Original Research Article

A clinical study of feto-maternal outcome of tocolytic agent nifedipine as compared to Isoxsuprine Hydrochloride in preterm labour

Farzana Zahir[1*], Kalyan Kumar Nath[2], H H Choudhury[3]

[1]Assistant Professor, [2]Registrar, [3]Retired Professor and HOD, Department of Obstetrics and Gynaecology, Assam Medical College and Hospital, Dibrugarh, Assam, INDIA.
Email: sajeedfarah@hotmail.com

Abstract

Introduction: Preterm labor and 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. or even greater in developing countries (23.3% in India) and it accounts for 40–75% of neonatal deaths. Incidence of preterm labor and delivery shows increasing trends in countries where data is available **Aims and Objectives:** To find out foetal and maternal outcome in the study group and to compare its efficacy with Isoxsuprine Hydrochloride. **Methodology:** A one-year study was undertaken in the department of Obstetrics and Gynaecology Assam Medical College and Hospital, Dibrugarh from 1st August 2005 – 31st July 2006, to find the tocolytic efficacy of Nifedipine and its foeto-maternal outcome and to compare clinically the efficacy with that of Isoxsuprine Hydrochloride. This was a Randomized Clinical Study. 100 patients with preterm labour were included in the study randomly. **Result:** The mean time taken to lessen or stop uterine contractions sufficiently was significantly less in the Nifedipine Group (1.64±1.015 hrs) than in the Isoxsuprine Group (11.94±10.557 hrs). p<001.There is a significant difference between the mean prolongation of pregnancy by Nifedipine (46.13±17.78 days) and by Isoxsuprine (27.35±20.60 days). p<0.001 which is very highly significant. The mean birth weight in Nifedipine group was 2.618±0.366 kg and in Isoxsuprine 2.156±0.624 kg. This observed difference was highly significant. Maternal Mortality was nil in both the groups. The Perinatal mortality was 1(2%) in Nifidipine , was significantly lower as compared to Isoxsuprine group 8 (16%).The successful tocolytic effect was significantly higher in Nifedipine group(100%) as Compared to Isoxsuprime (70%). **Conclusions:** In our study we have found Nifedipine as a better, safer and effective tocolytic compared to Isoxsuprine in the management of preterm labour.
Key Words: Preterm Labor, Nifedipine, Isoxsuprine.

[*]**Address for Correspondence:**
Dr. Farzana Zahir, Assistant Professor, Department of Obstetrics and Gynaecology, Assam Medical College and Hospital, Dibrugarh, Assam, INDIA 786002.
Email: sajeedfarah@hotmail.com
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INTRODUCTION

Preterm labor and 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[1,2,3,4]. It could be due to assisted reproductive techniques, psychosocial stress, or medically induced prematurity. Many different classes of drugs have been used for tocolytic therapy.[4]These include beta mimetics such as ritodrine and terbutaline; magnesium sulfate; prostaglandin inhibitors (for example, indomethacin, ketorolac); calcium channel blockers such as nifedipine; nitrates (for example, nitroglycerine); oxytocin receptor blockers (for example, atosiban), and others. Each tocolytic has a unique mechanism of action, side effects, and degree of complexity to administer[5]. Several Cochrane reviews have compared individual tocolytic drugs with placebo or

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other tocolytics.[6,7,8,910]. In the absence of a single high quality, randomized controlled trial comparing all tocolytic therapies, uncertainty remains about which is the most effective in delaying preterm delivery[11].Nifedipine, a calcium channel-blocker, has emerged as a potentially safer and better tolerated tocolytic agent.[12,13,14] Nifedipine inhibits smooth muscle contraction by impeding the flow of calcium across the muscle cell membrane[15].Successful treatment of preterm labour with nifedipine has been reported. [16,17.]

AIMS AND OBJECTIVES

To find out foetal and maternal outcome in the study group and to compare its efficacy with Isoxsuprine hydrochloride.

METHODOLOGY

A one-year study was undertaken in the department of Obstetrics and Gynaecology Assam Medical College and Hospital, Dibrugarh from 1st August 2005 – 31st July 2006, to find the tocolytic efficacy of Nifedipine and its foeto-maternal outcome and to compare clinically the efficacy with that of Isoxsuprine Hydrochloride. This was a Randomized Clinical Study. 100 patients with preterm labour were included in the study randomly. 50 received Nifedipine (Group A) and 50 received Isoxsuprine (Group B) by Lottery. Blinding was not done due to the difference in the form of both drugs administration. Patients in Group A and Group B were compared in a concurrent parallel design. Patients included were with Painful uterine contraction at an interval of at least 10 minutes recorded for at least 30 minutes, each contraction lasting for at least 30 seconds. Minimal cervical changes in the form of effacement and dilation (not more than 3 cm). Intact Membranes. No administration of tocolytics for the previous 7 days. Patients having the conditions like; Severe PIH, Chorioamnionitis, Cardiac diseases., Advanced Labour; Foetal factors like IUGR , IUD, Foetal Anomaly incompatible to life, Foetal Distress were excluded from the study. Maternal Diabetes and an otherwise uncomplicated twin pregnancy were not excluded from Nifedipine tocolysis were excluded from the study.

Mode of Drug administration: Patients were hospitalized in both the groups.

Group A - Nifedipine group – 50 patients were Pre-hydrated with Ringer Lactate solution at 100ml / hrs or at least till loading Nifedipine Administration. Loading dose: - Nifedipine 5 mg orally given every 15 minutes upto a maximum of 8 doses or till uterine contraction ceases whichever is earlier. Then maintained with 10 mg orally 3 hours after the last loading dose and continued 8 hourly for next 48 hours and then Nifedipine 10mg retard twice daily orally for at least 7 days (if required upto 36 weeks) If the uterine contractions did not reduce with the maximum loading dose the tocolysis was considered a failure.

Group B – Isoxsuprine group - 50 patients received Isoxsuprine in the following manner. Loading dose: - 40mg of Isoxsuprine in 500ml of Ringer Lactate was given as I/V Infusion starting at 0.08mg/min (1 ml/min– 15/16 drops /min) depending on the status of uterine contraction and occurrence of side effects. Maintenance dose: - 10 mg Isoxsuprine orally after 3 hours of stopping I/V infusion and continued 8 hourly of 7 days (if required till term).

RESULTS

Table 1: Feto-Maternal Outcome of Tocolysis

PARAMETERS	NIFEDIPINE (50)	ISOXSUPRINE (50)	STATISTICAL SIGNIFICANCE
Mean time taken for tocolysis (hrs)	1.64±1.015	11.94±10.557	p<0.001
Mean prolongation of pregnancy(days)	46.13±17.78	27.34±20.60	p<0.001
Mean gestational age at delivery(wks)	38.06±1.707	35.48±3.215	p<0.001
Mean birth weight (kg)	2.618±0.366	2.156±0.624	p<0.001
Maternal mortality	Nil	Nil	---
Perinatal mortality	1 (2%)	8 (16%)	P<0.05
Successful Tocolysis	100%	70%	p<0.001

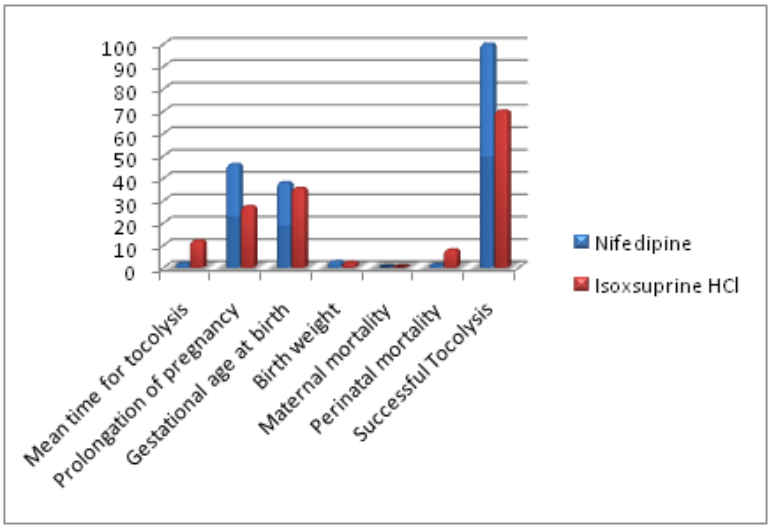

Figure 1: Feto-maternal outcome of tocolysis

The mean time taken to lessen or stop uterine contractions sufficiently was significantly less in the Nifedipine Group (1.64±1.015 hrs) than in the Isoxsuprine Group (11.94±10.557 hrs). p<001.
There is a significant difference between the mean prolongation of pregnancy by Nifedipine (46.13±17.78 days) and by Isoxsuprine (27.35±20.60 days). p<0.001 which is very highly significant. The mean birth rate was in Nifedipine group was 2.618±0.366 and in Isoxsuprine 2.156±0.624 this observed difference was highly significant.
Maternal Mortality was nil in both the groups. The Perinatal mortality was 1(2%) in Nifidipine, significantly lower as compared to Isoxsuprine group 8 (16%).
The successful tocolytic effect was significantly higher in Nifedipine group(100%) as Compared to Isoxsuprine (70%).

Table 2: Maternal Side Effects Across the study groups

Adverse Effects	NIFEDIPINE (50)		ISOXSUPRINE (50)	
	No. of patients	Percentage	No. of patients	Percentage
Tachycardia	-	-	36	72%
Hypotension	-	-	23	46%
Dizziness	4	8%	-	-
Palpitation	3	6%	14	28%
Pul. Edema	-	-	-	-
Hot Flushes	9	18%	-	-
Headache	1	2%	-	-
Chest-Pain	-	-	-	-

Table 2: Maternal Side Effects Across the Tocolysis were headache, flushing, tachycardia (defined as increase in pulse rate by more than 20bpm), hypotension (defined as drop in diastolic BP by more than 15mmHg), palpitation and dizziness

Table 3: Perinatal Side Effects Across The Study Groups

Perinatal Complications	NIFEDIPINE (50)		ISOXSUPRINE (50)	
	No.of patients	Percentage	No. of patients	Percentage
Fetal Tachy.	-	-	7	14%
Neonatal jaundice	3	6%	14	28%
RDS	2	4%	4	8%
Birth Asphyxia	2	4%	2	4%
NEC	-	-	1	2%
Mortality	1	2%	8	16%

Table 3: Of the perinatal side effects observed during the study, only fetal tachycardia can probably be attributed to the drug side effects, other parameters, since were seen at birth, may not be due to the effect of the drugs. The confirmation could not be done, as the blood drug levels were not estimated.

Table 4: Range Of Efficacy Of The Tocolytic Drugs Used In The Study

RANGE OF EFFICACY	NIFEDIPINE (50)	ISOXSUPRINE (50)
EXCELLENT	22 (44%)	18 (36%)
GOOD	24 (48%)	11 (22%)
SATISFACTORY	4 (8%)	6 (12%)
POOR (FAILURE)	NIL	15 (30%)

Thus Nifedipine has been excellent as a tocolytic without any maternal or fetal side effects in 44% cases and without any failure cases. Isoxsuprine has been excellent in 36% cases with 30% failure cases.

DISCUSSION

Preterm labour remains one of the unconquered frontiers in the present day Obstetrics. It refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of the cervix before 37 completed weeks of gestation (WHO recommendation1972). In India, for legal purposes viability is defined as any gestation carried beyond 28 weeks.

Preterm labour complicates 5-10% of pregnancies and accounts for about 75-80% of perinatal morbidity and mortality (after exclusion of genetic and anatomical defects).

The incidence of preterm labour amongst the labour room admissions (patients in labour) in the present study was found to be 6%. This is similar to the others data.

Author	Year	Place	Incidence
Rush *et al*	1976	UK	5.1%
Fuchs F	1976	USA	7.6%
NZ Health Statistic Report	1978	NZ	6.7%
Devi PK	1980	India	12-18%
Das andGogoi	1986	India	9.8%
Tamby Raja	1991	Singapore	6%
Creasy RK	1993	USA	10.6 %
Present Study	Aug.05-Jul.06	Dibrugarh	6%

Unfortunately, the incidence of preterm labour has changed very little over the last 30 years. Isoxsuprine was the first beta mimetic drug used to inhibit preterm labour in 1961. In the light of its unpleasant side effects and efficacy its therapeutic value is now found to be limited. Ulmsten *et al* first used Nifedipine, a calcium channel blocker as a tocolytic in 1980. Based on the results of the studies included in the Cochrane Review-2005, Issue 2 [8,9,10] comparing the effects of Calcium channel blockers (mainly Nifedipine) with that of other tocolytics (mainly beta mimetics), calcium channel blockers are shown to be more effective tocolytic agents with improvement of some clinically important neonatal side effects and marked reduction in adverse maternal side effects.

Tocolytic Efficacy: The tocolytic efficacy was analyzed under six categories: Successful tocolysis, Duration of prolongation of pregnancy from starting of therapy, Mean gestational age at delivery, Cervical status as a factor in determining tocolytic efficacy, Maternal side effects of the therapy, Fetal/neonatal side effects of the therapy. In the present study, successful tocolysis defined as prolongation of pregnancy by more than 48 hours, during which parenteral corticosteroids were given to hasten lung maturity, was achieved in 100% with Nifedipine and 70% with Isoxsuprine. The mean prolongation of pregnancy in the present study was 46.13±17.78 days with Nifedipine vs. 27.35±20.60 days with Isoxsuprine, which is highly significant ($p<0.001$). Following are the Results of Different Studies

Studies	Prolongation of pregnancy (in days)	
	Nifedipine	Isoxsuprine
Patki *et al*	23.2±16.8	14.5±18.4
Kalita *et al*	31.68±10.2	23.08±17.82
Kedar *et al*	22.4±15.6	16.5±14.5

All the above studies show a greater prolongation of pregnancy with Nifedipine and our study results are also similar. Maternal Outcome: The present study found hypotension, tachycardia, palpitation, flushing (hot flushes), headache and dizziness as common side effects. There was no case of drug discontinuation in the Nifedipine group due to side effects but 3 cases in the Isoxsuprine group required discontinuation due to persistent tachycardia and hypotension. Mean gestational age at delivery and Mean Birth weight were significantly more in Nifedipine group vs. Isoxsuprine group ($p<0.001$) in our study which is similar to the study by Rayamajhi *et al*. Other adverse effects noted were neonatal jaundice, respiratory distress syndrome, birth asphyxia and necrotizing enterocolitis (NEC) in both the groups as shown in Table 3 (results and observations). Similar adverse effects have been reported in other clinical trials also but it is difficult to say whether these effects are due to the tocolytic agents or due to the prematurity of the babies. In the present study there were 1 (2%) perinatal mortality in the Nifedipine group and 8 (16%) in the Isoxsuprine group. In both the groups babies were preterm ≤34 weeks. Out of the 8 babies in the Isoxsuprine group 6 were delivered due to tocolytic failure. In the Nifedipine group the baby that died was a still born due to cord prolapse.

CONCLUSIONS

In our study we have found Nifedipine as a better, safer and effective tocolytic compared to Isoxsuprine in the management of preterm labour.

However, further trials are required involving larger population and with different dose regimen to throw more light on this aspect.

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