A comparative study of oral nifedipine and intravenous ritodrine as tocolytic agents

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ABSTRACT

Background: Tocolytics used in clinical practice are betamimetics, calcium channel blockers, magnesium sulphate, non-steroidal anti-in?ammatory agents, and atosiban (oxytocin receptor antagonist). This wide range of tocolytic agents in use is testament to the fact that we still do not have an ideal drug available.

Aim: To evaluate and compare the tocolytic effect of oral nifedipine with intravenous ritodrine in treatment of preterm labour.

Methods: This randomized study was conducted between Dec'2005 & Nov'2007. Sixty women presenting with preterm labour between 24 weeks and 34 weeks of gestation were enrolled. The group A (n=30) received oral nifedipine and group B (n=30) received intravenous ritodrine for tocolysis. Women were followed up till the time of delivery and neonatal outcome was recorded.

Results: Statistically significant prolongation of pregnancy for $\geq$7 days was found in nifedipine group in comparison to ritodrine group ($p<.05$). Nifedipine was well tolerated by most patients. Multiple side effects were encountered in 6.67% of patients in nifedipine group compared to 33.33% in ritodrine group ($p<.01$). Birth weight of neonates was significantly higher in nifedipine group ($p<.05$).

Conclusion: Oral nifedipine should be preferred to intravenous ritodrine because of higher efficacy, greater ease of administration and lack of side effects.

Key words: preterm birth, ritodrine, nifedipine, tocolysis, side effects

INTRODUCTION

Preterm labour is a leading cause of perinatal morbidity and mortality. It is associated with 60%-80% of death of infants without congenital abnormalities.[1] In India, incidence of preterm labor is 23.3% and of preterm delivery is 10-69%.[2,3] The criteria proposed by the American College of Obstetricians and Gynaecologists[3](1997) to document preterm labor includes- contractions of 4 in 20 minutes or 8 in 60 minutes plus progressive changes in cervix ,cervical dilatation>1 cm and effacement of $\geq$80%. Various modalities that have been used for inhibition of preterm labour are bed rest, hydration, sedation, beta sympathomimetics (isoxuprine and ritodrine), magnesium sulphate, prostaglandin synthetase inhibitors (indomethacin), calcium channel blockers (nifedipine), oxytocin antagonist (atosiban) and nitric oxide donors (nitroglycerine).

Ritodrine, a beta sympathomimetic, is one such agent which is commonly used as tocolytic agent. But, it has serious maternal and fetal side effects limiting its use. Nifedipine, a calcium channel blocker, is an effective smooth muscle relaxant with low toxicity and low teratogenicity. 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. However studies in human pregnancies did not show any significant alteration in uterine blood flow. This study was undertaken to evaluate and compare tocolytic effect of oral nifedipine and intravenous ritodrine with comparison of results in light of available literature.

MATERIALS AND METHODS

This hospital based comparative study was

conducted after obtaining permission from the institutional ethical committee. Sixty multipara consenting women aged between 20 to 30 years with gestational age of 24 to 34 weeks with singleton pregnancy fulfilling definition of preterm labour were included in the study. Participants were randomized into two groups by using computer generated random numbers till desired sample size was achieved. Group A received oral nifedipine 30 mg stat in first hour followed by 10 mg 6 hourly for maximum duration of 48 hours. Group B received ritodrine infusion at the rate of 50 µg per minute and the dose was increased every 10 minutes by 50µg per minute. Indications for discontinuation were stoppage of uterine contractions, pulse exceeding 120 beats per minute, appearance of toxicity, a maximal dose of 350µg per minute, or till 12 hours duration. Tablet ritodrine 10 mg every 2-4 hours (maximum dose 120mg/day) was started for next 36 hours. All patients received antenatal corticosteroids for foetal lung maturity. Blood pressure, pulse, and side effects were monitored for 48 hrs. Women were followed up till time of delivery and after delivery neonatal outcome was recorded. Statistical analysis: Descriptive statistics were used wherever applicable. For continuous variables student 'T' test was applied. To see association among variables chi square test was used. *p* value of <0.05 was taken as significant.

RESULTS

Participants in both the groups were compared for various parameters that could adversely affect the outcome of the study, and was found to be non-significant *(Table 1).* Statistically significant prolongation of pregnancy for ≥7 days and ≥36 weeks of gestation was observed in Group A. Mean gestational age at the time of delivery was 34.67± 2.73 weeks in Group A, and 32.95±2.68 weeks in Group B (p<.01). *(Table 2)* Mean birth weight of neonates was 2.51 ± 0.61 kg in Group A compared to 2.12 ± 0.74 kg in Group B (p <.05). Neonatal intensive care unit (NICU) admissions were less in Group A but were statistically not significant. Nifedipine was well tolerated by the patients and did not cause cessation of tocolysis in any women. One third patients of Group B had multiple side effect compared to 6.67% patients in Group A (p<.01).(Table3).

Table 1. Distribution of patients according to various parameters

Parameters	Group-A n=30	Group-B n=30	p-value
Age (yrs) Mean ± SD	25.50 ± 3.63	25.97 ± 3.23	> 0.05
Gestation age (wks)	31.17 ± 2.33	30.77 ± 2.00	> 0.05
Mean ± SD No. of contractions /	2.93 ± 0.51	2.60 ± 0.66	> 0.05
10min Mean ± SD H/O Previous	3	4	>0 .05
preterm birth			
Cervical Dilatation (cm) Mean ± SD	1.23 ± 1.06	1.05 ± .92	> 0.05

Table 2. Mean ± SD of various parameters at the time of delivery

Parameters	Mean ± SD Group-A n=30	Group-B n=30	p-Value
Absolute prolongation of gestation (days)	24.50 ± 20.05	14.33 ± 19.03	< 0.05
Gestation age at the time of delivery (wks)	34.67 ± 2.73	32.95 ± 2.68	< 0.01

Table 3. Distribution of side effects

Side Effects	Group -A n=30	Group - B n=30	X2	p-value
Tachycardia	10.00 %	33.33 %	3.532	> 0.05
Palpitation	3.33 %	26.67 %	4.706	< 0.05
Headache	10.00 %	16.67 %	0.144	>0.05
Chest Pain	0.00 %	20.00 %	-	-
Nausea	0.00 %	10.00 %	-	-
Pulmonary edema	0.00 %	10.00 %	-	-
Vomiting	0.00 %	3.33 %	-	-
Flushing	6.67 %	0.00 %	-	-
Patients with > 1 side effects	6.67 %	33.33 %	6.284	<0.01

DISCUSSION

This study compares the efficacy, side effects, neonatal outcomes and safety of Nifedipine with Ritodrine in the suppression of preterm labor. That baseline characteristics of the study population like maternal age, mean gestational age, cervical

dilatation or effacement, number of contractions per 10 minutes were comparable to characteristics of study population in earlier studies.[4-7] In our study prolongation of gestational period by >7 weeks or till 36 weeks of gestation in patients receiving nifedipine were comparable to studies done by Read MD & Wellby DE et al, Al Qattan F et al, Papatsonis et al and Maitra N et al.[2,6,7,8,9] In 91.5% subjects on nifedipine, labour was delayed for 2 weeks compared to 62.9% subjects on ritodrine. Nifedipine was better tolerated than ritodrine as had been observed by various researchers.[7,9] Nifedipine caused fewer side effects which subsided after few hours and did not necessitate any special treatment whereas Ritodrine group had more frequent and serious side effects. According to Kupferminc et al[5] total percentage of patient experiencing side effects were 27% in Nifedipine group and 77% in Ritodrine group ($p<0.01$).

Perinatal outcome like higher mean birth weight and significantly fewer NICU admissions was better in nifedipine group compared to ritodrine group, which is comparable to earlier studies.[6]

CONCLUSION

Oral Nifedipine is a cheaper, effective alternative and has less serious, fewer side effects. It was more successful in delaying the delivery for 48 h which would enhance fetal lung maturity by use of corticosteroids.

AUTHOR NOTE

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REFERENCES

1. Anotayanonth S, Subhedar NV, Garner P, Neilson JP, Harigopal S. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev.* 2004 Oct 18;(4):CD004352.
2. Maitra N, Christian V, Kavishvar A. Tocolytic efficacy of nifedipine versus ritodrine in preterm labor. *Int J Gynaecol Obstet.* 2007 May;97(2):147-8.
3. Singh U, Singh N, Seth S. A prospective analysis of etiology and outcome of preterm labour. *J Obstet Gynecol India.* 2007;57:48-52.
4. Ferguson JE 2nd, Dyson DC, Schutz T, Stevenson DK. A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome. *Am J Obstet Gynecol.* 1990 Jul;163(1 Pt 1):105-11.
5. Kupferminc M, Lessing JB, Yaron Y, Peyser MR. Nifedipine versus ritodrine for suppression of preterm labour. *Br J Obstet Gynaecol.* 1993 Dec;100(12):1090-4.
6. Papatsonis DN, Van Geijn HP, Adèr HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. *Obstet Gynecol.* 1997 Aug;90(2):230-4.
7. Papatsonis DN, Kok JH, van Geijn HP, Bleker OP, Adèr HJ, Dekker GA. Neonatal effects of nifedipine and ritodrine for preterm labor. *Obstet Gynecol.* 2000 Apr;95(4):477-81.
8. Read MD, Wellby DE. The use of a calcium antagonist (nifedipine) to suppress preterm labour. *Br J Obstet Gynaecol.* 1986 Sep;93(9):933-7.
9. Al-Qattan F, Omu AE, Labeeb N. A prospective randomized study comparing nifedipine versus ritodrine for the suppression of preterm labour. *Medical Principles and Practice.* 2000;9(3):164-73.