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Original Research Article

The Efficacy and Safety of Extraamniotic Mannitol along with Carboprost (PGF2α) and Intracervical Misoprostol (PGE1) in Second Trimester Termination of Pregnancy: A Prospective Comparative Clinical Study

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Abstract

Introduction: Second trimester termination of pregnancy accounts for around 10 to 15% of all abortions annually. These can be performed either medically or surgically. The aim of this study is to compare the efficacy and safety of extraamniotic mannitol along with carboprost (PGF2α) and intracervical misoprostol in second trimester termination of pregnancy.

Result: The most common indication for termination of pregnancy was intrauterine fetal demise (41.7% in mannitol group and 45.8% in misoprostol group). Second trimester termination of pregnancy success rate was significantly higher in the extra-amniotic mannitol along with PGF2α group as compared to intracervical misoprostol group (95.8% v/s 75%, $p<0.05$).A significantly shorter duration from induction to delivery was observed in the extra-amniotic mannitol along with PGF2α group as compared to intracervical misoprostol group (19.3 ± 4.2 v/s 22.3 ± 2.1 hours, $p<0.01$).Incidence of side effects like pyrexia, diarrhea, abdominal pain and headache were significantly lower in the mannitol group as compared to misoprostol group.

Conclusion: Extra-amniotic mannitol along with carboprost (PGF2α) is an effective and safe method for second trimester termination of pregnancy. The success rate of extra amniotic mannitol along with PGF2α was significantly higher with notably shorter induction-abortion interval. A remarkable lower hospital stay and fewer side effects were seen in patients induced by mannitol along with PGF2α.

Keywords: Extraamniotic Mannitol, Carboprost, Misoprostol, Second Trimester Termination Of Pregnancy.

Introduction

Abortion is defined as the termination of a pregnancy before viability of the fetus.[1] Annually, mid-trimester termination of pregnancy accounts for around 10 to 15% of all abortions.[1,2] These can be performed either medically or surgically. Both approaches are safe and effective with distinct benefits and drawbacks.[3,4]

Prostaglandin analogues PGE1 and PGF2α have been shown to activate the myometrium.[5] They may be given by extra-amniotic, intra-amniotic, intramuscular, oral, vaginal, and sublingual routes. 15 Methyl PGF2α tri-methamine salt resists degradation by 15dehydrogenase and is hence active for a longer period of time. It operates more selectively on myometrium than on the smooth muscles of the digestive tract.[6] Numerous dose-dependent side effects are more with misoprostol, including diarrhea, stomach discomfort, headache, menstrual cramps, nausea, flatulence, chills, and pyrexia.[7,8]

Extra-amniotic administration of 0.1% ethacridine lactate and mannitol induces membrane separation and increased uterine muscular tension, culminating in uterine muscle contraction. Ethacridine lactate possesses oxytocic properties of itself.[9] Prostaglandins such as PGF2α and PGE1 may be utilised to augment its effects.[10-12] Mannitol is a polyhydric alcohol with a diuretic effect and no pharmacological activity. If an excessive quantity of mannitol is infused, serum sodium rises; hence, regular administration of saline with the usage of mannitol may cause hypernatremia.[13,14] Use of 20% mannitol extra-amniotically in medical termination of pregnancy (MTP) cases appears to be superior to the use of glucose, which promotes the growth of bacteria. The mechanism of its action is unknown, but it may act on the decidual cells in a manner similar to that postulated to explain the mechanism of hypertonic saline, which causes necrosis of the decidua and amniotic epithelium, resulting in the release of prostaglandins (PGs) that induce myometrial contractions.[15-17]

Although safe, prostaglandins have cost constrains, contrary to that mannitol is readily available and relatively cheap.[18,19] This present study aimed to compare the effectiveness and safety of extra-amniotic mannitol, in conjunction with PGF2α and intracervical misoprostol in the second trimester termination of pregnancy.

Methodology

This prospective non-randomized comparative clinical study was conducted from 01 February 21 to 30 July 22, in the department Obstetrics and Gynecology, at a tertiary care center in southern Rajasthan. The study was done as per the guidelines of principles of declaration of Helsinki. The study was approved by institutional ethical committee (GU/HREC/EC/2021/1904). After obtaining written and informed consent, all patients with 14-20 weeks of gestation with USG finding suggestive of fetal malformation incompatible with life, Intrauterine Fetal Demise (IUFD) and Severe oligohydramnios not responding to treatment were included in the study. Patients with recurrent and inevitable abortion, history of bronchial asthma, epilepsy, preterm premature rupture of membrane (PPROM), chorioamnionitis, hepatic diseases, renal disorders, severe anemia, and cardiovascular diseases were excluded from the study.

Considering prevalence of second trimester termination of pregnancy to be 15% and 95% confidence level with 10% absolute error, total sample size came out to be 48 and ratio of group A (extraamniotic mannitol with PGF2α) to group B (misoprostol) is 1. Minimum sample size needed for both group was 24. Subjects in group A were given extraamniotic mannitol and PGF2α. In this

technique, a 16 Fr Foley's catheter was placed intracervically and inflated with 20cc of normal saline under strict aseptic circumstances. The quantity of mannitol to be injected into the additional amniotic space was estimated using the formula 10ml/week of gestation up to a maximum of 150ml [10]. Following the addition of 250µg of PGF2α to the mannitol, the solution was injected into the uterine cavity. The catheter was clamped and secured to the patient's thigh in order to retain its position and traction was given to the device. Typically, the bulb gets expelled after the cervical dilation reaches 2 to 3 centimetres. If the bulb did not come out even after 24 hours of insertion, then traction was given to the catheter and uterine contractions were evaluated. In Group B subjects, 600 µg of misoprostol was administered intracervically, followed by 300 µg every six hours for a total of four doses. In both the arms whenever required to augment the uterine contractions, oxytocin infusion was administered at a rate of 20mIU/min and its dosage was titrated according to the uterine contractions, with a maximum of 30units/12 hr. The induction-abortion interval was calculated and all the adverse effects were noted in a pre-designed structured proforma. All the patients were kept under observation for 24 hours after the delivery. At the time of discharge, patients were asked to follow up after 15 days.

The analysis included profiling of patient's data on different demographic, laboratory and clinical parameters. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data were expressed as absolute number and percentage. Cross tables were generated and chi square test was used for testing of associations and student t test was used for comparison of quantitative parameters. P-value < 0.05 was considered statistically significant. All analysis was done using SPSS software, version 24.0.

Results

A total of 48 patients were included in present study, 24 in each group. Mean age of the patients in Group A and Group B was 26.9±2.7 years and 27.9±2.9 years respectively (p value 0.19). In this study 64.6% of all patients were multiparous. At the time of termination of pregnancy, 70.8% of all patients were 14-16 weeks of gestation (Table 1). In present study, the most common indication for termination of pregnancy was intrauterine fetal demise (41.7% in Group A and 45.8% in Group B) followed by different trisomy (20.8% versus 16.7%), neural tube defect (16.7% in both groups), hydrops fetalis (8.3% versus 16.7%). Both the groups were comparable as per indication (Table 2).

Group A has significantly shorter duration from induction to abortion in comparison to Group B (19.3 ± 4.2 hour versus 22.3 ± 2.1 hour, p value < 0.01) (Table 3). To augment the uterine contractions oxytocin was required in 29% in group A versus 25% in group B (p=0.74). The post-operative stay was significantly shorter in mannitol group (24.3 ± 7.9 v/s 49.8 ± 2.8 hours, p value < 0.01).

The most common side effect in Group A was vomiting (33.3%) followed by pyrexia (12.5%). In Group B most common side effects were pyrexia and diarrhea (45.8%). The details and comparison of side effects are summarized in table 4. The incidence of pyrexia, diarrhea, abdominal pain and headache were significantly lower in the Group A as compared to Group B (Table 4). Termination of pregnancy was successful in 95.8% in the Group A, which was significantly higher than that in the Group B (success rate - 75%, p value < 0.05) (Table 5).

Table 1: Comparison of Demographic features between Group-A and Group B

Parameters		Group A Mannitol	Group B Misoprostol	P value
Mean age		26.9 ± 2.7	27.9 ± 2.9	0.19
Parity	Primi gravida	29.20%	41.70%	0.35
	Multi gravida	70.80%	58.30%	
Period of gestation	14-16 weeks	70.8%	70.8%	0.72
	16-18 weeks	20.8%	25%	
	18-20 weeks	8.3%	4.2%	

Table 2: Comparison of mannitol and misoprostol groups according to indication of termination of pregnancy

		Group		Total
Indication		**Mannitol**	**Misoprostol**	
Intrauterine fetal demise	N	10	11	21
	%	(41.70%)	(45.80%)	(43.80%)
Hydropsfetalis	N	2	4	6
	%	(8.30%)	(16.70%)	(12.50%)
Neural tube defect	N	4	4	8
	%	(16.70%)	(16.70%)	(16.70%)
Trisomy 21/13/18	N	5	4	9
	%	(20.80%)	(16.70%)	(18.80%)
Multiple anomalies	N	3	1	4
	%	(12.50%)	(4.20%)	(8.30%)
Total	N	24	24	48
	%	(100.00%)	(100.00%)	(100.00%)
		p value* = 0.76		
*analyzed using chi-square test				

Table 3: Comparison of Mannitol and Misoprostol groups according to duration from induction to abortion (hours)

		Group		Total
Duration from induction to abortion (hours)		**Mannitol**	**Misoprostol**	
Up to 12	N	1	0	1
	%	(4.20%)	(0.00%)	(2.10%)
13 to 18	N	10	1	11
	%	(41.70%)	(4.20%)	(22.90%)
19 to 24	N	11	20	31
	%	(45.80%)	(83.30%)	(64.60%)
More than 24	N	2	3	5
	%	(8.30%)	(12.50%)	(10.40%)
Total	N	24	24	48
	%	(100.00%)	(100.00%)	(100.00%)
		p value* < 0.01		
Mean duration		19.3 ± 4.2	22.3 ± 2.1	
		p value** < 0.01		
*analyzed using chi-square test; analyzed using independent t test				

Table 4: Comparison of mannitol and misoprostol groups according to adverse effects

		Group		Total	
Adverse effects		**Mannitol**	**Misoprostol**		**p value***
Vomiting	N	8	6	14	0.52
	%	(33.30%)	(25.00%)	(29.20%)	
Pyrexia	N	3	11	17	< 0.05
	%	(12.50%)	(45.80%)	(35.40%)	
Diarrhea	N	1	11	17	< 0.01
	%	(4.17%)	(45.80%)	(35.40%)	
Abdominal pain	N	1	7	12	< 0.05
	%	(4.17%)	(29.20%)	(25.00%)	
Headache	N	1	9	15	< 0.01
	%	(4.17%)	(37.50%)	(31.30%)	
*analyzed using chi-square test					

Table 5: Comparison of mannitol and misoprostol groups according to success rate of termination of pregnancy

		Group		Total
Success rate of medical TOP		**Mannitol**	**Misoprostol**	
No	N	1	6	7
	%	(4.20%)	(25.00%)	(14.60%)
Yes	N	23	18	41
	%	(95.80%)	(75.00%)	(85.40%)
Total	N	24	24	48
	%	(100.00%)	(100.00%)	(100.00%)
		p value* < 0.05		
*analyzed using chi-square test				

Discussion

The present study primarily aimed at comparing the efficacy and safety of extra-amniotic mannitol along with carboprost (PGF2α) and intracervical misoprostol in second trimester termination of pregnancy. The study further compared both groups in terms of adverse effects and duration of hospital stay. Very few studies have been done to compare the extra-amniotic mannitol with PGF2α and intracervical misoprostol. In this study both the groups were comparable as per demographic features and indications of pregnancy termination. The common indications for second trimester termination are intrauterine fetal demise (40-50%) followed by neural tube defects (25-30%) and trisomies (10-15%).[20,21] The most common indications for termination of pregnancy in present study was intrauterine fetal demise (41.7% in Group A and 45.8% in Group B) followed by trisomies (20.8% versus 16.7%), neural tube defect (16.7% in both groups), hydrops fetalis (8.3% versus 16.7%).

The present study showed significantly shorter induction abortion interval in mannitol group (19.3 ± 4.2 v/s 22.3 ± 2.1 hours, p value < 0.01) and these results are supported by several studies in literature. Ghorab *et al* showed significantly shorter induction to abortion interval in the mannitol group as compared to misoprostol group.[21] Similarly, Gupta *et al*. found the induction abortion interval ranged between 2 to 10

hours, with the majority of patients beginning labour within 3 to 4 hours with mannitol. [22] The longest induction abortion interval was 45 hours, whereas 80% of cases aborted in 30 hours, and 100 percent of women delivered within 36 hours. In the study conducted by Deshmukh *et al*. extra-amniotic 20% mannitol solution was used to induce abortion in 40 patients between 11 and 20 weeks of gestation. The longest induction-abortion interval was 72 hours. Pregnancy was terminated within 48 hours in 86.8% of the patients, while 63.1% aborted within 36 hours. The induction abortion interval ranged from 2 to 60 hours however the majority of women aborted within 24 hours. The average duration from induction to abortion was 23.2 hours.[23]

Contrary to the results of this study, Ajmani *et al* found no significant variation in the induction- abortion interval in both groups. The misoprostol group had a mean interval of 13.8 hours, while 17.3 hours was noted in the PGF2α group ($p = 0.081$).[24] In addition, Ahmad *et al*. found that the mean induction-abortion interval was shorter with misoprostol than with PGF2α. The misoprostol group had duration of 7.1 hours compared to 9.46 hours in PGF2α group. [20] Similar results were reported by Niaz *et al*, the mean time to terminate a pregnancy with misoprostol was 13.16 ± 1.9 hours, but with PGF2α was 16.07 ± 3.2 hours. The duration was much shorter in the misoprostol group ($p < 0.01$).[25] However in all of these studies only PGF2α was compared with misoprostol and mannitol was not used that can be possible explanation.

In the present study, the most common side effect in the mannitol group was vomiting (33.3%) and in the misoprostol group, most common side effect were pyrexia and diarrhoea (45.8%). The incidence of pyrexia; diarrhea, abdominal pain and headache were significantly lower in the mannitol group as compared to misoprostol group (Table 4). Gupta *et al*. found 40% of patients in the misoprostol group complained of shivering and fever, while 50% of patients complained of vomiting and diarrhoea. In the patients receiving mannitol along with carboprost, none reported any adverse effects.[22] Similarly no adverse effects were noted with extra-amniotic mannitol regime in the study conducted by Deshmukh *et al*.[23]

For more than a century, numerous chemicals have been administered extra-amniotically to terminate pregnancies. Due to the risk associated with intra-amniotic administration, extra-amniotic instillation of abortifacients has gained popularity.[26] Mannitol is an osmotic diuretic, polyhydric alcohol that cannot be metabolized in the body. Its method of action is not fully known, however it may have a comparable effect on decidual cells to that of hypertonic saline. Prostaglandins have been shown to be effective abortifacients capable of terminating pregnancy at any stage of gestation. Rapid metabolic inactivation necessitating numerous dosages and systemic adverse effects including nausea, vomiting, diarrhea, and hypotension are problems associated with systemic usage of prostaglandins.[27] To address these issues, prostaglandins may be administered locally into the extra-amniotic region, where the desired effect can be generated with lower dosages and fewer adverse effects.

The success rate for termination was significantly higher in mannitol with PGF2α group (95.8%) in comparison to intracervical misoprostol group (75%). The various studies showed success rate in range of 65-80% in PGF2α group and 65-100% in misoprostol group. [20-25]

Present study observed a significantly lower length of hospital stay in the mannitol group as compared to misoprostol group (24.3 ± 7.9 v/s 49.8 ± 2.8 hours, p value < 0.01). Ajmani *et al*. identified a comparable duration of

hospital stay between the misoprostol and PGF2α groups, contrary to this study results. The authors found that the average length of hospitalisation was 2.3 days in the misoprostol group and 2.5 days in the PGF2α group (p = 0.40). [24] However again mannitol was not used in this study.

Small sample size and single centre experience were few limitations of present study. The study participants were not randomized so probably a large, multicentre, randomized trial would probably better answer the problem.

Conclusion

Several methods of second trimester pregnancy termination are described in literature. Extra-amniotic mannitol along with PGF2α is an effective and a safe method for second trimester termination of pregnancy. The success rate of extra amniotic mannitol along with PGF2α was significantly higher with notably shorter induction-abortion interval. A remarkable lower hospital stay and fewer side effects were seen in patients induced by mannitol along with PGF2α.

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