGF_2\alpha$ experienced significant blood loss (>500 ml) and was transfused. No such problem occurred when misoprostol was used. Average blood loss for misoprostol group was 198 ml while it was 238 ml for $PGF_2\alpha$. Therefore we do not consider that this approach to management imposes any unacceptable risk from blood loss. Thirty out of 50 patients underwent ultrasonography to confirm the retained products of conception and they were found in 52% cases of $PGF_2\alpha$ treated group and evacuated. On the other hand only 20% of cases with misoprostol had to undergo evacuation. Therefore we advocate re-evacuation of uterus if there is significant blood loss when treating such cases with uterotonic agents.

Infection has frequently been sited as an important complication, but the results of our study would dispute this. Though there was no evidence of sepsis in all cases, all women were subsequently given prophylactic antibiotics after discharge, only one (case treated by $PGF_2\alpha$) had microbiological evidence of infection and none required hospitalisation or intravenous antibiotics.

A review of 65 studies revealed that the frequency of diagnosed and/or treated infections after medial abortion was very low (0.92%) and varied among regimens. Results seem to confirm that with respect to infectious complications, medical abortion is safe and effective option for second trimester pregnancy termination.[21,22]

Appropriate randomised trials of sufficient size should undergo such comparative study to test for optimal drug for the management of second trimester foetal demise. From our results, these trials will have to be large because important complications appear to be uncommon.

CONCLUSION

The regimen of using misoprostol 200 µg vaginally alone for a maximum of four doses with a success rate of 100% is a cheaper, more effective and rapid method of medical termination of second trimester pregnancy with less complications when compared with $PGF_2\alpha$ usage.

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