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ORIGINAL ARTICLE

Nifedipine and Isoxpurine in arresting preterm labor- A Comparative Study

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ABSTRACT:
Background: Preterm labor and delivery are of the most important complications of pregnancy and have a major role in neonatal mortality and morbidity. Management of preterm labor and prevention from preterm delivery in order to lower these risks have always been under serious concern. The purpose of this study was to compare the effect of isoxpurine hydrochloride and nifedipine as tocolytic drugs for preterm labor. **Materials and Method:** A prospective cohort study of 416 antenatal women with preterm labor was conducted in the Department of Obstetrics & Gynecology. Out of 200 women found eligible for tocolysis, 100 were given isoxpurine hydrochloride while the other 100 were given nifedipine randomly. The data obtained was statistically analyzed. **Results**: Nifedipine was twice more effective than isoxpurine hydrochloride as a tocolytic agent as a tocolytic agent (*P* value 0.04) while side effects were comparable (*P* value 0.124). In early-diagnosed preterm labor, nifedipine had higher efficacy than isoxpurine and also higher efficacy than its own in late diagnosed preterm labor. **Conclusion**: Nifedipine is recommended for aborting preterm contractions because it has fewer side-effects, superior efficacy and greater ease of administration than isoxsuprine
Keywords: Preterm birth, Betamethasone, nifedipine, Prematurity nifedipine, Isoxpurine hydrochloride

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INTRODUCTION

Preterm delivery is a common obstetric problem in which delivery takes place between 24 weeks and before 37 completed weeks of gestation. The rate of preterm deliveries varies from country to country and from institution to institution, but lies between 5 and 10% of all births. Preterm delivery affects 11% in U.S. or even greater in developing countries (23.3% in India) and it accounts for 40–75% of neonatal deaths. It could be due to assisted reproductive techniques, psychosocial stress, or medically induced prematurity.[1-3]

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.[4,5] 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

A prospective cohort study of 416 antenatal women with preterm labor was 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 chorioamnionitis, ante-partum hemorrhage, fetal distress, intra-uterine demise, or any medical contraindication to tocolysis were allowed delivery.

Out of 200 women found eligible for tocolysis, 100 were given isoxpurine hydrochloride while the other 100 were given nifedipine randomly. 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.

RESULTS

Table 1: Maternal factors in both treatment groups

Factors	Nifedipine (100)	Isoxsuprine (100)
Mean age (years)	22.7	24.6
Parity		
Primigravidae (*n*)	48	45
Multigravidae (*n*)	52	55
Cases in subgroup A		
Uterine cont <30 s &Cx dilatation <2 cm	62	60
Cases in subgroup B		
Uterine cont>30 s or Cx dilatation >2 cm	38	40
Mean cervical effacement (%)	31	32
Rupture of membranes (*n*)	31	15

Table 1 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.

Table 2: Comparative effect of tocolytic therapy in two groups

Admission delivery interval	Group-I nifedipine (*n* = 100)			Group II isoxsuprine (*n* = 100)			Total	*P* value
	A (62)	B (38)	Overall (100)	A (120)	B (80)	Overall (100)	(*n* = 200)	
<48 h Failure rate	6	14	20 (20%)	12	20	32 (32%)	52 (26%)	
≥48 h <37 Weeks successful tocolysis& preterm delivery			72			68	700	
≥37 Weeks successful tocolysis with term delivery			88			68	78	
Success rate	56	24	80 (80%)	48	20	68 (68%)	148 (74%)	0.004

Out of 200 cases of PTL, 122 belonged to subgroup A and 78 belonged to subgroup B. Analysis of the tocolytic effect in the two subgroups showed that subgroup A has better success rate (*P* value 2.04×10^{-5}) as compared to subgroup B. The success rate of nifedipine (56/62) was significantly higher (*P* value 0.005.45) than that of isoxpurine (40/60) in subgroup A. The comparative efficacy of the two drugs was similar in subgroup B (*P* value 0.05).

There were 108 cases of preterm rupture of membranes, out of which 78 were allowed spontaneous labor due to reasons described before, while 31 cases were given tocolysis. Failure rate was reported to be quite high i.e., (14/31) 45.1% in cases with ruptured membranes compared to only (38/119) 31.9% in cases with intact membrane. No significant difference in outcome was noted in nifedipine & isoxsuprine groups. Induction of labor was carried out in 12 out of 17 cases of successful tocolysis while the other ten delivered after 1 week by spontaneous labor.

Maternal side effects were noted in 15% cases of nifedipine group and 22% of isoxsuprine group with

no significant statistical difference (*P* value 0.124). 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.

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

Despite advances in perinatal medicine the incidence ofpreterm birth has increased since the early 1980.Neonatal morbidity and mortality increase with preterm delivery. For example, the incidence of severeintraventricularhemorrhage decreases after 27 weeks and rare after 32 weeks and incidence of necrotizing andrespiratory distress syndrome also decreases with advancing gestational age.A number of tocolytics have been advocated for the treatment of threatened preterm labor in order to delaydelivery. The rationale is that a delay in delivery may beassociated with improved neonatal morbidity or mortality. Nitric oxide donors, such as nitroglycerin, havebeen used to relax the uterus. This review addresses their efficacy, side effects and influence on neonatal outcome.There was reduction in number of deliveries less than 37weeks with nitric oxide donors when compared withalternative tocolytics. Side effects were reduced inwomen who received nitric oxide donors rather than othertocolytics. However, women were significantly morelikely to experience headache when nitric oxide donors had been used.[5,6,7]

Cochrane review 2004 on preterm labor concludes that tocolysis is definitely indicated before 34 weeks gestational age. This is because of the reduction in number of women delivering within next 7 days and resultant decrease in neonatal morbidity from RDS, necrotizing enterocolitis, intra-ventricular hemorrhage and neonatal jaundice. [5]

In our study, it was found that tocolysis delayed delivery in 38% of total cases and maximum (46.8%) 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 74%. Pregnancies were prolonged up to 36 completed weeks in 36% cases by nifedipine compared to 29% by isoxsuprine.

Smith and Woodland compared the tocolytic effect of nifedipine with terbutaline and found similar efficacy (71 vs. 68%) of the two drugs.[6]Jannet et al. 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).[7]

Similarly another study conducted by Nishaet al[11] showed that 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). Authors concluded that 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

CONCLUSION

Nifedipine is recommended for aborting preterm contractions because it has fewer side-effects, superior efficacy and greater ease of administration than isoxsuprine

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