ROLE OF ORAL MIFEPRISTONE AS A CERVICAL PRIMING AGENT FOR INDUCTION OF LABOUR

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ABSTRACT

BACKGROUND

Mifepristone is a 19 nor-Steroid with a greater affinity for the progesterone receptor and thus blocks the action of progesterone at a cellular level. As a fall in the level of progesterone considered one of the important events in the onset of spontaneous labour, it therefore seems likely that this drug may be useful on induction.

Aim- To study the effectiveness and safety of Mifepristone as a cervical priming agent for induction of labour to determine the Maternal and foetal outcome.

MATERIALS AND METHODS

This prospective clinical trial was carried out in the Department of Obstetrics and Gynaecology, K.A.P.V Medical College & Mahatma Gandhi Memorial Hospital, Trichy during the period of January 2016 to December 2016 in 100 patients divided into study and control group equally.

RESULTS

In this study, study population comprised of 100 patients with equal no of patients in the study and control group. 66 (66%) patients were primi gravida, 24 (24%) were multigravida, with no significant difference across the groups. The mean Bishop score at inclusion was 1.48 in the study group and 1.12 in the control group with no significant differences between the groups. The mean treatment to induction to active stage interval was 24.08 hours in the Mifepristone treated group when compared to 30.25 hours in the Prostaglandin treated group. Subjects in the Mifepristone group progressed about 6 hours (mean difference) earlier than subjects in placebo group to active stage of labour and this difference was statistically significant. Mean induction to delivery interval was 28.60 in Mifepristone group when compared to 35.44 in placebo group. The rate of normal and assisted vaginal deliveries was 96% in the mifepristone treated group when compared to 72% in the placebo treated group with a significant P value The rate of caesarean deliveries (28.3%) was comparably less in the mifepristone treated group than the Prostaglandin treated group (46.6%).

CONCLUSION

In our study we found that Mifepristone as a pre-induction cervical ripening agent had better proven efficacy especially in primi gravida women as similarly proved by various other earlier standard trials. The need for reinduction/augmentation with other cerviprime agents/oxytocics were also reduced in the Mifepristone treated groups. The results are encouraging with no significant adverse effects on mother and fetus.

KEYWORDS

Mifepristone, Bishop Score, Induction of Labour.

HOW TO CITE THIS ARTICLE: Ramesh B, Vidyaravi, Mareeswari. Role of oral mifepristone as a cervical priming agent for induction of labour. J. Evid. Based Med. Healthc. 2018; 5(3), 280-285. DOI: 10.18410/jebmh/2018/57

BACKGROUND

Human parturition has been termed 'labour' in recognition of the hard work that the parturient as well as the uterine myometrium have to perform in order to deliver the fetus. The ideal method of induction of labour would mimic exactly the onset of spontaneous labour.[1] Induction is indicated when the benefits to either the mother or the fetus outweigh those of continuing the pregnancy. Mifepristone is a 19 nor–Steroid with a greater affinity for the progesterone receptor and thus blocks the action of progesterone at a cellular level. As a fall in the level of progesterone considered one of the important events in the onset of spontaneous labour, it therefore seems likely that this drug may be useful on induction.[2]

Aim of Study- To study the effectiveness and safety of mifepristone as a cervical priming agent for induction of labour and to determine the Maternal and fetal outcome.

Financial or Other, Competing Interest: None.
Submission 16-12-2017, Peer Review 22-12-2017,
Acceptance 13-01-2018, Published 15-01-2018.
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DOI: 10.18410/jebmh/2018/57

MATERIALS AND METHODS

This prospective clinical trial was carried out in the Department of obstetrics and gynaecology, K.A.P.V Medical College and Mahatma Gandhi memorial hospital, Trichy during the period of January 2016 to December 2016. Two groups (Group I & Group II).

Group I- 50 pregnant women were given tablet mifepristone 200 mg orally on day 1. They were observed for maternal vitals, uterine activity, bleeding or draining per vaginum and fetal heart rate. After the wait period of 24 hours or when the Bishop score was ≥ 6, when the cervical dilatation was > 2cm, or when the membranes ruptured or when the patient was well in labour whichever is earlier. Labour was accelerated with oxytocin drip.

Group II- 50 pregnant women pregnant were given placebo on day 1. They were observed for maternal vitals, uterine activity, bleeding or draining per vaginum and fetal heart rate. After the wait period of 24 hours, depending on the Bishop score they were either induced with cerviprime gel or augmented with oxytocin drip.

Inclusion Criteria- Singleton pregnancy in cephalic presentation, Postdated uncomplicated pregnancy, Term uncomplicated pregnancies.[3] with unfavourable cervix (Bishop score <4). Intra uterine fetal death, Gestational hypertension, No contraindications for prostaglandins or mifepristone.

Exclusion Criteria- Premature rupture of membranes, Malpresentations, Cephalopelvic disproportion, Bad obstetric history or history of previous abortions.[4] Previous history of caesarean section or any uterine surgery, Multiple pregnancy, Elderly primi gravid (age >35 years).[5], Oligohydramnios.[6]

Maternal vitals, uterine activity and fetal heart rate were monitored clinically. Partogram was maintained for all patients and used to record all the clinical events during the course of labour. Watch for the rupture of membranes. If membranes not ruptured ARM was done at 3cm cervical dilatation. Per vaginal examination was done if there was rupture of membranes or once in 2 hours in active phase of labour. The pulse rate, blood pressure, temperature and urine output were recorded. Delivery particulars duration of each stage of labour blood loss at third stage of labour and baby particulars were recorded. Mother and baby were observed for postnatal complications if any. Data were analysed and all the values were expressed as mean ± standard deviation or as percentages. Statistical comparison was performed by students paired and unpaired t-test and chi-square test. Statistically significant difference (P<0.05).

The Efficacy was Assessed by the Following Criteria-

- Favourability of the Bishop score at 24 hrs.[7]
- Any need for induction with cerviprime gel.[8]
- The need of oxytocin for augmentation of labour
- Duration of labour.
- Drug administration to delivery interval.
- The mode of delivery.
- Cesarean section rate.
- The 5 minute Apgar score, neonatal complications.[9] and incidence of neonatal mortality and maternal complications.

Success of Induction was assessed by the Criteria

- Patients who delivered vaginally within 48 hours following of the start of induction.10
- Bishop score of ≥ 6 at the end of 24 hours.

Failure of Induction was assessed by the following Criteria

- Patients who delivered vaginally after 48 hours of start of induction.
- Patients who underwent caesarean section.

RESULTS

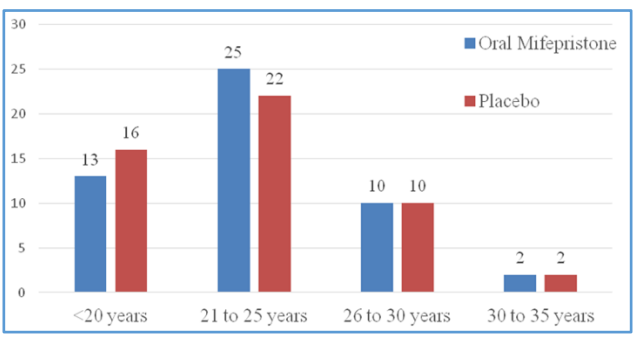

Figure 1. Bar chart Showing Age Distribution of the Study Population (n=100)

Mean age- 23.18 years, Standard deviation- 3.614 years Minimum- 19 years, Maximum- 34 year. Chi-square value- 0.502, p value- 0.918.

Comments- Age distribution of the 2 groups were similar and the minor difference observed was not statistically significant (p>0.05). Hence both the groups are comparable.

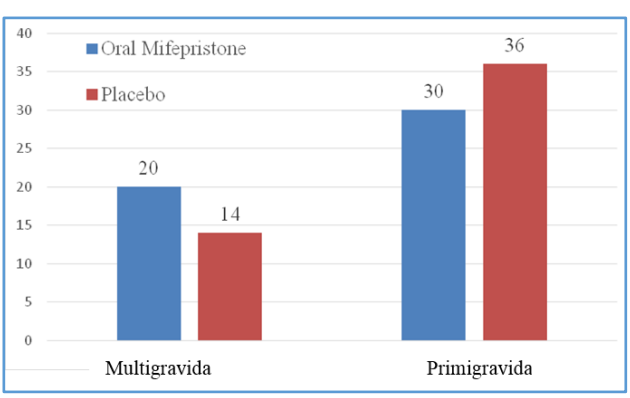

Figure 2. Bar chart Showing Distribution of the Study Population According to Parity (n=100)

Chi-square value- 1.604, p value- 0.205.

Comments- The difference in distribution of the study population according to parity was not statistically significant (p>0.05) between the groups. Hence both the groups are comparable.

Indication for Induction	Mifepristone Group N (%)	Placebo Group N (%)	Total N (%)
Prolonged pregnancy	37 (74%)	37 (74%)	74 (74%)
Gestational hypertension	11 (22%)	12 (24%)	23 (23%)
IUGR	2 (4%)	1 (2%)	3 (3%)
Total	**50 (100%)**	**50 (100%)**	**100 (100%)**

Table 1. Distribution of the Study Population according to Indication for Induction of Labor (n=100)

Chi-square value- 0.377, p value- 0.828.

Comments: The difference in indications for induction of labor was not statistically significant (p>0.05) between the groups.

Bishop Score at Baseline	Mean Score	Std. Deviation	Mean Difference	p value	95% Confidence Interval
Mifepristone group	1.48	0.953	0.360	0.057	-0.011 to 0.731
Placebo group	1.12	0.918			

Bishop Score after 24 Hours	Mean Score	Std. Deviation	Mean Difference	p value	95% Confidence Interval
Mifepristone group	6.26	1.536	3.80	<0.001	3.271 to 4.329
Placebo group	2.46	1.092			

Table 2. Comparison of Bishop Score among the Two Groups (n=100) Student "T" test

Comments- 1. Subjects in the Mifepristone group were not so different from subjects in placebo group with the respect to Bishop score at baseline as the mean difference was not statistically significant (p>0.05).

2. However, Subjects in the Mifepristone group had a higher Bishop score after 24 hours than subjects in placebo group and this difference was statistically significant.

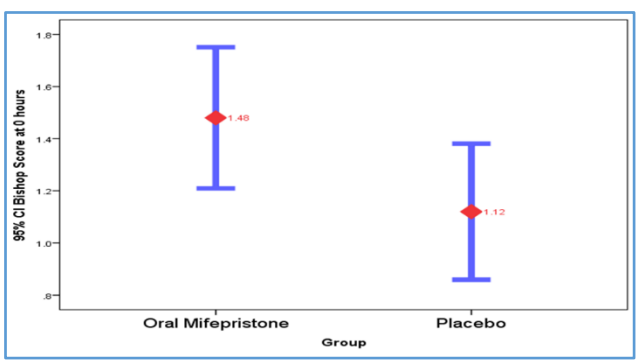

Figure 3. Box plot Showing Distribution of the Study Population According to Bishop Score at 0 Hours among the Two Groups (n=100)

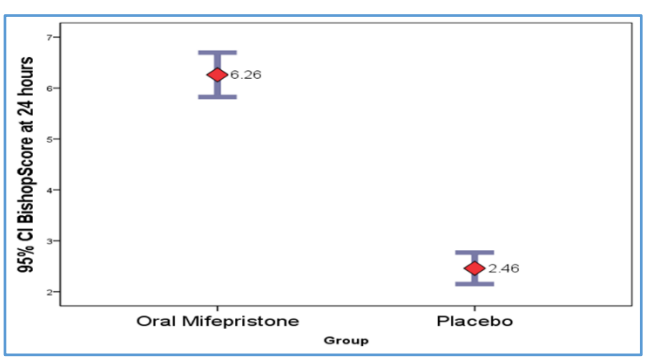

Figure 4. Box Plot Showing Distribution of the study Population according to Bishop Score at 24 hours among the Two Groups (n=100)

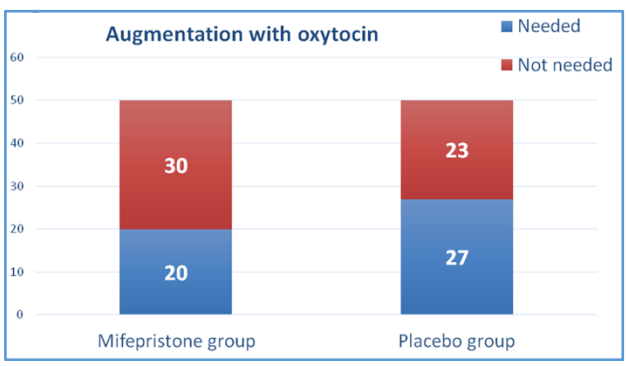

Figure 5. Bar chart Showing Distribution of the Study Population According to need for Augmentation with Oxytocin (n=100)

Chi-square value- 1.967, p value: 0.161.

Comments- The difference in need for augmentation of labor with oxytocin was not statistically significant (p>0.05) between the 2 groups.

Dinoprostone Gel	Mifepristone Group N (%)	Placebo Group N (%)	Total N (%)
Needed	9 (18%)	47 (94%)	56 (56%)
Not needed	41 (82%)	3 (6%)	44 (44%)
Total	**50 (100%)**	**50 (100%)**	**100 (100%)**

Table 3. Distribution of the Study Population According Need for Dinoprostone (Cerviprime) Gel (n=100)

Chi-square value- 58.604, p value- <0.001.

Comments- Very few Subjects in the Mifepristone needed cervical priming with Dinoprostone gel than subjects in placebo group and this difference was statistically Significant. Hence the use of oral Mifepristone greatly reduces the need for cervical priming with Dinoprostone gel.

Number of Doses of Dinoprotone Gel (N)	Mean Number of Doses	Std. Deviation	Mean Difference	p value	95% Confidence Interval
Mifepristone Group (9)	1.00	0.001	-0.510	0.012	-0.905 to 0.117
Placebo group (47)	1.51	0.585			

Table 4. Comparison of Number of Doses of Dinoprotone Gel Administered among the Two Groups (n=56) Student "T" test

Comments- Among the subjects who needed cervical priming with Dinoprostone gel, subjects in the Mifepristone group needed fewer doses than subjects in placebo group and this difference was statistically significant. Hence the use of oral Mifepristone greatly reduces the not only the need for cervical priming with Dinoprostone gel but also the number of doses needed.

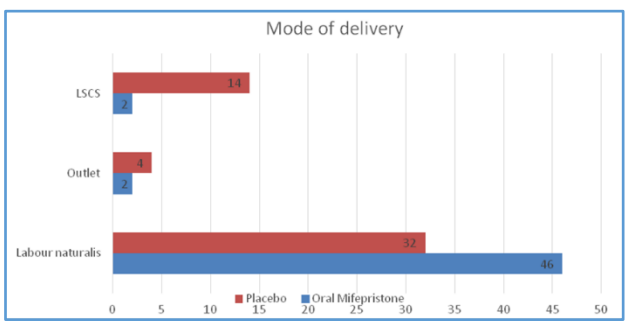

Figure 6. Bar chart Showing Distribution of the Study Population According to Mode of Delivery (n=100)

Chi-square value- 12.179, p value- 0.002.

Comments- The difference in mode of delivery was statistically significant (p>0.05) between the 2 groups with fewer subjects in the mifepristone group needing LSCS.

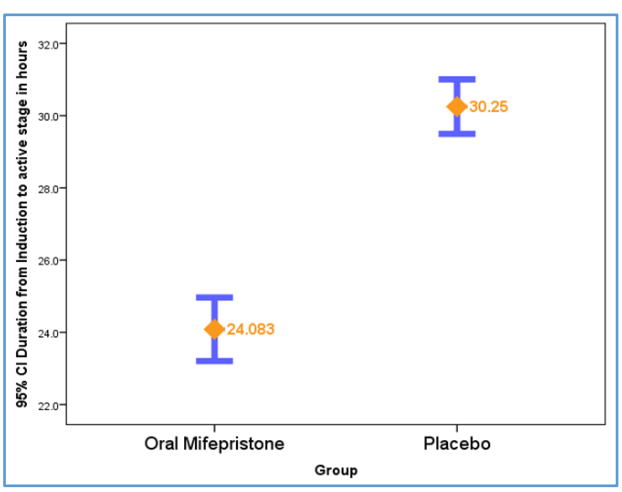

Figure 7. Box Plot of Time Duration from Induction to Active Stage of Labor among the Two groups (n=84)

Subjects in the Mifepristone group progressed about 6 hours (mean difference) earlier than subjects in placebo group to active stage of labor and this difference was statistically significant. Also, the use of oral mifepristone shortened the duration from induction to active stage ranging from 5 hours to 7 hours based on the 95% confidence interval.

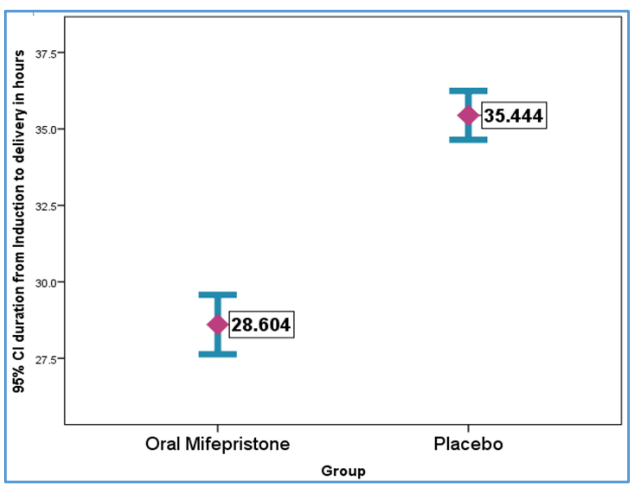

Figure 8. Box Plot of Time Duration from Induction to Delivery of Labor among the Two Groups (n=84)

Subjects in the Mifepristone group progressed to delivery in about 7 hours (mean difference) earlier than subjects in placebo group and this difference was statistically significant. Also the use of oral mifepristone shortened the duration from induction to delivery in the range of 5 hours 30 minutes to 8 hours based on the 95% confidence interval.

Birth weight (N)	Mean Birth Weight	Std. Deviation	Mean Difference	p value	95% Confidence Interval
Mifepristone group (50)	2.918	0.4079	-0.038	0.606	-0.183 to 0.107
Placebo group (50)	2.956	0.3208			

Table 5. Comparison of Birth Weight among the Two Groups (n=100) Student "T" test

Comments- There was no statistically significant difference in the mean birth weight between the 2 groups.

Apgar Score	Group	Mean Birth weight	Std. Deviation	Mean Difference	p value	95% Confidence Interval
0 minutes	Mifepristone	5.46	0.973	0.540	0.004	0.172 to 0.908
	Placebo	4.92	0.877			
5 minutes	Mifepristone	7.38	0.753	0.460	0.003	0.156 to 0.764
	Placebo	6.92	0.778			

Table 6. Comparison of Apgar Score among the two Groups (n=100) Student "T" test

Comments- There was a statistically significant difference in the mean APGAR score between the 2 groups both at 0 minutes and 5 minutes with babies born to the subjects in the Mifepristone group having a better APGAR score than those born to the subjects in placebo group.

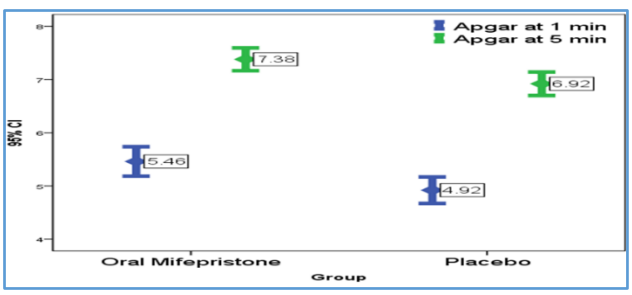

Figure 9. Box plot of Comparison of Apgar Score among the Two Groups (n=100)

Maternal Complications	Mifepristone Group N (%)	Placebo Group N (%)	Total N (%)
Fever	2 (4%)	5 (10%)	7 (7%)
GI symptoms	3 (6%)	3 (6%)	6 (6%)
Abdominal cramps	4 (8%)	0	4 (4%)
Uterine contractile abnormalities	0	4 (8%)	4(4%)
PPH	0	1 (2%)	1(1%)
Puerperal sepsis	0	0	0
No complications	41 (82%)	37 (74%)	78 (78%)
Total	**50 (100%)**	**50 (100%)**	**100 (100%)**

Table 7. Distribution of the Study Population According to Maternal Complications (n=100)

Chi-square value- 10.491, p value- 0.062.

Comments- The difference in occurrence of maternal complications was not statistically significant (p>0.05) between the 2 groups.

Fetal Complications	Mifepristone Group N (%)	Placebo Group N (%)	Total N (%)
Respiratory distress	2 (4%)	3 (6%)	5 (5%)
Meconium aspiration syndrome	2 (4%)	5 (10%)	7 (7%)
Transient tachypnea of newborn	1 (2%)	0 (0)	1 (1%)
No complications	45 (90%)	42 (84%)	87 (87%)
Total	**50 (100%)**	**50 (100%)**	**100 (100%)**

Table 8. Distribution of the Study Population According to Fetal Complications (n=100)

Chi-square value- 2.589, p value- 0.459.

Comments- The difference in occurrence of fetal complications was not statistically significant (p>0.05) between the 2 groups.

NICU Admission	Mifepristone Group N (%)	Placebo Group N (%)	Total N (%)
No	46 (92)	42 (84)	88 (88)
Yes	4 (8)	8 (16)	12 (12)
Total	**50 (100)**	**50 (100)**	**100 (100)**

Table 9. Distribution of the Study Population According to need for NICU Admission of the Babies (n=100)

Chi-square value- 1.515, p value- 0.218.

Comments- The difference in need for NICU admission of the babies was not statistically significant (p>0.05) between the 2 groups.

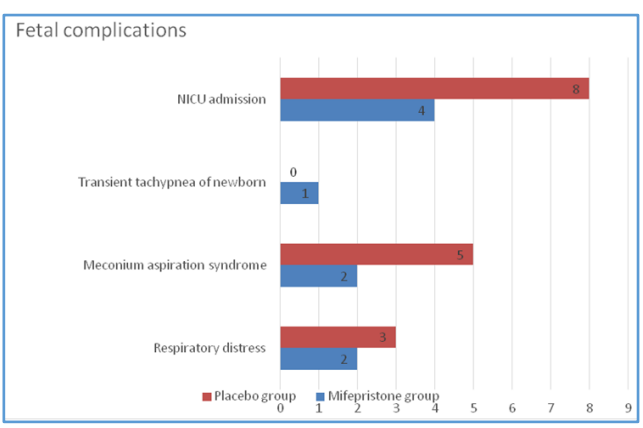

Figure 10. Bar chart of Showing Fetal Complications among the Two Groups (n=100)

DISCUSSION

In this study, study population comprised of 100 patients with equal no of patients in the study and control group. There were no significant statistical differences between the treatment groups in demographics or medical or obstetrics history. 66 (66%) patients were primi gravida, 24 (24%) were multigravida, with no significant difference across the groups. The mean Bishop score at inclusion was 1.48 in the study group and 1.12 in the control group with no significant differences between the groups. The mean treatment to induction to active stage interval was 24.08 hours in the Mifepristone treated group when compared to 30.25 hours in the Prostaglandin treated group. Subjects in the Mifepristone group progressed about 6 hours (mean difference) earlier than subjects in placebo group to active stage of labor and this difference was statistically significant. Mean induction to delivery interval was 28.60 in Mifepristone

group when compared to 35.44 in placebo group. The rate of normal and assisted vaginal deliveries was 96% in the mifepristone treated group when compared to 72% in the placebo treated group with a significant P Value The rate of caesarean deliveries (28.3%) was comparably less in the mifepristone treated group than the Prostaglandin treated group (46.6%). About 23% of patients who were given oral mifepristone delivered within 24 hours while all the patients in the placebo group delivered between 25 to 48 hours duration from induction and this difference is statistically significant. Very few subjects in the mifepristone group needed cervical priming with Dinoprostone gel. Among the subjects who needed Dinoprostone gel, subjects in the Mifepristone group needed fewer doses than subjects in the placebo group and this difference was statistically significant. Also the use of oral mifepristone shortened the duration from induction to active stage ranging from 5 hours to 7 hours based on the 95% confidence interval. Of the 4% mifepristone treated women who underwent caesarean section both were done in view of fetal distress. Among the 14 (28%) placebo treated women 6 (12%) cases were for failed induction, 8 (16%) cases were done for fetal distress. There was statistically significant difference in mean Apgar score between the two groups. Both at 0 and 5 minutes with the babies born to subjects in the mifepristone group having the better APGAR score than those born to the subjects in placebo group.

Meconium passage inutero occurred in 2 (4%) infants of the mifepristone treated group which is less when compared to 5 (10%) infants in the placebo treated group. In the need for reinduction with dinoprostone gel was less with mifepristone treated groups (18%) when compared with the placebo treated groups (94%) which is statistically significant. The need for augmentation with oxytocin was less with study group when compared to placebo group (54%).

Hence the use of oral mifepristone greatly reduces not only the need for cervical priming with dinoprostone gel but also the number of doses needed.

CONCLUSION

In our study we found that mifepristone as a pre-induction cervical ripening agent had better proven efficacy especially in primigravid women as similarly proved by various other earlier standard trials. The need for reinduction/augmentation with other Cerviprime agents/oxytocics were also reduced in the mifepristone treated groups. This study aimed to assess the safety and efficacy of mifepristone as a pre-induction cervical ripening agent in term pregnancies and to study its adverse effects on mother and fetus. The results are encouraging with no significant adverse effects on mother and fetus. Further efforts can be put forth to probe the study further and prove the effectiveness of the drug and its efficacy. Further studies can be done comparing 200 mg of mifepristone with 400 mg or even higher doses if found favorable. It promises to be a more compliant drug in near future.

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