

A RANDOMIZED CONTROL TRIAL OF IV RITODRINE AND ORAL NIFEDIPINE IN THE MANAGEMENT OF PRETERM LABOR

Obstetrics & Gynaecology

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ABSTRACT

BACKGROUND: Preterm birth is a common cause of neonatal morbidity and mortality, the incidence being about 6-11%. As there is an increasing trend, the need for best tocolysis in terms of safety and efficacy is necessary to decrease neonatal mortality and morbidity.

METHODS: The study included 200 cases of preterm labor from the labor room of Department of Obstetrics and Gynecology, KIMSH, Bangalore, who satisfied the inclusion and exclusion criteria and were randomly assigned into either Nifedipine group (n=100) or Ritodrine group (n=100).

RESULTS: 100 cases in the Nifedipine group and Ritodrine group respectively were evaluated for the prolongation of pregnancy for more than 48 hours. The mean gestational age in each group was 32.58 ± 1.95 weeks and 32.88 ± 1.92 weeks in Nifedipine group and Ritodrine group respectively. Significant side effects were observed in Ritodrine group, such as tachycardia, hypotension, headache, breathlessness and pulmonary edema. Nifedipine group had very few side effects, namely tachycardia and headache. There was a significant increase in fetal heart rate in Ritodrine group and no changes of fetal heart rate in Nifedipine group. However, prolongation of pregnancy for > 48 hours and till term in both Nifedipine group and Ritodrine group were similar and there was no statistical significance.

CONCLUSIONS: In this study both Nifedipine and Ritodrine found to be were efficacious in prolongation of pregnancy for more than 48 hours. However, Ritodrine caused significantly more maternal side effects and fetal tachycardia and oral Nifedipine proved to be very safe and efficacious as a tocolytic agent.

KEYWORDS

Tocolysis, Preterm labor, I V Ritrodine , oral Nifedipine, Preterm labor, Tocolysis

BACKGROUND

Preterm birth is defined as birth between the age of viability and at less than 37 weeks period of gestation, is the most important single determinant of adverse infant outcome in terms of both survival and quality of life^{1,2,md3}.

Preterm labor remains one of the last frontiers of the present-day obstetrics. Prematurity together with its complications remains the most important preventable cause of perinatal mortality and morbidity. The cost of preterm neonatal care is not feasible to all classes of society especially in the developing and underdeveloped countries. Therefore, it is necessary to prevent preterm labor not only in view of cost but also to provide a healthy baby⁴.

Preterm birth is a common cause of neonatal morbidity and mortality, the incidence being about 6-11%⁴.

Gestational age can be calculated from maternal report of last menstrual period (LMP), by ultrasonography, especially in the first trimester when variability in fetal development is lowest or by postnatal physical assessment.^{5, 6} The most accurate measure for determining GA in non-in vitro fertilization pregnancies is by ultrasound (either trans-vaginal or trans-abdominal)⁷, and pregnancies dated using this method have a lower incidence of being induced for post-term labor (GA ≥ 42 wks.)⁸

Postponing delivery for 48 hours with tocolysis to allow for maternal steroid administration or antenatal transportation to center where neonatal intensive care units (NICU) are available is needed in threatened preterm labor.

Therefore, accurate prediction, prophylaxis and management of preterm labor have become a major goal in modern obstetrics.

The inhibition of myometrial contractions is called tocolysis and an agent administered to that end is referred to as tocolytic⁹. The goal of tocolysis is to cause cessation of uterine contractions in patients with preterm labor.

Currently a variety of pharmacological agents are available to treat preterm labor. The incidence of troublesome side effects and the debatable efficacy of these agents prompt to search for the better drug. The drugs used should be effective and should have least maternal or fetal complications.

Beta adrenergic agonist like Ritodrine is the only drug approved by Food and Drug Administration for tocolysis¹, being effective orally and parentally. Meta-analysis has concluded that Ritodrine has no significant beneficial effects on perinatal mortality, prolongation of pregnancy to term, neonatal morbidity, or birth weight. Therefore, the clinical efficacy of beta-adrenergic effects is doubtful. At the same time the use of these agents is associated with several side effects like palpitation, pulmonary edema, myocardial ischemia, hypotension, fetal tachycardia and hypoglycemia.

Nifedipine, a dihydropyridine calcium channel blocker, is an effective smoothmuscle relaxant with low toxicity and no teratogenicity. It may represent an attractive therapeutic alternative due to its relaxing effects on myometrium.

This study was undertaken to compare the efficacy of Nifedipine, a calciumchannel antagonist with Ritodrine (Beta sympathomimetic) in the treatment of preterm labor.

AIMS AND OBJECTIVES

AIM

To study the efficacy of IV ritrodine and oral Nifedipine in the short management of preterm labor.

OBJECTIVES

PRIMARY OBJECTIVE -

To study the efficacy of IV ritrodine and oral Nifedipine in the short management of preterm labor.

SECONDARY OBJECTIVE -

To study the patient's drug tolerance and its side effects.

METHODS

After obtaining institutional ethical clearance, all patients during the study period of 3 years with a diagnosis of preterm labor in the Department of Obstetrics and Gynecology from Kempegowda institute of medical sciences and hospital, Bangalore, meeting the inclusion and exclusion criteria were included in the study and that accounted for 200 patients. It is a prospective randomized cohort study for a period of three years. Total 200 patients, randomized into two groups of 100 patients in Ritodrine group and Nifedipine group respectively were included in the study. An informed and written consent was taken from all the subjects. All those patients who satisfied the inclusion and exclusion criteria were taken into the study. The

inclusion and exclusion criteria were as follows:

Inclusion Criteria

- Singleton pregnancy in cephalic presentation with gestational age between 28-36 weeks.
- Uterine contractions four in 20 min or eight in 60 min lasting for 30 seconds or more
- Cervical dilatation 1 to 3 cms.
- Cervical effacement 80% or lesser.
- Intact membranes.
- No previous administration of tocolytics

Exclusion Criteria

- Maternal and fetal indications for termination of pregnancy like medical conditions requiring emergency termination of pregnancy/ intrauterine death/ lethal fetal anomalies etc.
- Past medical history of Cardiovascular diseases, Diabetes mellitus, Bronchial asthma, Pregnancy induced hypertension, Severe anemia, Antepartum hemorrhage
- Multiple pregnancy and Malpresentation
- Uterine malformations
- Cervical dilation >4cm

Patients were recruited after satisfying the inclusion and exclusion criteria and were randomized into two groups. Detailed history was taken; period of gestation was calculated from naeages rule in patients with known Last menstrual period, otherwise, assessed by clinical examination and ultrasound. Detailed general physical examination, systemic examination, obstetric examination was done and endocervical and high vaginal swabs were taken. Necessary investigations were sent including CRP, ESR, and serology.

As mentioned before patients were divided into two groups randomly.

Group –A: 100 patients received inj. Ritodrine 100mg in 500ml ringer lactate solution at the rate of 50mcg/min (5drops/min). It is increased by 50mcg every 15 minutes until the uterine contractions subsided (maximum rate – 350mcg/min – 35 drops/min)

Group–B: 100patients received oral Nifedipine. Loading dose of 20mg initially followed by 10-20mg three to four times daily adjusted to the uterine activity for up to 48 hours.

All the patients received Injection Betnesol 12mg 2doses 24hours apart.

Patients were monitored to look for any side effects and to assess the efficacy of these agents to prolong the pregnancy for >48 hours and were followed up till term.

Statistical Analysis

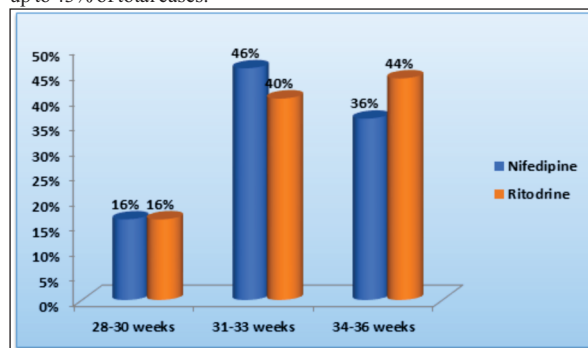
The Statistical analysis was performed by STATA 11.2 (College Station TX USA). Chi square test for goodness of fit were used to measure the association between the age distribution, parity, previous history of PTD, Prolongation of pregnancy in days, cause of pre-term, maternal side effects, Prolongation of pregnancy till term and fetal tachycardia with treatment groups (Nifedipine and Ritodrine) and these expressed as frequency and percentage. Students independent sample t-test were used to measure the significance difference between the age, period of gestation with treatment groups and these expressed as mean and standard deviation. $P < 0.05$ is considered as statistically significant.

RESULTS

During this study period total number of deliveries that were conducted in the department of obstetrics and gynecology were around 1850 per year out of which 265 cases were diagnosed with preterm labor per year. The incidence of preterm labor was found to be 14.37% per year. 200 patients who consented for the study were selected and randomized into two groups. The study included patients between 19 years to 34 years of age. Majority of the cases belonged to age group between 19-25 years. The mean age in Nifedipine group and Ritodrine group were 24.44 ± 4.15 and 25.64 ± 3.85 respectively. There was no statistical significance between the two groups as p value was 0.137. It was observed that most of the cases of preterm were seen in young age group of 19 years to 25 years and reduced incidence of preterm labor in age group between 31 years - 34 years (18 cases).

In our study multigravida were in majority in both the groups accounting up to 114 cases, where in 50 cases belonged to Nifedipine

group and 64 cases in Ritodrine group. Primigravida cases accounted up to 43% of total cases.



Graph 1: Period of gestation (In weeks)

The incidence of preterm labor was found to be maximum between the gestational age of 31-33 weeks ($n = 86$), followed by 34-36 weeks ($n = 80$) weeks and 34 cases between 28-30 weeks gestation. The mean POG was found to be 32.88 ± 1.92 weeks in Ritodrine group and 32.58 ± 1.95 weeks in Nifedipine group and the range of POG was 29-36 weeks in Nifedipine group and 28-36 weeks in Ritodrine group. There was no statistical significance between the two groups, where the p value was 0.439.

Most of the cases who were diagnosed with preterm labor did not have previous history of preterm delivery (86%), only 14% of patients had previous history of preterm delivery which was not found to be statistically significant, p value = 1.000.

Table 1: Prolongation Of Pregnancy

Duration of prolongation	Nifedipine	Ritodrine	Total	P-Value
≤48 Hours	4 (4%)	22 (22%)	26	0.007
>48 Hours	96 (96%)	78 (78%)	174	
Total	100	100	200	

As our study was to monitor the short term effect of Ritodrine and Nifedipine, The patients were divided into two categories as in < 48 hours and > 48 hours. The prolongation of pregnancy up to > 48 hours was observed in 176 patients, where Nifedipine was 96% and Ritodrine and 78% of cases. There was statistical significance in prolongation of labor >48 hours in both Ritodrine and Nifedipine where p value was 0.007. Out of the 200 cases, 88% cases in Nifedipine group and 74% in Ritodrine group had prolongation of pregnancy till term.

Table 2: Causes Of Preterm Labor

Causes	Nifedipine	Ritodrine	Total	P-Value
Idiopathic	56 (56%)	70 (70%)	126	0.029
Lower Genital Tract Infection	18 (18%)	2 (2%)	20	
Polyhydramnios	10 (10%)	18 (18%)	28	
Urinary Tract Infection	16 (16%)	10 (10%)	26	
Total	100	100	200	

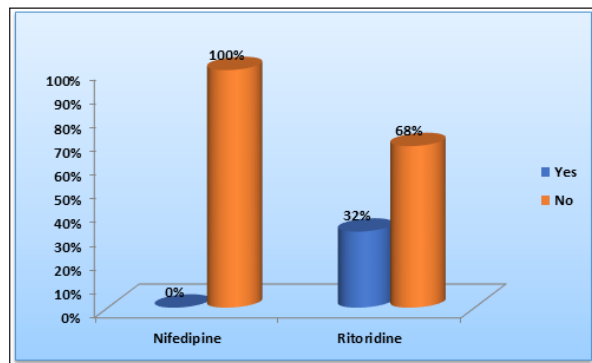
The above mentioned table shows various etiological factors which were the cause of preterm labor in both Nifedipine and Ritodrine group. The most common cause of Preterm labor was idiopathic cause which was 63% followed by polyhydramnios, Urinary tract infection and lower Genital Tract Infections which were 14%, 13% and 10% respectively. There was statistical significance found for the cause of preterm labor here the p value was 0.029.

Table 3: Maternal Side-effects

Maternal side effects	Nifedipine	Ritodrine	Total	P-Value
Tachycardia	14 (14%)	50 (50%)	64	<0.001
Hypotension	0	14 (14%)	14	0.006
Breathlessness	0	12 (12%)	12	0.013
Headache	8 (8%)	0	8	0.041
Pulmonary edema	0	2 (2%)	2	0.315

Ritodrine group had various side effects such as tachycardia, hypotension, breathlessness and pulmonary edema. Almost 50% of cases under Ritodrine group had tachycardia, 14% of patients in Ritodrine group had hypotension and around 12 patients had

breathlessness. Two patients developed pulmonary edema with Ritodrine as a tocolytic agent. Ritodrine was associated with significant side effects as and when compared with Nifedipine group. The p value was <0.001 for tachycardia and 0.006 for hypotension. Breathlessness also was found to be a significant side effect where p value was 0.013. The most common side effect noted in Nifedipine group was tachycardia which was about 14%, followed by headache which was 8%.



Graph 2: Incidence Of Fetal Tachycardia

There was significant rise in fetal heart rate in Ritodrine group as 32% of cases in Ritodrine group had fetal tachycardia, whereas Nifedipine group did not have any rise in fetal tachycardia. The rise in fetal heart rate in Ritodrine group was statistically significant where p value was <0.001.

DISCUSSION

Despite of various advances in perinatal medicine, preterm birth is one of the major causes of infant morbidity and mortality. Preterm delivery continues to frustrate satisfactory reproductive outcome. Throughout the years a variety of tocolytic agents are used to suppress preterm labor. The goal of tocolysis is to cause cessation of uterine contractions in patients with preterm labor. Conservative management of the patients with threatened preterm labor with tocolytics will reduce the neonatal morbidity, mortality and the cost of neonatal care.

Beta sympathomimetics agonists are the most commonly used tocolytic agent. However, the incidences of troublesome side effects have led to continuous search for other novel tocolytic agent. Many recent studies have shown that Nifedipine is safer, better tolerated, and effective with no fetal side effects. Hence this study was undertaken to study the efficacy of Ritodrine and Nifedipine as a short term tocolytic and to study the side effects of these drugs.

The incidence of preterm labor in our hospital was 14.37%. Various studies done worldwide also show a similar range of incidence. World Health Organization also shows a similar range 5-18% of incidence of preterm labor. In US, the incidence of preterm have declined over the last decade, the least being 9.57% in 2014¹⁰. However, in 2015, the rate of preterm birth was 9.62%.¹¹ Despite this decline current incidence rates are still 5-10% which accounts for 70-80% of infant morbidity¹²

The primary purpose of tocolytic therapy is to delay preterm labor for 48 hours to allow the maximum benefit of glucocorticoid therapy to decrease the incidence of respiratory distress syndrome by increasing the production of surfactant in the fetal lungs, to prevent neonatal morbidity and mortality. Our study aimed at short term tocolytic effect of both Ritodrine and Nifedipine. Our study showed prolongation of labor >48 hours in 96% of cases which was comparable with other studies as shown in table: A study done by Srisuda Songthamvat showed an incidence of 9.7% cases which failed to delay prolongation of labor more than 48 hours, where in our study also showed an incidence of 4% of cases who failed to achieve prolongation of labor more than 48 hours

The efficacy of Ritodrine in prolonging preterm labor by more than 48 hours in our study was comparable to various other studies such as Purushottam Bankatlal (2011) the incidence was 68.3%.

Incidence of failure in prolongation of labor for more than 48 hours in Ritodrine group in our study was 22% which was similar in other studies as well, such as Charu Jain (2016) wherein it was 24%.

In our study 96% of cases in Nifedipine group remained undelivered for 2 days as compared to 78% of cases in Ritodrine group.

Many similar studies done in the US used 30 mg of oral nifedipine as loading dose, But in this study 20mg of oral nifedipine as loading dose was sufficient enough for Indian built population to bring about the desired therapeutic effect.

Ritodrine group had more frequent and life-threatening complications which necessitated immediate medical attention, whereas Nifedipine was much safer drug when compared with Ritodrine with very few side effects which did not necessitate any medical attention, vigilant monitoring or termination of tocolytic agent. Hence nifedipine was considered more patient friendly.

Nifedipine, a calcium channel blocker, inhibits transmembrane influx of extracellular calcium ions across myocardial and vascular smooth muscle cell membrane without changing serum calcium concentration. Thus, Nifedipine has both vasodilatory effect and positive chronotropic effect on blood vessels and heart respectively. Our study showed tachycardia and headache as a predominant side effect of the drug due to its vasodilatory and chronotropic effect. There was no significant fall in blood pressure due to Nifedipine. There was minimal reduction of blood pressure on second and third dose of Nifedipine, but was not significant as when compared to Ritodrine.

Our study showed the incidence of palpitations in Nifedipine group as 8%, which was similar in various studies conducted by Jaju. P. B and Cararach, where the incidence of palpitations was 8% and 5.1% respectively. Similarly, the incidence of headache in Nifedipine group in our study was 14%, 20% in study conducted by Jaju. P. B and 4% in study conducted by Cararach. No other significant side effects were observed in Nifedipine group. The increase in maternal heart rate was statistically significant when compared to headache.

Ritodrine is an adrenergic beta 2 agonist which acts on bronchial walls, blood vessels and other smooth muscles can also cause vasodilation, bronchodilation and uterine relaxation. Our study showed marked side effects with Ritodrine which included tachycardia, breathlessness, hypotension, headache and pulmonary edema. Palpitations was the most common side effect found in patients on Ritodrine which was 50% of total cases in Ritodrine group, followed by hypotension and headache which were 14% each. The incidence of breathlessness was 12% and pulmonary edema was 2% in Ritodrine group. A similar study conducted by Kim M K showed an incidence of 47% of patients having tachycardia, 20.7% patients with breathlessness and 3% of cases with pulmonary edema.

Fetal heart rate also was monitored during the tocolytic therapy. Nifedipine did not have any effect on fetal heart rate, whereas Ritodrine increased the fetal heart rate significantly which was statistically significant requiring fetal monitoring but did not require cessation of drug administration. The incidence of fetal tachycardia in Ritodrine group was 32% in our study. Similarly various other studies also have showed a similar effect where Nifedipine had no effect on fetal heart rate, but Ritodrine has a positive chronotropic effect on fetal heart. A study conducted by Jaju. P. B also showed an incidence of 40% of fetal tachycardia.

CONCLUSION

Nifedipine in comparison with Ritodrine in the management of preterm labor is significantly safer and associated with fewer maternal side effects as both short and long term tocolytic agents. It eliminates the need for intensive maternal monitoring as required in case of IV Ritodrine.

Both Nifedipine and Ritodrine were successful in delaying the delivery for 48 hours which would enhance fetal lung maturity by use of corticosteroids and reduced neonatal morbidity and mortality. The mean prolongation of gestation was higher for Nifedipine when compared to Ritodrine.

Ritodrine was associated with significant rise in fetal heart rate, however Nifedipine had no effect on fetal heart rate. Nifedipine has the ease of oral administration as compared to IV Ritodrine.

Other relative advantages are lack of influence on carbohydrate metabolism in contrast with Ritodrine.

Hence, we recommend the use of oral Nifedipine as it is safer, cheaper and effective with very few side effects when compared to IV Ritodrine for management of preterm labor.

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