THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (September–October 2011) 61(5):512–515
DOI 10.1007/s13224-011-0080-1

ORIGINAL ARTICLE

Comparative Study of Nifedipine and Isoxpurine as Tocolytics for Preterm Labor

Singh Nisha · Singh Uma · Seth Shikha

Received: 13 April 2009 / Accepted: 21 June 2011 / Published online: 29 October 2011

Abstract

Objectives This study was done to compare isoxpurine hydrochloride and nifedipine as tocolytic drugs for preterm labor.

Methods A prospective cohort study of 832 antenatal women with preterm labor was conducted in the Department of Obstetrics & Gynecology. Out of 400 women found eligible for tocolysis, 200 were given isoxpurine hydrochloride while the other 200 were given nifedipine randomly. The data obtained was statistically analyzed on SPSS 10.0 of Windows 2003.

Results Incidence of preterm labor was 22% while the incidence of preterm delivery was 20.9%. Nifedipine was twice more effective than isoxpurine hydrochloride as a tocolytic agent as a tocolytic agent (P value 0.006) while side effects were comparable (P value 0.133). In early-diagnosed preterm labor, nifedipine had higher efficacy than isoxpurine (P value 6.45×10^{-6}) and also higher efficacy than its own in late diagnosed preterm labor (P value 2.08×10^{-5}).

Conclusions There is a high incidence of preterm labor in India. Nifedipine is a better tocolytic drug than isoxpurine hydrochloride, especially when started with the earliest signs of preterm labor.

Singh N. (✉), Associate Professor · Singh U., Professor · Seth S., Senior Resident
Department of Obstetrics & Gynecology, CSM Medical University (former KGMC), A-172 South City, Lucknow, UP, India
e-mail: nisha.kgmc@gmail.com

Keywords Uterine tocolytics · Preterm birth · Betamethasone · Prematurity nifedipine · Isoxpurine hydrochloride

Introduction

Preterm labor & delivery is one of the biggest challenges for obstetricians and so are the preterm babies for the pediatricians. Preterm delivery affects 11% in U.S. [1] or even greater in developing countries (23.3% in India) [2] and it accounts for 40–75% of neonatal deaths. Incidence of preterm labor and delivery shows increasing trends in countries where data is available [1–4]. It could be due to assisted reproductive techniques, psychosocial stress, or medically induced prematurity.

Prediction and prevention of preterm labor is not possible despite extensive research on the subject. So, we have to face preterm labor and manage our patients according to their gestational age. Preterm labor before 34 weeks needs to be arrested for at least 48 h so that fetal pulmonary maturity is attained using betamethasone. Delivery between 34 and 37 weeks reduces the risk of respiratory distress syndrome but does not exempt the baby from other complications of prematurity. Thus tocolytic agents are frequently used in obstetric practice. β-adrenergic receptor blocking agent isoxsuprine hydrochloride and calcium channel blocker nifedipine are two commonly used tocolytic agents in India. This study was done to compare their efficacy and analyze the overall

outcome of preterm labor using tocolytics in a tertiary care center of India.

Material and Method

This was a prospective cohort study of 832 antenatal women conducted in the Department of Obstetrics & Gynecology. Written informed consent was taken from the subjects recruited in the study.

Antenatal women between 22 and 37 weeks of gestation with preterm labor as per the ACOG criteria (i.e., four uterine contractions in 20 min with or without cervical dilatation >1 cm. or effacement 80% or greater) were recruited in the study. They were evaluated thoroughly by detailed history, clinical examination and ultrasonography if not done before. Amniotic membrane status was noted on vaginal examination.

Female patients with gestational age greater than 36 completed weeks, those in active phase of labor (cervical dilatation >4 cm), those with clinical picture of chorio-amnionitis, ante-partum hemorrhage, fetal distress, intra-uterine demise, or any medical contraindication to tocolysis were allowed delivery. This group comprised of 432 cases.

Remaining 400 female patients with preterm labor were given tocolysis with either isoxsuprine hydrochloride or nifedipine as per the instructions in the sealed white envelopes that were opened on recruiting the woman for the study. Group I constituted subjects who were given 20 mg oral Nifedipine initially followed by 10 mg at 4 hourly intervals for 48 h. Drug dose was gradually tapered every 24 h and then stopped. If contractions persisted at 90 min, the first 10 mg dose was started at the same time. Group II constituted subjects who were given injection Isoxsuprine 10 mg intramuscularly and repeated at 6 h interval for 48 h. Patients who responded were switched over to 20 mg oral retard tablet given 12 hourly as maintenance therapy for 1 week. In both groups subjects were strictly monitored for uterine contractions, maternal pulse rate, palpitation and fetal heart rate. In case of any serious side effects os progression of labor, the respective drug was stopped.

All the patients were stratified into subgroups A (uterine contractions <30 s & cervical dilatation <2 cm) and B (uterine contractions >30 s or cervical dilatation >2 cm) for comparing the efficacy in early or late onset tocolysis.

All women with preterm labor were investigated for infection by complete hemogram, urine and vaginal swab culture. Antibiotics were provided to cases having significant pathogen count in urine or vaginal culture accordingly. Women with gestational age less than 34 completed weeks were given 12 mg Betamethasone intramuscularly that was repeated after an interval of 24 h.

Goal of tocolysis was to delay delivery for 48 h in patients with ruptured membranes and through 36 completed weeks of gestation in patients with intact membranes. Tocolysis was considered failed if uterine quiescence was not achieved despite maximum dose and delivery occurred within 48 h. Patients, in whom delivery was delayed for at least 48 h, were taken as cases of primary success. They were transferred to antenatal ward and discharged home after two additional days in hospital for bed rest with bathroom privileges. Patients were followed till delivery and data was recorded about side effects that patients developed during the treatment, time interval between admission and delivery and neonatal outcome.

Statistical analysis was done using SPSS 10.0 of Windows 2003.

Results

Out of total 3,768 antenatal admissions during the study period, 832 (22%) were admitted for preterm labor. Total live births in the same duration were 3,228 out of which 676 were preterm deliveries giving an incidence of preterm delivery of 20.9%. Out of 832 cases of PTL, 400 were given tocolysis.

Gestational age wise distribution of cases and their final outcome is shown in Table 1. There was no significant difference in various confounding factors between the two groups as shown in Table 2**.**

Table 3 shows the overall effect of the two types of tocolytic therapy. Overall success rate of tocolysis was 74%. Successful tocolysis was achieved in 80% cases of nifedipine group and 68 % cases of isoxpurine group showing a statistically significant (*P* value 0.006) advantage in nifedipine group.

Out of 400 cases of PTL, 244 belonged to subgroup A and 156 belonged to subgroup B. Analysis of the tocolytic effect in the two subgroups showed that subgroup A has better success rate (*P* value 2.08×10^{-5}) as compared to subgroup B. The success rate of nifedipine (112/124) was significantly higher (*P* value $6.45 \times 10^{-60)}$ than that of isoxpurine (80/120) in subgroup A. The comparative efficacy of the two drugs was similar in subgroup B (*P* value 0.09).

There were 216 cases of preterm rupture of membranes, out of which 156 were allowed spontaneous labor due to reasons described before, while 62 cases were given tocolysis. Failure rate was reported to be quite high i.e., (28/62) 45.2% in cases with ruptured membranes compared to only (76/338) 22.5% in cases with intact membrane. No significant difference in outcome was noted in nifedipine &

Table 1 Ditribution of preterm labor cases according to gestational age ($n = 832$)

Gestation age	Preterm labor cases (no.)	Tocolysis group (no.)			Preterm deliveries (no.)
		Nifedipine	Isoxsuprine	Total	
<28 weeks	30	10	8	18	24
28–34 weeks	314	100	92	192	222
34–36 weeks	404	90	100	190	346
>36 weeks	84	–	–	–	84
Total number	832	200	200	400	676

Table 2 Maternal factors in both treatment groups

Factors	Nifedipine (200)	Isoxsuprine (200)
Mean age (years)	24.7	25.6
Parity		
Primigravidae (*n*)	96	90
Multigravidae (*n*)	104	110
Cases in subgroup A		
Uterine cont <30 s & Cx dilatation <2 cm	124	120
Cases in subgroup B		
Uterine cont >30 s or Cx dilatation >2 cm	76	80
Mean cervical effacement (%)	62	65
Rupture of membranes (*n*)	32	30

isoxsuprine groups. Induction of labor was carried out in 24 out of 34 cases of successful tocolysis while the other ten delivered after 1 week by spontaneous labor.

Maternal side effects were noted in 17% cases of nifedipine group and 23% of isoxsuprine group with no significant statistical difference (P value 0.133). Nausea, vomiting, headache and palpitation were main side effects in both groups. Flushing was common with nifedipine and tachypnoea was reported in one case with isoxsuprine. No case of pulmonary edema was noted in any of the groups.

During the study period, 716 preterm babies were born through 676 preterm deliveries. Neonatal mortality was 30% before 34 weeks as compared to 3.4% after 34 weeks of gestation. It was significantly higher (29.1%) even in babies who received betamethasone (P value 2.8×10^{-30})

Neonatal morbidity was seen in the form of septicemia, encephalitis and RDS (respiratory distress syndrome). RDS was significantly lower (P value 0.029) in those who received betamethasone but the overall morbidity did not show significant difference with or without betamethasone (P value 0.043). There were two intrauterine demises in less than 34 weeks gestation, one in nifedipine group and another in isoxsuprine group.

Discussion

Incidence of preterm labor is quite high in our country [2] compared to developed countries (11% in USA) [1]. It has been found to be 22% in our study. Obstetricians face the challenge of managing an established preterm labor with pharmacological agents, which differ in uterine specificity, efficacy and side effects both maternal and fetal. These tocolytic drugs inhibit uterine contractions and relax the uterine myometrium by different mechanisms leading to arrest of preterm labor.

Beta-sympathomimetics act through cyclic GMP to inhibit uterine contractions while calcium channel blockers directly inhibit calcium ion influx across the cell membrane, thus decreasing the smooth muscle tone. In our study, we compared the two tocolytic drugs commonly used in India i.e. isoxsuprine hydrochloride (beta-agonist) and nifedipine (calcium channel blocker).

Cochrane review 2004 [5] on preterm labor concludes that tocolysis is definitely indicated before 34 weeks gestational age. This is because of the reduction in number of

Table 3 Comparative effect of tocolytic therapy in two groups

Admission delivery interval	Group-I nifedipine ($n = 200$)			Group II isoxsuprine ($n = 200$)			Total	*P* value
	A (124)	B (76)	Overall (200)	A (120)	B (80)	Overall (200)	($n = 400$)	
<48 h Failure rate	12	28	40 (20%)	24	40	64 (32%)	104 (26%)	
≥48 h <37 Weeks successful tocolysis & preterm delivery			72			68	140	
≥37 Weeks successful tocolysis with term delivery			88			68	156	
Success rate	112	48	160 (80%)	96	40	136 (68%)	296 (74%)	0.006

women delivering within next 7 days and resultant decrease in neonatal morbidity from RDS, necrotizing enterocolitis, intra-ventricular hemorrhage and neonatal jaundice. In our study, it was found that tocolysis delayed delivery in 39% of total cases and maximum (47.9%) in 28–34 weeks gestation age group, which is the most vulnerable group. This delay in delivery allows time for the steroids to accelerate pulmonary maturity and improve the neonatal survival.

Contrary to the situation in developed countries, neonatal morbidity and mortality is significantly higher in developing countries despite the standard use of betamethasone. As is evident from the results of the present study, delaying delivery up to 36 weeks gestational age benefits the neonate to overcome other problems of prematurity.

In the present study, nifedipine shows significantly better efficacy (80%) in delaying delivery for 48 h as compared to Isoxsuprine only 68%. Pregnancies were prolonged up to 36 completed weeks in 36% cases by nifedipine compared to 29% by isoxsuprine.

Smith and Woodland [6] compared the tocolytic effect of nifedipine with terbutaline and found similar efficacy (71 vs. 68%) of the two drugs. Jannet et al. [7], on comparing salbutamol with nicardipine on 45 cases of preterm labor in each group found that both mean gestational age of delivery and percentage of deliveries after 37 weeks were higher in nicardipine group (P value < 0.05).

Various studies have compared ritodrine with nifedipine and found that both are equally effective in suppressing preterm labor but side effects were significantly less with nifedipine [8–12]. In our study also no significant difference was noted in maternal and neonatal side effects but less side effects were noted in nifedipine group. Side effects reported with nifedipine were headache [5] and palpitation.

Preterm premature rupture of membranes (PPROM) is one of the most common causes of preterm labor. Tocolysis in such cases is less effective than with intact membranes. Delivery could be delayed by 48 h in 55% cases of PPROM against 78% in intact membranes group. No significant difference was noted in efficacy of two tocolytic drugs in this respect.

The RCOG [13] recommends that if a tocolytic drug is to be used, ritodrine is no longer the first choice. Atosiban and nifedipine appear to be preferable as they have fewer adverse effects and seem to have comparable effectiveness. The "choice" of tocolyic agent, which could improve neonatal outcome with no maternal or neonatal side effect, has not yet surfaced.

Conclusion

Nifedipine has been found to be more effective than isoxsuprine in this large-scale study. In subgroup A (early PTL) significant difference can be seen in success rates among the two tocolytics agents, indicating thereby that early initiation of tocolysis with nifedipine is definitely beneficial in cases of preterm labor.

Acknowledgment We acknowledge the contribution of all patients and doctors of Department of Obstetrics and Gynecology, CSM Medical University involved in this study.

References

1. Martin JA, Kochank KD, Strobino DM, et al. Annual summary of vital statistics 2003. Pediatrics. 2005;115:619–39.
2. Begum F, Buckshee K, Pande JN. Risk factors associated with preterm labor. Bangladesh Med Ras Coune Bull. 2003;29:59–66.
3. Bibby E, Stewart A. The epidemiology of preterm birth. Neuro Endocrinol Lett. 2004;25:43–7.
4. Shingairai AF, Siaban DH, Godfrey BW. Risk factors for prematurity at Harare maternity hospital, Zimbabwe. Int J Epidemiol. 2004;33:1194–201.
5. King JF, Flenady VJ, Papatsonis DNM et al. Calcium channel blockers for inhibiting preterm labor (cochrane review). The cochrane library. Chichester: Wiley; 2004.
6. Smith CS, Woodland MB. Clinical comparison of oral nifedipine and subcutaneous terbutaline for initial tocolysis. Am J Perinatol. 1993;10:280–4.
7. Jannet D, Abankwa A, Guyard B, et al. Nicardipine versus salbutamol in the treatment of premature labor. Eur J Obstet Gynecol Reprod Biol. 1997;73:11–6.
8. Bracero LA, Leikin E, Kirshenbaum N, et al. Comparison of nifedipine and ritodrine for the treatment of preterm labor. Am J Perinatol. 1991;8:365–9.
9. Papatsonis DN, Van Geijn HP, Adèr HJ, et al. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. Obstet Gynecol. 1997;90:1023–4.
10. Kupferminc M, Lessing JB, Yaron Y, et al. Nifedipine versus ritodrine for suppression of preterm labor. Br J Obstet Gynaecol. 1993;100:1090–4.
11. Garcia-Velasco JA, Gonzalez AG. Prospective, randomized trial of nifedipine versus ritodrine in threatened preterm labor. Int J Gynaecol Obstet. 1998;61:239–44.
12. Koks CA, Brolmann HA, de Kleine MJ, et al. A randomized comparison of nifedipine and ritodrine for suppression of preterm labor. Eur J Obstet Gynecol Reprod Biol. 1998;77:171–6.
13. RCOG. Tocolytic drugs for women in preterm labor. In: Clinical guideline no. I (B). London: RCOG Press; 2002.