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ORIGINAL ARTICLE

Nifedipine Versus Ritodrine for Suppression of Preterm Labor and Analysis of Side Effects

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Abstract
Objectives To compare the tocolytic efficacy of Nifedipine and Ritodrine, their adverse effects and neonatal outcome.
Design Prospective randomized trial.
Methods One hundred twenty women with clinical features of preterm labor fulfilling designated inclusion and exclusion criteria were enrolled in the study. They were allocated to either nifedipine group or Ritodrine group by using simple randomization technique. Tocolytic efficacy, maternal side effects and neonatal outcomes were evaluated. Tools of statistical analysis used were Epi Info software and Chi square test.
Results Tocolysis was successful i.e., prolongation of pregnancy for 48 h in 54 (90%) women in Nifedipine group as compared to 41 (68.3%) women in Ritodrine group (P value = 0.003 and $\chi^2 = 8.54$). The prolongation of pregnancy up to 37 weeks was observed in 28 women (46.6%) in Nifedipine group compared to 16 women (26.6%) in Ritodrine group (P value = 0.033). 18 women (30%) in Nifedipine group had side effects compared to 48 women (80%) in Ritodrine group (P value < 0.001). Neonatal outcome was similar in both the groups.
Conclusion Oral Nifedipine is cheaper and effective alternative which has fewer and less serious side effects as compared to I.V. Ritodrine for suppression of the preterm labor.

Keywords Preterm labor · Nifedipine · Ritodrine · Tocolysis

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Introduction

Preterm labor remains one of the unconquered frontiers in the present era of obstetrics. Its incidence is about 7–9% of pregnancies accounting for three quarters of the mortality and morbidity among newborns without congenital anomalies [1]. Throughout the years a variety of drugs with different pharmacologic principles are used to suppress preterm labor. The choice is limited by their efficacy safety and side effects. Ritodrine, Beta sympathomimetic, is one such agent which is commonly used tocolytic. It has serious maternal and fetal side effects limiting its use [2]. Therefore it is necessary to search for better tocolytic drug which should be effective and safe with minimal side effects.

Nifedipine, a calcium channel blocker, is an effective smooth muscle relaxant with low toxicity and low teratogenicity [3]. There is growing evidence that nifedipine is effective in suppressing preterm labor with minimum maternal and fetal side effects. It relaxes the uterus by inhibiting inward flow of calcium ions across uterine smooth muscle cells.

In some animal studies the administration of nifedipine has been associated with decrease in uterine blood flow

resulting in fetal hypoxia and acidosis [4]. However studies in human pregnancies did not show any significant alteration in uterine blood flow.

Questions still remain concerning the tocolytic effectiveness and side effects of nifedipine. In this paper, we present the results of a prospective randomised study which was designed to compare the efficacy of oral Nifedipine with I.V. Ritodrine.

Material and Methods

This study was conducted at Shri. B. M. Patil Medical College Hospital and Research Centre, Bijapur, during October 2006 to September 2008. One hundred and twenty women with preterm labor fulfilling inclusion and exclusion criterion were enrolled. Sixty women were assigned to Nifedipine group and sixty women to Ritodrine group by simple randomisation technique. The groups were similar with respect to maternal age, gestational age and parity.

Preterm labor was diagnosed as regular uterine contractions of four in 20 min with cervical dilatation of >1 cm and effacement of 80% or more as proposed by ACOG guidelines.

Inclusion criteria were singleton pregnancy with vertex presentation between 28 and 36 weeks with cervical dilatation of 1–3 cms and intact membranes. Exclusion criteria were antepartum haemorrhage, pregnancy induced hypertension, congenital anomaly, intrauterine growth retardation, bronchial asthma, diabetes mellitus, cardiovascular diseases, severe anemia, hydramnios and chorioamnionitis.

Hospital Ethics committee approved the study. Informed consent was taken from all the participants. Detailed history was taken. Thorough general, systemic obstetric, per speculum and per vaginal examination was done. Each woman was investigated for Hb%, TC, DC, Urine-Routine, Blood group & Rh typing, HIV, HBsAg, USG and High vaginal swab for culture & sensitivity.

Group 'A' comprised of sixty women who were given oral Nifedipine. It was administered as an initial oral loading dose of 30 mg. If uterine contractions persisted after 90 min, another 20 mg Nifedipine was given orally. If labor was suppressed after the first or second dose, a maintenance dose of 20 mg Nifedipine was given orally every 8 hourly till 37 wks or till delivery whichever occurs early. However if uterine contractions persisted for 60 min after the second dose, the treatment was considered as 'Nifedipine failure'.

Group 'B' was constituted by 60 women who were given intravenous Ritodrine. 100 mg of Ritodrine (two ampoules of Ritodrine each containing 50 mg) was added to 500 ml of ringers lactate. The infusion was started at the rate of 50 μg/min and increased by 50 μg every 15 min until the uterine contractions stopped, up to maximum rate of 350 μg/min. Infusion was stopped if unacceptable side effects developed like palpitations, chest pain and tachycardia >120/min.

I. V. infusion of Ritodrine drip was continued for 24 h after the cessation of uterine contractions Oral Ritodrine 10 mg tablet was given 30 min before stopping IV drip and continued every 6 h till 37 weeks of pregnancy or delivery whichever occurs early. Tocolysis was considered successful if delivery was deferred for at least 48 h.

All women in the study were given 12 mg betamethasone I. M. and repeated after 24 h to enhance fetal lung maturity. Antibiotic prophylaxis in the form of oral 250 mg of amoxicillin and 250 mg of cloxacillin 8th hourly was given to all women. Metronidazole was added if there were signs of bacterial vaginosis.

Treatment failure was said to exist if uterine relaxation was not achieved despite administration of described maximum dose or development of significant side effects which necessitated discontinuation of therapy. Data regarding mean prolongation of pregnancy (at 48 h, 1 week, 37 weeks), side effects, failure of treatment, and gestational age at delivery, Apgar score and neonatal details were recorded. Patient variables, results of tocolysis, side effects and neonatal outcomes were analyzed statistically by Fischer's exact test wherever appropriate to determine significance ($P < 0.05$), Chi-square analyses with Yate's correction by Epi-info software.

In this hospital incidence of preterm delivery was 10% during the study period.

Results

As seen in Table 1 there was no significant difference among the various characteristics in both groups (P value > 0.05). 85% of Nifedipine group and 90% of Ritodrine group were between 16 and 25 years of age. Primigravida were in majority in both the group i.e. 75% in Nifedipine group and 80% in Ritodrine group. 66.6% of Nifedipine group & 58.3% of Ritodrine group were booked cases. More number of women was between gestational age of 32–34 weeks being 60% in Nifedipine group and 58% in Ritodrine group.

Table 2 shows that the prolongation of pregnancy up to 48 h was seen more in Nifedipine group as compared to Ritodrine group (P value $= 0.004$, $\chi^2 = 8.54$ and df $= 1$). It is statistically significant. This shows that Nifedipine was more successful in delaying delivery for 48 h enabling corticosteroids to enhance fetal lung maturity.

The prolongation of pregnancy up to 7 days was comparable in both groups. Prolongation of pregnancy till 37 weeks was seen in 46.6% in Nifedipine group as compared to 26.6% in Ritodrine group. P value is 0.0371 which is statistically significant.

Table 1 Characteristics on admission in the two groups

Characteristics	Nifedipine ($n = 60$)	Ritodrine ($n = 60$)
Maternal age (years)	22	2
Gestational age (weeks)	33	33
Parity		
0	45 (75%)	48 (80%)
≥1	15 (25%)	12 (20%)
Booked	40 (66.6%)	35 (58.3%)
Unbooked	20 (33.3%)	25 (41.7%)

Table 2 Prolongation of pregnancy with tocolytic therapy

	Nifedipine ($n = 60$)	Ritodrine ($n = 60$)	P value
<48 h	06 (10%)	19 (31.6%)	0.0069
Up to 48 h	54 (90%)	41 (68.3%)	0.0069
Up to 7 days	42 (70%)	36 (60%)	0.338
Up to 37 weeks	28 (46.6%)	16 (26.6%)	0.0371

Table 3 Outcomes in treatment groups

	Nifedipine	Ritodrine	P value
Success, n (%)	54 (90%)	41 (68.3%)	0.003
Failure, n (%)	6 (10%)	19 (31.6%)	0.002

Table 3 shows that failure was more in Ritodrine group as compared to Nifedipine group, P value is 0.0034 & $\chi^2 = 8.54$, it is statistically significant.

Table 4 shows comparison of side effects, Out of sixty women treated with Nifedipine 12 (20%) had headache, 5 (8%) had palpitation and 3(5%) had flushing. These side effects were not severe enough to discontinue therapy. Out of sixty women treated with Ritodrine, 25 (41.6%) women had palpitations, breathlessness in 3 (5%) and pulmonary oedema was seen in 2(4%) women. In two women with pulmonary oedema, therapy was discontinued. In rest of the women drip rate was reduced. Fetal tachycardia developed in 24 (40%) women and nausea-vomiting occurred in 6 (10%) women.

48 women (80%) in Ritodrine group had side effects as compared to 18 women (30%) in Nifedipine group (P value < 0.0001). It is statistically significant.

Table 5 shows that the mean gestational age at birth in Nifedipine group was 35 weeks 3 days and in Ritodrine group it was 34 weeks. The difference is not statistically significant.

Number of admissions to NICU was 55 and 65% in Nifedipine group and Ritodrine group respectively. Perinatal deaths in Ritodrine group was 9 (15%) as compared to 6 (10%) in Nifedipine group. Respiratory distress syndrome was 13.3% in Nifedipine group and 16.6% in Ritodrine group. The causes of perinatal death were Respiratory Distress Syndrome, septicemia, intraventricular hemorrhage. Neonatal outcome are comparable in both the groups.

Table 4 Side effects associated with tocolytic therapy

Side effects	Nifedipine $n = 60$	Ritodrine $n = 60$
Palpitation	5 (8%)	25 (41.6%)
Breathlessness	–	3 (5%)
Headache	12 (20%)	–
Flushing	3 (5%)	–
Pulmonary oedema	–	2 (1.1%)
Nausea & vomiting	–	6 (10%)
Fetal tachycardia	–	24 (40%)

Table 5 Neonatal outcome

Parameters	Nifedipine group $n = 60$	Ritodrine group $n = 60$
Mean gestational age at birth	35 weeks 3 days	34 weeks
Birth weight	2050 g	1900 g
NICU admission	33 (55%)	39 (65%)
Perinatal death	6 (10%)	9 (15%)
Respiratory distress syndrome	8 (13.3%)	10 (16.6%)

Four women in Ritodrine group had pronounced fall in blood pressure (BP) for which reduction of dosage was necessary. Two women developed pulmonary oedema which was managed with stopping the IV drip, oxygen and diuretics. Nausea and vomiting were successfully treated with antacids and antiemetic.

In Nifedipine group there was fall in systolic BP by 10 mm of Hg in 20 women and diastolic BP by 10 mm Hg below the baseline in 24 women after administration of second dose of drug. This decrease in BP did not necessitate any special treatment. Headache, flushing subsided after few hours without any specific measure.

Discussion

This study compares the efficacy, side effects, neonatal outcomes and safety of Nifedipine with Ritodrine in the suppression of preterm labor. The survival analysis shows that at 48 h, which is relevant because it permits use of steroids to promote lung maturity. 90% of Nifedipine group remain undelivered compared to 68.3% in Ritodrine group which is statistically significant (P value 0.003). The prolongation of pregnancy till fetal maturity was seen in 46.6% in Nifedipine group and 26.6% in Ritodrine group which shows significant difference (P value 0.0371).

The efficacy of Nifedipine in the present study is comparable with other study groups of Kupferminc et al. [1]

and Ferguson et al. [2]. The efficacy of Ritodrine is comparable to other studies in prolongation of pregnancy up to 7 days but at 48 h and up to 36 weeks the number of women who remain undelivered was lower when compared to the studies of Kupfermic et al. [1] and Ferguson et al. [2]. This study shows the significant difference in the tocolytic effects of Ritodrine & Nifedipine.

Nifedipine caused fewer side effects which subsided after few hours and did not necessitate any special treatment where as Ritodrine group had more frequent and serious side effects for which two women had to discontinue therapy. In the present study palpitation was common side effect, seen in 41.6% of women and fetal tachycardia in 40% of women. Most common side effect in Nifedipine group was headache as seen in 20% of women.

Ferguson [2], Meyer [3], Kupferminc [1] and Papatsonis [4] all found Nifedipine to be associated with significantly fewer maternal side effects as compared to Ritodrine. James [2] had to stop therapy in three women because of chest pain in Ritodrine group. Kedar [5] points out in his study that β sympathomimetics are not suitable for women with cardiovascular disease or diabetes where as Nifedipine exhibits greater selectivity for inhibition of uterine activity with very minimum effect on maternal cardiovascular and metabolic changes. Administration of Nifedipine in retard form is equally effective.

We also evaluated hemodynamic side effects in the present study. There was reduction in both systolic and diastolic BP following oral administration of second dose of Nifedipine in 24 women. However these changes were not significant and were less when compared to decrease in BP associated with Ritodrine. Observed fall in BP are unlikely to be of physiological importance.

Four women in Ritodrine group had pronounced fall in BP for which reduction of dosage of drug was necessary. Maitra [6] found both agents to cause increase in pulse rate, fetal heart rate and decrease in BP which was statistically significant. Kupferminc [1] found that fall in mean arterial and diastolic BP and rise in maternal heart rate were significantly greater with Ritodrine than with Nifedipine. Similar decrease of BP was also noted by Read and Wellby [7] and Ferguson [2] and all of them felt that it was unlikely to be if pathological significance.

James [2] also demonstrated Nifedipine treatment to be useful to delay delivery in treatment failures with Ritodrine and vice versa. This is cross over therapy. These two drugs act through different cellular mechanism to achieve uterine quiescence. In his study he could not demonstrate any adverse fetal hemodynamics and cardiorespiratory effects when Nifedipine was used because of minimum changes in maternal hemodynamics. In a study by Kashnian et al. [8] in which Atosiban was compared with Nifedipine showed that the efficacy in delaying delivery for more than 48 h in order to undergo steroid therapy as well as side effects of both the drugs were similar.

Present study showed comparable neonatal outcomes in both groups. Papatson [4] in his study showed lower NICU admission in Nifedipine group.

Maitra's [6] study observed similar APGAR scores in both groups. Nifedipine does not interfere with interpretation of fetal heart rate tracing as does Ritodrine, which may be important in timely diagnosis of intra uterine infection in preterm rupture of membranes.

Conclusion

Nifedipine was more successful in delaying the delivery for 48 h which would enhance fetal lung maturity by use of corticosteroids. The mean prolongation of gestation was higher for Nifedipine group when compared to Ritodrine group.

Oral Nifedipine is a cheaper, effective alternative and has fewer, less serious side effects and less hemodynamic compromise when compared to I.V. Ritodrine for suppression of preterm labor.

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