Mifepristone for cervical ripening and induction of labour

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Abstract

Objective: To study the efficacy of oral mifepristone in pre induction cervical ripening and induction of labour in term pregnancy.

Materials and Methods: This is a single blind randomised control trial. 200 women with term pregnancy and bishop score < 6 were recruited and randomly allocated into two groups. Women who received tablet mifepristone 400 mg were assigned to study group (n=100) and who received placebo orally were assigned to control group (n=100). At the end of 48 hours, change in the bishop was assessed and accordingly induction/ augmentation of labour was done. Analysis regarding safety and efficacy of the drug was done with regards to maternal and perinatal outcome

Results: Among 200 women, 100 received mifepristone and 100 received placebo. In mifepristone group, 75% patients entered into labour within 48 hours of induction as compared to 48% in placebo group. The mean time interval between induction to start of labour pains was 28 hours 54 min in group A and 42 hours 18 min in group B. This difference was statistically significant. (p=0.000). In the study group 70% patients delivered within 48 hours of treatment as compared to 38% patients in control group. Mean induction delivery interval was 35 hours 38 min in study group and 49 hours 52 min in control group (p=0.000). There were fewer caesareans in the mifepristone treated group (10%) than placebo group (20%) particularly for failed induction (2 versus 6) and non progress of labour (2 versus 5). There was no statistically significant different in perinatal outcome between two groups.

Conclusion: Mifepristone has modest affect on cervical repining when given 48 hour prior to labour induction and appears to reduce need for further induction compared to placebo. Mifepristone is a simple and effective method of inducing labour in women with term pregnancy and unripe cervix. The use of Mifepristone provides an interesting new alternative to classic uterotonic agents when induction of labour is necessary.

Keywords: Mifepristone, Induction of labour, Misoprostol, Caesarean section, Bishop score.

Introduction

In an ideal world all pregnancies would go to term and labour would begin spontaneously. The progress of Medicine in general and of Obstetrics has allowed the termination of pregnancy at term or close to term for high risk pregnancies with maternal or foetal indication. Induction of labour is defined as an intervention designed to artificially initiate the uterine contractions leading to progressive dilation and effacement of cervix and birth of the baby.

The state of cervix is a major contributor for successful labour. When delivery is necessary and ripening has not had time to occur this natural process has to be accelerated.[1] Labour induction in unfavourable cervix is a difficult and lengthy procedure, extenuating for both mother and obstetrician. So when labour induction is performed favourable cervix is fundamental to a good outcome.[2] The status of cervix can be assessed by Bishop pelvic scoring system. Bishop score of less than 6 usually requires cervical ripening agent.[3]

Membrane sweeping and amniotomy for those females keen to avoid as much intervention as possible has been shown to result in established labour.[4] There is widely held view that the manipulation of the cervix and vagina during the amniotomy provokes release of oxytocin from the posterior pituitary via the Ferguson reflex and this is followed a few minutes later by release of prostaglandins into the uterine vein, encouraging uterine contractility.[5]

Among mechanical methods balloon catheters, hygroscopic dilators derived from seaweed (Laminaria japonicum) and synthetic osmotic dilators (Dilapan, Lamicel) have shown to trigger release of endogenous prostaglandins or extract water from cervical tissue and cause cervix to expand.[6] Trans cervical Foley ′s catheter and extra amniotic saline infusion have been successfully used for cervical ripening and labour induction.[7]

During the past 15 years the introduction of PGE1 (misoptrostol), a methyl analogue has been the major focus of attention for labour induction as it is cheaper and easy to store because of thermo stability. Currently only prostaglandin E2 (PGE2) is licensed for use for labour induction in case of viable pregnancies.[1]

Mifepristone (RU-486), the progesterone receptor blocker has a dramatic effect upon reducing induction to abortion intervals during the second trimester therapeutic abortions. So it was hoped that a similar effect might be seen for labour induction at term.[8] As it is a 19 nor - steroid which has greater affinity for progesterone receptors than does progesterone itself, it blocks the action of progesterone at the cellular level. It

antagonizes progesterone and thus increases sensitivity of the uterus to prostaglandins and initiates the labour.[9]

Mifepristone has been recently used in cases of post-term pregnancies in comparison with a group receiving placebo. It does reduce the need of other drugs to induce labour. When compared to placebo there is evidence that risk for C-section is lower for women treated with Mifepristone.[10]

It probably is a new field for future research on cervical ripening and labour induction in viable pregnancies. But more research is needed to establish the optimal application, safety and efficacy of Mifepristone as an agent for cervical ripening and labour induction.

Materials and Methods

The study has been carried out in the Department of Obstetrics and Gynaecology, Kamla Nehru State Hospital for Mother and Child, Indira Gandhi Medical College, Shimla for a period of one year w.e.f. 1st April 2012 to 31st March 2013 on 200 pregnant females scheduled for planned delivery for various indications. Subjects were divided into 2 groups with 100 each. Group A included females who received tablet Mifepristone 400mg and Group B females received placebo in form of vitamin C. External appearance of the placebo was similar to that of Mifepristone tablet.

Inclusion criteria:

Singleton pregnancy with

i. cephalic presentation
ii. term pregnancy
iii. maternal or foetal indications for labour induction
iv. women in whom labour induction could be deferred for 48 hours
v. unfavourable cervix with Bishop's score < 6

Exclusion criteria:

i. Non vertex presentation
ii. >1 previous caesarean section
iii. Multiple pregnancy
iv. Parity 5 or more
v. Diabetes Mellitus
vi. Contraindication to vaginal delivery
vii. Renal failure, hepatic disorder, adrenal insufficiency
viii. Women on aspirin or NSAIDS for last 15 days
ix. Women on anticoagulant therapy or corticosteroids
x. Blood clotting disorders
xi. Known hypersensitivity to prostaglandins or Mifepristone

Preliminary procedure

In all women under study, detailed history, general physical examination, systemic examination and obstetrical examination including per vaginum was done and all investigations as in attached proforma were carried out. Informed written consent was taken.

Drugs used in study

1. Mifepristone tablet 400mg
2. Vitamin C tablet

Method of study

Total number of 200 females planned for induction with Bishop's score of less than 6 were selected for the study. Hundred of these women were given tablet Mifepristone 400mg orally (Group A). Hundred consecutive women admitted for the induction of labour comparable to Group A received placebo in form of vitamin C (Group B). Before the medication was given, Bishop's score was assigned by vaginal examination. Number of women going in spontaneous labour within 48 hours of administration of the drug was noted. If the labour did not start within 48 hours, vaginal examination was repeated and Bishop's score was calculated. If Bishop's score was ≥ 6, amniotomy was done and oxytocin was started. If Bishop's score still remained unfavourable (< 6) then the female was induced with intracervical prostaglandinE2 gel (0.5mg). Women with previous caesarean section were induced with Foley's catheter. Subjects were assessed after eight hours and second dose of prostaglandin E2 was instilled if Bishop's score did not improve. Examination was repeated again after 6 hours of second dose of PGE2 gel and if Bishop's score still remained unfavourable, caesarean section was performed for failed induction. If at any stage Bishop's score was 6 or more amniotomy was done and oxytocin infusion was started.

Active stage of labour was monitored partographically. Mode of delivery was noted down. Apgar score was recorded.

Efficacy of the drug was assessed by the number of women who went into spontaneous labour within 48 hours of Mifepristone administration or by Bishop's score of 6 or more at 48 hours.

The statistical difference between two groups was evaluated by using student t test and Chi square test. The p value of < 0.05 was considered as statistically significant.

Results

Out of 100 study group women (Total n=200), maximum number of patients were between 25-29 years in both groups i.e.63% in group A and 65% in group B. The mean age was 25.54 years in group A and 25.75 in group B. Most of the patients who received labour induction were nulliparous i.e 58% patients in group A and 52% patients in group B (p=0.102). The mean gestational age at induction was 39.9 weeks in group A and 40.07 weeks in group B (p=0.561).

Table 1: Characteristics of study and control group

Characteristic	Group-A (Study Group) N =100	Group –B (Control Group) N=100	P value
Maternal age in yrs	25.54 years	25.75 years	0.572
Gestational age	39.9 weeks	40.07 weeks	0.567
Parity			0.102
i. Nulliparous	58	52	
ii. Para 1	22	16	
iii. Para 2	18	24	
iv. Para 3	2	8	

The median Bishop score in group A and group B was 3

Table 2: Bishop Score Before Induction

Bishop Score	Group A (Study Group) N=100	Group B (Control Group) N=100
2	12	10
3	33	36
4	35	29
5	20	25

The mean time interval between induction to start of labour pains was 28 hours 54 min in group A and 42 hours 18 min in group B. This difference was highly significant statistically. (p=0.000)

Table 3: Time interval between induction to onset of labour pains

Time(hrs)	Group A (Study Group) N=100	Group B (Control Group) N=100	P value
0-12	27	7	0.000
12-24	20	14	
24-36	17	14	
36-48	11	13	
>48	25	52	

During the first 48 hours following treatment, 75 women treated with Mifepristone and 48 treated with placebo went into labour (p=0.048). Bishop score of less than 6 was found in 20 women in Mifepristone group and 50 in placebo group which was highly significant statistically (p=0.000).

Table 4: Outcome at 48 hours after induction

Outcome	Group A (Study Group) N=100	Group B (Control Group) N=100	P value
Spontaneous labour	75	48	0.000
Bishop Score ≥ 6	5	2	
Bishop Score <6	20	50	

15 patients in group A and 42 patients in group B required Dinoprostone gel for further induction. This difference was highly significant (p=0.000).

Table 5: Mode of induction in patients with unfavourable Bishop Score at 48 hours.

Mode of induction	Group A (Study Group) N=20	Group B (Control Group) N =50	P value
Dinoprostone gel	15	42	0.000
Foley' s Catheter	5	8	

The mean induction to delivery interval in group A was 35.38 hrs and 49.52hrs in group B. Induction to delivery interval between the 2 groups was highly significant (p=0.000).

Table 6: Time Interval between Induction To Delivery

Time(hrs)	Group A (Study Group) N=100	Group B (Control Group) N=100	P value
0-12	14	2	0.000
12-24	19	6	
24-36	24	14	
36-48	13	16	
>48	30	62	

Eighty two patients in group A had normal vaginal delivery as compared to 71 in group B. Ten patients in group A and 20 in group B had caesarean sections. The difference was statistically significant.(p=0.001)

Table 7: Mode of Delivery

Mode of delivery	Group-A (Study Group) N=100	Group-B (Control Group) N=100	P value
Normal Vaginal delivery	82	71	0.001
LSCS	10	20	0.124
-Failed induction	2	6	
-Non progressof labour	2	5	
-Fetal distress	6	9	
Instrumental delivery	8	9	
-Fetal distress	7	8	
-Prolonged 2nd stage	1	1	

6 patients had nausea and vomiting, 2 had hyperthermia after mifepristone use.

8 patients in group A had meconium stained liqour as compared to 12 in group B. 2 patients in group A and 3 patients in group B had atonic PPH. The difference was not statistically insignificant. (p=0.732).

The mean birth weight was 2.75kg in study group and 2.74kg in control group. The mean birth weight is comparable in both groups (p=0.910). Two babies in group A and 1 in group B had Apgar score <7 at 5 minute. These needed resuscitation. Neonatal hyperbilirubinemia was observed in 8 babies in group A and 7 in group B. Observations regarding neonatal outcome were comparable in both groups.

Discussion

Research continues to invent and modify doses of different drugs for induction of labour. Mifepristone has been used to induce labour or to allow pregnancy to be terminated. In the present study, we opted for 400 mg mifepristone as a tablet and women will get the exact dose without fail.

The incidence of nulliparity was 58% in study group and 52% in control group in present study. The distribution of pregnancies and deliveries did not differ significantly between the two groups which was comparable to frydman et al[11] and stenlund et al.[12] In study by Mc Gill, 72% patients in each group were nulliparous. In all these studies most of the women who received labour induction were nulliparous.

The median Bishop Score at the start of induction was similar in both groups which was comparable to stenlund et al[12] and Elliot et al.[13] During the first 48 hours after the treatment was started 75% women who were given Mifepristone and 48% who were given placebo went into labour which was comparable to Elliot et al[13] and Giacolone et al.[14]

In Frydman[11] study, spontaneous onset of labour occurred in 31(54%) patients in study group but only in 10(18%) patients in placebo treated females. The number of patients with onset of labour pains within 48 hours of induction was less than the present study. As Mifepristone success is known to increase with gestation age in late pregnancy and especially after 40 weeks, the difference in gestation age at inclusion in our study and Frydman et al study could partly explain our positive result.

In our study statistically significant improvement was observed in mean time interval between induction to onset of labour pains which was 28 hrs 54 min in study group and 42 hrs 18 min in control group (p=0.000) which was comparable to Stenlund et al.[12]

Mean induction delivery time was 35 hours 38 min in study group and 49 hours 52 min in control group. It was significantly more in control group indicating that Mifepristone is an efficient inducing agent at term pregnancy (p=0.000) which is comparable to Stenlund[12] and Wing et al.[4,3]

In our study caesareans were performed in 10% women in group A and 20% in group B. Elliot et al observed higher rate of caesarean section i.e. 36% and 26% in Mifepristone and control group respectively probably because the dose of Mifepristone used in their study was 200 mg where as in our study it was 400 mg.

Women with unripe cervix treated with mifepristone more likely went into spontaneous labour than women of expectant management after 48 hours. Mifepristone in contrast to well established methods of labour induction, like usage of misoprostol or oxytocin or dinoprostone is not the direct inducer of uterine contractions. Main goal of mifepristone usage is preparation for natural start of labour or optimisation of next steps of induction process (to decrease induction delivery interval and to reduce dose of direct inductors of uterine contractions).[15,16] Cervical ripening and shorter interval to delivery were related to decrease in frequency of meconium stained amniotic fluid.

Mifepristone is well tolerated in pregnant females. Indeed many women have used this medication at a dose of 600 mg, for first trimester abortion or late termination of pregnancy with an abnormal or dead fetus. In keeping with literature we observed no significant increase in adverse effects among females taking Mifepristone.[11-14] Only minor side effects were observed in form of nausea and vomiting, headache, sweating and hyperthermia. Similar side effects were observed by Elliot et al[13] and Lelaidier et al.[18]

Patients had only minor gastrointestinal side effects in form of nausea, vomiting, hyperthermia, headache and sweating. These were comparable in both groups. None of the patient in Mifepristone group had hypertonus or tachysysole which was comparable to Wing et al.[15] Mean birth weight of the babies in present study is less than the other studies but it is in conformity to the average birth weight in India.[6]

Conclusion

Mifepristone is a simple and effective method of inducing labour in women with term pregnancy and unripe cervix. The use of Mifepristone provides an interesting new alternative to classic uterotonic agents when induction of labour is necessary. There were no significant difference in main maternal and neonatal outcomes between mifepristone use and placebo. The potential advantages of Mifepristone over prostaglandins or oxytocin requires further evaluation, mainly for situations in which these are contraindicated as in scarred uterus.

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