J Obstet Gynecol India Vol. 57, No. 2 : March/April 2007 Pg 131-134

ORIGINAL ARTICLE

The Journal of Obstetrics and Gynecology of India

Maternal and fetal cardiovascular side effects of nifedipine and ritodrine used as tocolytics

Maitra *Nandita*, Christian *Vincent*, Verma *RN*, Desai *VA*

Department of Obstetrics and Gynaecology, Government Medical College, Surat.

OBJECTIVE(S) : To evaluate and compare the side effects and tolerability of nifedipine and ritodrine in preterm labor.

METHOD(S) : Seventy consecutive women with clinical features of preterm labor fulfilling designated inclusion and exclusion criteria were enrolled in the study. They were alternately allocated to receive nifedipine or ritodrine. Tocolytic efficacy, maternal side effects, and tolerability were evaluated.

RESULT(S) : Both drugs caused an increase in pulse rate and fetal heart rate, and decrease in systolic and diastolic blood pressure. These changes were statistically significant in the ritodrine group. Side effects were seen in 5.7% women in the nifedipine group and 34.2% women in the ritodrine group. In the ritodrine group 85. 7% women had completed therapy with 8.57% having intolerable side effects and 14.28% having failed in arresting preterm labor. In the nifedipine group, 97.14% had completed therapy and 2.8% had failed in arresting preterm labor.

CONCLUSION(S) : Nifedipine was more successful in arresting preterm labor with less side effects and better tolerability as compared to ritodrine.

Key words : nifedipine, ritodrine, tocolysis

Introduction

Preterm birth is a common complication in pregnancy, and has been reported to cause up to 85% of early neonatal deaths [1]. It can be responsible for brain damage (brain white matter damage), respiratory distress syndrome (bronchopulmonary dysplasia)[2], infection, and possibly long term psychological effects.

Ritodrine, a ?$_2$ mimetic and nifedipine a calcium channel blocker are commonly used tocolytics for the suppression of preterm labor. Calcium channel blockers are characterized by their ability to inhibit calcium influx through potential sensitive channels and possibly also through receptor operated channels[3]. Maternal side effects of nifedipine are uncommon and include flushing, headache, dizziness and sweating of palms [3]. Rarely constipation, diarrhea, heartburn, dyspnea and chest pain have been reported. Tachycardia occurs commonly but is seldom associated with palpitation and appears to have no adverse effects. A reduction in blood pressure in normotensives is clinically insignificant. Nifedipine is rated as a category C drug with respect to its use in pregnancy. No specific congenital defects in the human fetus have been reported.

Ritodrine is a phenylethylamine derivative with high selectivity for uterine ?2 receptors. High selectivity of ritodrine for uterine ?2 receptors facilitates a uterine relaxant action, which is not accompanied by excessive cardiac effect mediated by ?2 activity. Infusion of ritodrine like other ? adrenergic agonists, has resulted in frequent and at times serious side effects such as hypotension, tachycardia, pulmonary edema, electrocardiographic changes, and metabolic side effects [4].

We evaluated the maternal and fetal side effects and tolerability of nifedipine and ritodrine used as tocolytics for

Paper received on 26/04/2006 ; accepted on 05/12/2006

Correspondence :
Dr. Nandita Maitra
15, Gautamnagar Society
Race Course Road, Baroda 390 007
Tel. 0265 2355142

the suppression of preterm labor.

Methods

Seventy consecutive women coming with symptoms of preterm labor and fulfilling designated inclusion criteria were recruited and alternately assigned to either nifedipine or ritodrine treatment. Thirty five women (odd numbers) were allocated to ritodrine (Group A) and 35 (even numbers) to nifedipine (Group B). Sample size was calculated on the premise that in order to detect a difference of 10 bpm in maternal pulse and 10 mm Hg in maternal blood pressure at an alpha level of 5% and for a power of 80%, it would be required to recruit at least 73 women across the two groups.

Informed consent was taken. Approval was obtained from the hospital ethics committee. The study was carried out over a period of one year. Women with a singleton pregnancy between 20 to 36 weeks gestation, intact membranes, and preterm labor (defined as regular uterine contractions of at least 1 in 10 minutes, during at least 1 hour with or without dilation or effacement) and with known last menstrual period (LMP) or an ultrasonography in first trimester, were included. Those with multiple pregnancy, ruptured membranes, abruptio placenta, fetal distress, and a known medical disorder contraindicating use of ?mimetic drugs were excluded.

Detailed history was taken and thorough general, systemic, and obstetric examinations done. A vaginal examination was carried out taking aseptic precautions. Each woman was investigated for hemoglobin estimation, albuminurea, glycosuria, bacterimia, blood group estimation, and random blood sugar. Electrolytes and total and differential leukocyte count were estimated. High vaginal swabs were taken.

Group A women were given intravenous ritodrine followed by oral ritodrine for 72 hours. Group B, women were given oral nifedipine for 72 hours. Subjects in both the groups were given injection betamethasone 12 mg for 2 doses 12 hours apart. Uterine activity cessation and maternal side effects if any were noted. Women in whom uterine activity did not cease in 6 hours or who developed side effects to first line drug were given tablet indomethacin 50-100 mg followed by 25 mg 6 hourly for 3 days. The dosage schedules for nifedipine and ritodrine were as per the recommendations of King et al [5] and Arias [6] respectively. Nifedipine was given in the dose of 20 mg orally followed by 20 mg orally after 30 minutes if contractions persisted, followed by another 20 mg orally after 30 minutes if contractions persisted and thereafter followed by 20 mg orally 3-8 hourly for 72 hours as required. Maximum dose did not exceed 160 mg/day. After 72 hours tocolytic therapy was omitted. No maintenance therapy was given. If the woman again developed preterm labor later in pregnancy the same schedule was followed.

Ritodrine by intravenous infusion (150 mg i.e., 3 ampoules in 500 mL of 5% dextrose giving 300 ?g ritodrine/mL) using altarwad pump or dial flow was started at the rate of 50 ?g/minute (0.33 mL/minute or 10 mL/hour), increased every 10 minutes by 50 ?g/minute (10 mL/hour) until contractions stoppoed. If maternal pulse rate increased to 120/minute or toxicity appeared the infusion was stopped. A maximum dose of 350 ?g/minute (70 mL/hour) was given. Once adequate dose was reached, it was maintained for 12 hours after contractions stopped. The dosage was not tapered down before switching to oral treatment. Estimation of blood glucose and serum potassium was done at the start and repeated 6 hourly. One tablet of 10 mg ritodrine was given 30 minutes before the infusion was discontinued. The administration of one tablet every 4 hourly was continued if required for first 24 hours as long as pulse rate did not exceed 120/minute. The dose was adjusted to 10 mg every 4 to 6 hours. Oral treatment was given for 3 days in all.

Statistical analysis

All data were entered and analyzed using EP 16 software. P value of <0.05 was considered statistically significant. Standard error of difference between two means was the test of significance used.

Results

Table 1 shows the base line vital signs such as systolic and diastolic blood pressure, and maternal and fetal pulse rate, and effect of nifedipine and ritodrine thereon. The baseline values were similar in the two groups.

Following treatment, the mean systolic blood pressure dropped significantly in both the groups, in the ritodrine group from 113.7 ± 6.4 mmHg to 102.6 ± 6.60 mm of Hg (P=0.0001) and in the nifedipine group from 114.91 ± 7.39 mm Hg to 107.14 ± 6.67 mm of Hg (P=0.0001). The mean pulse rate in ritodrine group before treatment was 90.40 ± 4.13/minute and after treatment it was 116.57±6.53/minute. This observation was statistically significant (P=0.0001). In the nifedipine group the baseline pulse was 91.45 ± 8.30/minute and after treatment it was 100.62 ± 10.09/minute (P=0.0001).

In the ritodrine group the fetal heart rate before treatment was 138.34 ± 5.07/minute and after treatment it was 166.71 ± 14.06/minute. This difference was statistically significant (P<0.0001). In the nifedipine group, the mean fetal heart rate was 140.57±5.91 minute before treatment and it was 158.80 ± 11.93 minute after treatment (P=0.0001) (Table 1).

Table 1 : Effect of ritodrine and nifedipine on maternal pulse and blood pressure and on fetal heart rate.

Drug	Before treatment [a,b]	After treatment [b]	P value
Ritodrine (n=35)			
Systolic blood pressure (mm Hg) (mean ± SD)	113.7 ± 6.4	102.6 ± 6.6 [c]	0.001
Diastolic blood pressure (mmHg) (mean ± SD)	78.60 ± 4.3	76.85 ± 6.8 [d]	0.2
Pulse/minute	90.40 ± 4.13	116.57 [e] ± 6.53 [e]	0.0001
Fetal heart rate/minute	138.34 ± 5.07	166.71 ± 14.06 [f]	0.0001
Nifedipine (n=35)			
Systolic blood pressure (mean ± SD)	114.91 ± 7.39	107.14 ± 6.67 [c]	0.0001
Diastolic blood pressure (mean ± SD)	79.71 ± 3.03	77.42 ± 5.60 [d]	0.04
Pulse/minute	91.48 ± 8.30	100.62 ± 10.09 [e]	0.0001
Fetal heart rate/minute	140. 57 ± 5.91	158.80 ± 11.93 [f]	0.0001

[a] The differences between before treatment values of ritodrine group and nifedifine group were statistically significant.

[b] Lowest values reached for systolic and diastolic blood pressures and maximum values recorded for pulse and fetal heart rates.

[c] P=0.0051 [d] P=0.07 [e] P=0.0001 [f] P=0.013

T**able 2. Comparison of side effects.**

Side effect	Nifedipine (n=35)		Ritodrine (n=35)	
	Number	Percent	Number	Percent
Maternal tachycardia (> 120/minute)	0	-	4	11.42
Hypotension (blood pressure<90/60mmHg)	0	-	0	-
Palpitation	0	-	2	5.71
Chest pain	0	-	1	2.85
Nausea	1	2.85	0	-
Vomiting	1	2.85	0	-
Headache	0	-	0	-
Dizziness	0	-	0	-
Fetal tachycardia (>180/minute)	0	-	2	5.71
Pulmonary edema	0	-	2	5.71
Diarrhea	0	-	1	2.88
Total	2	5.7 [a]	12	34.2 [a]

[a] P=0.003

Table 2 shows the side effects in the two groups. There was no significant difference between the two groups.

Two women in the ritodrine group showed presence of early basal lung crepitations. Lung crepitations disappeared promptly after giving furosemide. In both these women, ritodrine was discontinued and an alternative agent was given.

In the ritodrine group 85.7% (n=30) women completed therapy, 8.57% (n=3) had intolerable side effects, and 14.28% (n=5) had failed in arresting preterm labor. In the nifedipine group, 97.14% (n=34) women had completed therapy and 2.8% (n=1) had failed in arresting preterm labor.

Discussion

Nifedipine was better at prolonging pregnancy as compared to ritodrine but not statistically significantly so (97.14% vs 85.57%, P=0.2). Both agents caused an increase in pulse rate and in fetal heart rate, and decrease in systolic and diastolic blood pressure; the changes were statistically significant (Table 1). Side effects were present in 5.7% (n=2) women in the nifedipine group and 34.2% (n=12) in the ritodrine group (P=0.003).

Kupferminc et al [7] found that the fall in mean arterial and diastolic blood pressure and the rise in maternal heart rate were significantly greater with ritodrine than with nifedipine. In their study of the 30 women treated with ritodrine, 23 experienced at least one side effect compared with only eight women in the nifedipine group (P<0.001). Geijn et al [8], in a review of literature on nifedipine, found that myocardial infarction has been reported in about 4% of women and congestive cardiac failure or pulmonary edema in 2% of women on extended release nifedipine. Of the eight cases reported in the literature with myocardial infarction, two were healthy adults with normal electrocardiogram, one had asymptomatic ventricular septal defect, two had twins, one had triplets, and one had mitral valve prolapse. In these studies the dose of nifedipine used was higher than that in our study.

In a metaanalysis by Tsatsaris et al [9], nifedipine had minimal effects on maternal pulse rate, systolic and diastolic blood pressure, serum potassium, and blood sugar level.

Nifedipine has better tocolytic efficacy, less side effects, and better tolerability as compared to ritodrine. However, it has both vascular and cardiac effects, it vasodilates vessels, and exerts negative ionotropic and chronotropic effect depressing the heart. The incease in sympathetic tone compensates for these effects. These effects of nifedipine may under certain circumstances endanger life of women suffering from cardiac disease (overt or occult) or of those developing cardiomyopathy during pregnancy. These facts should be kept in mind and caution exercised when selecting women for treatment with nifedipine.

Conclusion

Nifedipine was more successful in arresting preterm labor with less side effects and better tolerability as compared to ritodrine. The limitation of this study is that this was not a randomized controlled trial and it recruited a small sample size. The rare but serious adverse effects of infedipine such as myocardial infarction and acute left ventricular failure quoted in literature could not be assessed in this study but should be kept in mind while administering this drug.

Acknowledgement

The authors are greatful to Dr. Abhay Kavishwar of the department of P&SM for help and guidance with the satistical analysis.

References

1. Steer P. The epidemiology of preterm labor. BJOG 2005;112 Suppl 1:1-3.
2. Dammann O, Leviton A, Gappa M et al. Lung and brain damage in preterm newborns, and their association with gestational age prematurity subgroup, infection/inflammation and long term outcome. BJOG 2005;112 Suppl 1: 4-9.
3. Fergusson JE 2nd, Schutz T, Perohe R et al. Nifedipine pharmacokinetics during preterm labor tocolysis. Am J Obstet Gynecol 1989;161:1485-90.
4. Li X, Zhang Y, Shi Z. Ritodrine in the treatment of preterm labor: a meta-analysis, Indian J Med Res 2005;121:120-7.
5. King JF, Flenady V, Papatsonis D et al. Calcium channel blockers for inhibiting preterm labour, a systematic review of the evidence and a protocol for administration of nifedipine. AN Z J Obstet Gynaecol 2003;43:192-8.
6. Arias F. Practical guide to high risk pregnancy and delivery, 2nd edn. New Dlehi, Elsevier. 2004;71-95.
7. Kupferminc M, Lessing JB, Yaron Y et al. Nifedipine versus ritodrine for suppression of preterm labour. Br J Obstet Gynaecol 1993;100:1090-4.
8. van Geijn HP, Lenglet JE, Botte AC. Nifedipine trials: effectiveness and safety aspects. BJOG 2005;112 Supplement 1 :79-83.
9. Tsatsaris V, Paptsonis D, Goffnet F et al. Tocolysis with nifedipine or beta-adrenergic agonists: a metaanalysis. Obstet Gynecol 2001;97:840-7.