ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Comparative Study of Safety and Efficacy of Ritodrine versus Nifedipine in the Management of Preterm Labor

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ABSTRACT

Aim of this study is to evaluate safety and efficacy of Ritodrine versus Nifedipine in the management of preterm labor. Total of 60 patients were randomized into 2 groups of 30 each. Patients in group A received Ritodrine and group B received Nifedipine. They were followed up from admission till delivery and discharge and analyzed for gestational age at onset of labor, associated risk factors, response to tocolytics, duration of prolongation of pregnancy and neonatal outcome. Chi-square test, student's T test and Mann-Whitney U-test were used for statistical analysis. P value <0.05 was considered as significant. Ritodrine significantly delayed pregnancy for up to 7 days compared to nifedipine (26 vs. 13, P <0.001). In Nifedipine group, duration of pregnancy was significantly delayed by > 7 days compared to Ritodrine (17 vs. 4, P <0.001). Among singletons, APGAR score was more in Nifedipine group (P <0.001) and incidence of NICU admission was significantly more in Ritodrine group (P <0.043). Among twins, birth weight of neonates was significantly more in Nifedipine group (P <0.001). Fetal complications and maternal side effects were not statistically significant in both groups. Ritodrine is more effective in delaying delivery for short duration of up to 7 days and Nifedipine for > 7 days and even till term.

Keywords: Ritodrine, Nifedipine, Tocolysis, APGAR score, NICU.

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ISSN: 0975-8585

INTRODUCTION

According to the World Health Organization (WHO) recommendation, preterm labor is defined as labor starting earlier than 37 completed weeks (less than 259 days) from the first day of the last menstrual period [1].

Preterm labor occurs in about 6-8% of total pregnancies. It is responsible for about 75-90% of all neonatal deaths, and 50% of childhood neurological disabilities. About 13 million preterm births occur worldwide annually [2]. Incidence of preterm labor in India is 23.3% and of preterm delivery is 10-69% [3]. Besides the inaccuracy of the diagnosis, there is uncertainty about the best strategies for managing preterm labor. The most effective intervention to improve newborn outcomes for women in preterm labor is the administration of corticosteroids. Pharmacological treatment of preterm labor should aim at preventing preterm delivery for at least 48 hours. Betamimetics are the only agents licensed for tocolysis in preterm labor in many countries and Nifedipine has recently been included as an antioxytocic (section 22.2) in the WHO Model List of Essential Medicines [4]. Hence this study was conducted to evaluate safety and efficacy of Ritodrine versus Nifedipine in the management of preterm labor.

Tocolytic agent is a medication that can inhibit labor, slow down or halt the contractions of the uterus (from the Greek word *tocos,* childbirth, and *lytic,* capable of dissolving). These are the agents that can significantly prolong pregnancy by either avoiding or ameliorating the squeal of preterm labor. The advantage of these agents is that they can delay delivery for time sufficient enough to allow administration of steroids and *in utero* transfer of mother to allow delivery in obstetric units along with supportive intensive care facilities. The growing interest in agents that could control uterine contractility beyond the earlier classical approaches of hormones and gastrointestinal spasmolytics led to the discovery of many agents in the early 1960s, such as nylidrine, isoxsuprine, and orciprenaline that could suppress uterine contractility as one of their many beta-agonist properties. Subsequently, two other approaches were used. One consisted of supplementing these drugs with agents, such as calcium antagonists and other beta - receptor agonists [5].

There are three principal indications for the use of tocolysis in the treatment of preterm labor:

- Prophylaxis- Therapy based on the presence of a risk factor or uterine activity alone, in the absence of documented cervical change, to prevent preterm labor.

- Acute therapy- Administration of parenteral agents by either intravenous or subcutaneous route for prompt control of acute episode of preterm labor for duration varying between 24-72 hours.

- Maintenance- The use of oral or subcutaneous medications for long-term tocolysis after cessation of preterm labor to prevent recurrence of uterine activity [6].

ISSN: 0975-8585

MATERIALS AND METHODS

This is a prospective study conducted from October 2006 to August 2008. In this study, 60 pregnant women experiencing preterm labor at 28-36 weeks were randomly selected. Patients who met following inclusion and exclusion criteria were enrolled into the study. Inclusion criteria: women with regular uterine contractions, at least 1 in every 10 min, lasting for 30-60 sec, with cervical effacement and dilatation less than 3cms, women aged between 19-35yrs, irrespective of their parity with/without rupture of membranes and women who did not receive any tocolytics in the past 7 days. Exclusion criteria: Any maternal complications like severe pre-eclampsia, eclampsia, Diabetes Mellitus, Cardiovascular diseases, Hyperthyroidism, and severe anaemia, history of Abruptio placentae, documented intrauterine infections, cervical dilatation more than 4cms, fetal distress and severe fetal growth restriction, congenital anomalies of fetus incompatible with life and intra uterine death.

Ethical clearance was obtained from the institutional ethical committee. Written informed consent was obtained from each patient. Women who met all inclusion and exclusion criteria's were randomly selected to receive either intravenous Ritodrine (group A) or oral Nifedipine (group B).

Treatment administered

Group A: In this group 30 patients received injection Ritodrine. 100mg was added to 500ml of 5% dextrose solution and started at the rate of 0.05mg/min (4 drops) and increased by 0.05mg every 30 minutes up to a maximum of 0.35mg/min till tocolysis established or maternal heart rate increases by more than 140 beats/ min. After which, the infusion rate was kept unchanged for at least 2 days unless contractions recurred, in which case infusion was readjusted to the rate that had achieved tocolysis. Depending on the clinical condition, IV dose of Ritodrine was reduced by 0.05mg/min every 2hours until 0.1mg/min was reached. Treatment with oral Ritodrine started 30-60mins before stopping IV infusion (peak plasma levels achieved within 30-60 minutes with 10mg oral dose). 10mg Ritodrine tablet was given every 2 hours for 24 hours with a maximum daily dose not exceeding 120mg. Next day, 1-2 tablets of ritodrine were given every 4-6 hours. The same dosage regimen was continued till 34 weeks. In case of recurrence, IV infusion of ritodrine was restarted with the same dosage regimen and then shifted to the same oral therapy as discussed above. Patient was carefully monitored for blood pressure, pulse, palpitation, and fetal heart rate response every 30 minutes for 2 hours and then 2 hourly till the completion of IV infusion.

Group B: In this group 30 patients received nifedipine at the dose of 20mg orally followed by another 20mg orally after 30 minutes if contractions persisted and thereafter followed by 20mg orally 3-8 hourly for 72 hours and maximum dose did not exceed 160mg/day. After 72 hours tocolytic therapy was omitted. No maintenance therapy was given. If the women developed preterm labor later in pregnancy, the same dose schedule was followed. Pulse, BP and fetal heart sounds were recorded at every half hourly on the first day then every 2 hourly on subsequent days.

Uterine contractions were monitored continuously for 2 hours after initiation of the study and then every 2 hours after initiation of the study and then every 15 minutes for 6-12 hours until a rate of four-contractions/ hour was detected. Then, contractions were checked every 30 minutes for 24-48 hours. Subjects in both the groups received injection Betamethasone 12mg IM for 2 doses 12 hours apart.

The tocolytic efficacy and tolerability profile was assessed in terms of the proportion of the women who were not delivered and who did not require alternative tocolysis at 48 hours, in addition to the assessment of the progression of labor. Safety outcomes were assessed in terms of maternal, fetal, and neonatal adverse events, which were reported on until the patient was discharged from the hospital.

Mode of delivery in both the groups was noted. After delivery, the neonates were evaluated for gestational age, birth weight and APGAR score at 1 and 5minutes were recorded. The babies were shifted to neonatal intensive care unit when needed. The baby and mother were followed up till discharge. Perinatal complications during hospital stay were recorded.
Statistical analysis was done by Chi-square test, student's T test and Mann-Whitney U-test. *P* value <0.05 was considered as significant.

RESULTS

Efficacy analysis

Majority of patients in both the groups were between 21-25yrs with mean age of 23.5 (±3.68) and 22.93 (±3.33) in ritodrine and nifedipine group respectively (table 1). A greater proportion of patients in the ritodrine group had a gestational age between 30-35 weeks (mean 32.48±2.72 weeks). In the nifedipine group majority of the patients were between the gestational ages of 30-32 weeks (mean 31.86±2.54) (table 2). With respect to distribution in relation to parity (gravida) majority of patients in both ritodrine group (56.7%) and nifedipine group (66.7%) were primi gravida (fig 1). In the ritodrine group prolongation of pregnancy by up to 7 days was more than in the nifedipine group (26 vs. 13, p<0.001). However, nifedipine significantly prolonged duration of pregnancy for more than 7 days compared to ritodrine (56.7% vs. 13.3%, p < 0.001) as shown in table 3.

Safety analysis

Perinatal Outcome: Outcome data for neonates was considered separately for singletons and twins. The singletons in the ritodrine group showed lower APGAR scores at 1 and 5 min after birth (p=<0.001). More number of neonates among singletons in the ritodrine group was admitted to NICU (neonatal intensive care unit) compared to nifedipine group (10 vs. 4, p=0.043) as shown in table 4.

Among twins, birth weight of neonates was significantly higher in the nifedipine group (p=0.001). Deaths occurred mainly because of respiratory distress syndrome, asphyxia and twin-transfusion syndrome, and the number being 3 and 2 among singletons and 1 each among twins in ritodrine and nifedipine groups respectively. One in the ritodrine group had

ISSN: 0975-8585

congenital anomaly and 1 in nifedipine had fetal tachycardia. However, there was no significant difference in fetal complications and deaths in both the groups (table 5).

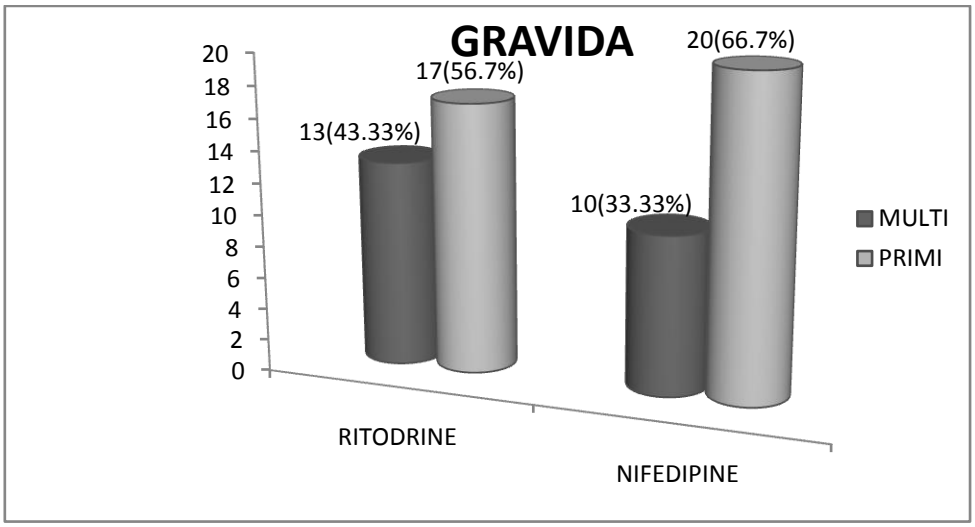

Fig 1 Distribution of patients in relation to parity (gravida)

Fig 1 describes distribution of patients in relation to parity (gravida). Majority of patients in both the groups were primi gravida with 56.7% in the ritodrine group and 66.7% in the nifedipine group.

AGE	RITODRINE (n=30)	NIFEDIPINE (n=30)
<20YRS	8 (26.66%)	9 (30%)
21-25YRS	12 (40%)	14 (46.66%)
26-30YRS	10 (33.33%)	6 (20%)
>30YRS	0 (0%)	1 (3.33%)
MEAN AGE (SD)	23.5 (±3.68)	22.93 (±3.33)

Table 1 Age Wise Distribution of Patients

POG (in Weeks)	GROUP	
	RITODRINE (n=30)	NIFEDIPINE (n=30)
27-29 wks	7 (23.30%)	5 (16.70%)
30-32 wks	9 (30%)	15 (50%)
33-35 wks	9 (30%)	6 (20%)
>35 wks	5 (16.7%)	6 (13.3%)
MEAN (SD)	32.48±2.72	31.86±2.54

Table 2 Distribution Based On Gestational Age at Admission

ISSN: 0975-8585

DOP (days)	GROUP		
	RITODRINE n=30 (%)	NIFEDIPINE n=30 (%)	*P* value [a]
upto 48hrs	12 (40%)	8 (26.7%)	0.273
<7 days	26 (86.7%)	13 (43.3%)	<0.001[b]
>7days	4 (13.3%)	17 (56.7%)	<0.001 [b]

Table 3 duration of prolongation of pregnancy

[a]Analysis by chi-square test, [b] Indicates significant difference with *p* value < 0.05

OUTCOME	RITODRINE (N=26)	NIFEDIPINE (N=28)	P VALUE
BIRTH WEIGHT (MEAN ± SD)	2.09 ± 0.598	2.11 ± 0.629	0.878[a]
APGAR SCORE AT 1 MIN MEAN (RANGE)	5.3 {3-7}	6.8 {5-8}	< 0.001[b,c]
APGAR SCORE AT 5 MIN MEAN (RANGE)	7.03 {5-9}	8.25 {6-9}	< 0.001 [b,c]
NICU ADMISSION	10 [38.5%]	4 [14.3%]	0.043[c d]
FETAL COMPLICATIONS	4 [15.4%]	2 [7.1%]	0.336 [d]
FETAL DEATHS	3 [11.5%]	2 [7.1%]	0.578[d]

Table 4 Outcome Data in Singletons

[a] analysis by *t*-test
[b] analysis by Mann-Whitney U-test
[c] Indicates significant difference with *p* value < 0.05
[d] analysis with chi-square test

OUTCOME	RITODRINE N=8	NIFEDIPINE N=4	P VALUE
BIRTH WEIGHT (MEAN ± SD)	1.49 ± 0.28	2.17 ± 0.174	0.001[a,b]
APGAR SCORE AT 1 MIN MEAN (RANGE)	5.37 (4-6)	6 (4-7)	0.283 [c]
APGAR SCORE AT 5 MIN MEAN (RANGE)	6.75 (5-8)	7.25 (6-8)	0.570 [c]
NICU ADMISSION	2 [25%]	1[25%]	1.0 [d]
FETAL COMPLICATIONS	2 [25%]	1 [25%]	1. 0 [d]
FETAL DEATHS	1 [12.5%]	1 [25%]	0.584 [d]

Table 5 Outcome Data in Twins

[a] Indicates significant difference with *p* value < 0.05
[b] analysis by *t*-test
[c] analysis by Mann-Whitney U-test
[d] analysis with chi-square test

Maternal side effects	Ritodrine n (%)	Nifedipine n (%)
Tremors	3 (10)	-
Palpitation	4(13.3)	-
Nausea, vomitimg	1 (3.33)	1 (3.33)
Constipation	-	4 (13.33)
Hypotension	-	1 (3.33)
Total	**8 (26.7)**	**6 (20)**

Table 6: Maternal Side Effects

A total of 8 patients in the ritodrine group (26.7%) and 6 (20%) in the nifedipine group had adverse events. Palpitation and tremors were the most common side effects in the ritodrine group, which was overcome by reducing the drip rate. In nifedipine group constipation was the most common side effect and one patient manifested with hypotension which was overcome by skipping the dose (table 6).

DISCUSSION

Preterm delivery is a major obstetrics problem associated with high perinatal mortality and morbidity. Tocolysis, the pharmacologic inhibition of uterine contractions, is currently the principal preterm birth preventive measure. Several therapeutic agents have been attempted to inhibit preterm labor such as ethanol, prostaglandin synthetase inhibitors, and Magnesium sulphate, Beta-sympathomimetics, oxytocin-antagonists, methylxanthines and calcium channel blockers.

The most commonly used tocolytic drugs in India are Beta-sympathomimetics, especially ritodrine hydrochloride. Ritodrine is a phenyl ethylamine derivative with high selectivity for uterine Beta 2-receptors. This facilitates a uterine relaxant action which is not accompanied by excessive cardiac effect mediated by Beta-2 activity. However, its use has been limited by its potentially serious maternal side effects such as hypotension, tachycardia, electrocardiographic changes, pulmonary edema and metabolic side effects. This had led to the discovery of several alternative drugs like calcium channel blockers. Nifedipine, a dihydropyridine calcium entry blocker has emerged as a potentially effective and well tolerated alternative tocolytic agent. It causes more prolongation of pregnancy and is associated with milder side effects such as flushing, headache, dizziness and sweating of palms, constipation, and rarely diarrhoea, heartburn, and dyspnoea and chest pain.

It is well documented that the incidence of severe neonatal side effects such as neonatal respiratory distress syndrome decreases with increasing gestational age. This can be prevented by concurrent administration of corticosteroids. As the beneficial effect of corticosteroids takes 48 hours to achieve maximal effect the aim of this study is to explore this possibility by comparing Ritodrine and Nifedipine in prolonging the duration of pregnancy for more than 48hours [7].

We have performed a prospective study to compare the safety and efficacy of ritodrine and nifedipine and evaluated the duration of prolongation of pregnancy including maternal side effects and neonatal outcome (one important strength being assessment of perinatal outcome was done separately in singletons and twins). We included women who presented with gestational age of 28-36 weeks with painful uterine contractions at the rate of at least 1 in every 10 min, lasting for 30-60 sec, with cervical effacement and dilatation less than 3 cms, irrespective of the status of membranes and gestation. After inclusion, women were allotted to receive either ritodrine or nifedipine. Women in both the groups were similar with respect to maternal age, parity and gestational age. The gestational age of the women was based on the date of last menstrual period with a reliable menstrual history and/or an ultrasound data performed before 20 weeks' gestation. The mean gestational age in the ritodrine group was 32.48 (±2.72) weeks and 31.86 (±2.54) weeks in the nifedipine group.

In our study dose of nifedipine was initiated with 20 mg orally and maintenance dose varied from 60-160 mg/day. Ritodrine was given as IV infusion at the rate of 50-350 µg/min depending upon the rate of suppression of uterine contractions. The dose used in our study was consistent with the doses used in previous studies conducted by Papatsonis et al [8], Koks et al [9] and Garcia-velasco & Gonzalez[10] except that in these studies nifedipine was initiated sublingually. Now it is known that there is not much difference between oral and sublingual routes on onset of action.

Our study shows that ritodrine was more effective in delaying the delivery for up to 7 days ($p < 0.001$) and nifedipine was more effective in delaying delivery for >7 days and up to term ($p < 0.001$). Papatsonis et al. [8] showed that nifedipine was more effective in delaying the delivery for > 48 hours. In a similar study conducted by Koks et al. [9] ritodrine was as effective as nifedipine in delaying the delivery. In our study, majority of patients in both the groups were delivered by vaginal route accounting for 80% and 76.7% in ritodrine and nifedipine group respectively. 16.7% in the Ritodrine group and 23.3% in the Nifedipine group babies were delivered by caesarean section. Indication for caesarean section was fetal distress and oligohydramnios. Only one (3.33%) patient in the ritodrine group was delivered by forceps due to difficult labor.

We analyzed the perinatal outcome separately in singletons and twins in terms of APGAR score at 1 and 5min, birth weight, NICU admission and fetal complications including fetal deaths. In the previous studies conducted by Papatsonis et al [8] Koks et al [9] and Garcia-velasco & Gonzalez [10], the incidence of NICU admission was more in the ritodrine group and there was no statistically significant difference with either birth weight or neonatal mortality in both the groups. In the present study, APGAR score among singletons at 1min and 5min was significantly more in the nifedipine group (6.8 & 8.25) compared to

ritodrine group (5.3 & 7.03) respectively which was statistically significant (p <0.0001). However, among twins, there was no statistically significant difference in APGAR scores at 1min and 5min. Birth weight of neonates among singletons was almost similar in both the groups whereas, among twins neonates weighed more in the nifedipine group than in the ritodrine group (p <0.001). Number of NICU admission among singletons was significantly higher in the ritodrine group than in the nifedipine group (10 vs. 4, p <0.04). However, there was no significant difference in the number of NICU admission among twins. The number of fetal complications was more and severe in the ritodrine group than in the nifedipine group though statistically not significant (10 vs 6).

As regards the maternal side effects, Studies conducted by Mawaldi et al [11] and Nandita et al [12] have shown that side effects seen with nifedipine were significantly lesser compared to ritodrine group. This is consistent with the present study. We found that nifedipine patients experienced fewer and milder side effects. In the ritodrine group 13.3% of patients experienced palpitation and 10% experienced tremors which were the major drawback of ritodrine and this necessitated dose reduction in these patients. In the nifedipine group 13.3% of patients experienced constipation, one patient manifested with hypotension which was overcome by skipping the dose. 3.33% of patients in each group experienced nausea and vomiting.

From the present study, it appears that the commonly used tocolytic Beta-2 agonist Ritodrine and calcium entry blocker Nifedipine have not shown significant difference in the type of delivery, on their effect in different age groups of patients, birth weight in singletons and neonatal mortality, but with APGAR score being significantly more in singletons in the Nifedipine group.

In the Ritodrine group, there was significantly higher NICU admission when compared to that in Nifedipine group, more fetal complications (statistically not significant) and significantly higher maternal side effects sometimes necessitating reduction in dose. But there was good short term tocolytic effect.

In the Nifedipine group, the most important statistically significant finding was its ability to prolong labor for more than seven days permitting administration of glucocorticoids for lung maturation and also delay labor up to term. Also, with less NICU admissions, less fetal complications and significantly lesser maternal side effects, Nifedipine appears to suit patients who do not tolerate Ritodrine because of side effects, or when fetal complications are likely. Finally, the findings may serve as a guidance to use Ritodrine for short term requirement of tocolysis such as in premature rupture of membranes and to prefer Nifedipine for prolongation of labor up to term depending on the requirement in a particular patient.

CONCLUSION

Though both Ritodrine and nifedipine can effectively prolong the pregnancy up to 48 hours, Nifedipine can prolong the pregnancy for more than 7 days and in some cases up to term. Although there were no statistically significant differences in the incidence of side effects in both the groups, Nifedipine because of its ease of administration, & cost

effectiveness proves to be a better tocolytic agent compared to Ritodrine, where longer duration is required. Ritodrine may be preferable for shorter duration of tocolysis. However, further studies are needed to assess differences in outcome separately in single gestation and twin gestation.

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