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Role of Nifidipine in Preterm Labour - A Prospective Study

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Abstract
Background: *Preterm labour and delivery remains a major cause of perinatal morbidity and mortality in the developing world. Numerous drugs and interventions have been used to prevent and inhibit the preterm labour but none have been found to be completely effective with the choice being further limited by their side effects profile. Tocolysis, the pharmacological inhibition of uterine contractions, is currently the treatment for preventing PTL.*
Objectives: *To assess the efficacy and pregnancy outcome of nifedipine in the treatment of preterm labour and to evaluate the maternal and fetal adverse effects associated with nifedipine.*
Methods: *This is a prospective randomized study, 100 antenatal cases with 28 to below 37 weeks of gestation with painful intermittent uterine contractions associated with cervical changes were considered for the study. They were given oral nifedipine and monitored for cessation of uterine contractions. Maternal and fetal side effects were also noted. The main outcomes include prolongation of pregnancy, maternal side effects and neonatal outcome.*
Results: *The mean prolongation of pregnancy was 30.41 days. Success rate with Nifedipine was found to be 92.8%. Significant maternal side effects such as hypotension and tachycardia were seen only in 2 patients. Facial flushing was the most common side effect observed in the study group.15% of the patients exhibited fetal tachycardia. 90% of the neonates had an apgar score of above 7 at 5 minutes with no incidence of neonatal morality or morbidity.*
Conclusions: *Nifedipine is a cost - effective, safe tocolytic agent with minimal adverse effects.*
Keywords: *Preterm labour; Tocolysis; Nifedipine.*

Introduction

Preterm birth refers to a birth that occurs before 37 completed weeks (less than 259 days) of gestation. Preterm labour is by far the leading cause of infant mortality in the United States and is also a major determinant of short- and long-term morbidity in infants and children.

Hypothermia, necrotizing enter colitis, high risk of infections, neuro-developmental disabilities, poor growth, recurrent illness, insulin resistance, hypertension and respiratory and cardiovascular complications are some of the short and long term complications of a premature infant. Hence the management of spontaneous preterm labor has special importance, and many studies have been carried out using different methods of treatment based on various suggested etiologies. Many tocolytic drugs are available. Among them, Nifedipine is considered the best treatment option for spontaneous preterm labor.

Aims and Objectives

To assess the efficacy, pregnancy outcomes and side effects of nifedipine in the treatment of preterm labour.

Source of Data

This is a prospective study carried out in the department of Obstetrics and Gynaecology of Karnataka Institute of Medical Sciences hubli Karnataka india over a period of one year from January 2012 to December 2013. 100 antenatal cases with less than 37 weeks of gestation with PTL were considered for the study. After obtaining the written and informed consent.

Inclusion Criteria

1. Gestational age less than 37 weeks (according to LMP and USG confirmation of first trimester),
2. Uterine contractions with a frequency of four per 20 min.
3. Cervical dilatation of one cm or more, and
4. Cervical effacement of 50% or more

Exclusion Criteria

1. Any suspicion intrauterine infection according to vital signs and maternal condition or fetal bradycardia.
2. Women where continuation of pregnancy is detrimental to health of the mother or fetus.

Method of collection of data

All pregnant women admitted to the labour ward were taken in this study as per the inclusion and exclusion criteria. A detailed history, physical and obstetric examination and routine investigations were done for all patients. Patients were monitored from admission to discharge.

Method of study

Patients were taken up for the study after diagnosing preterm labour based on inclusion criteria. 20 mg of oral nifedipine was prescribed every eighth hourly for 3-5 days .For women with continued contractions or blood pressure less than 90/50 mm Hg, administration of nifedipine was discontinued.

12 mg of betamethasone every 24 hours was prescribed for up to 48 hours to accelerate fetal lung maturity. 53

Uterine contractions, fetal heart rate and vital signs were monitored in all patients. Side effects were noted in all patients from the time of admission to discharge from the labour ward.

Results

Treatment was considered successful, if there was abolition of uterine contractions, no progression of cervical dilation, and also if contractions did not recur within 48 hours of cessation of therapy.

Treatment was deemed failure, despite maximal dose mentioned, if uterine relaxation was not achieved or patient or fetus developed some significant side effects that necessitated discontinuation of therapy.

Data regarding efficacy of drugs in terms of arrest of preterm labour, prolongation of pregnancy and the days gained in utero were noted. Details of mode of delivery, gestational age at the time of delivery, baby‘s sex, birth weight and Apgar score were noted.

Statistical analysis

Mean and standard deviation will be used for analysis of data obtained.

Characteristics of study population:

Table No.1: Age wise distribution of the patients

Age in years	Study group
18-20	20
21-23	34
24-26	20
27-29	19
>30	7
Total	100
Mean age	23.93
Minimum age	18
Maximum age	33
SD	3.81

Table No.2: Distribution of the patients according to prenatal care: Study group

	No of patients	Percentage
Booked	74	74
Unbooked	26	26
Total	100	100

Table No.3: Distribution of the patients according to parity:

Parity	No. of patients	Percentage
Nulliparous	49	49
Multiparous	51	51
Total	100	100

Table no.4: Risk factors for preterm delivery

Risk factor	No of patients	Percentage
Previous preterm	10	10
Abortions	19	19
Evidence of infection	17	17
Previous D&E	10	10
Physical and psychological stress	34	34
Multiple pregnancies	-	-
Coitus during pregnancy	06	06
Substance abuse	20	20
Anaemia	54	54
Uterine/cervical malformation	-	-
No risk factors found	38	38

Table no.5 Showing BP, maternal and foetal heart rate changes pre and post drug administration Study group

Drug administration	Pre drug	Post drug
Systolic blood pressure(mm Hg)		
Mean	121.10	113.04
Maximum	130	126
Minimum	100	90
SD	8.56	8.92
Diastolic blood pressure (mm Hg)		
Mean	75.70	75.92
Maximum	92	90
Minimum	70	70
SD	4.79	5.82
Maternal pulse rate(bpm)		
Mean	77.93	82.66
Maximum	98	110
Minimum	70	72
SD	3.83	7.14
Fetal heart rate(bpm)		
Mean	140.22	148.96
Maximum	152	170
Minimum	126	140
SD	5.08	8.58

In the present study, following drug administration, a mean drop of 8 mm of Hg of systolic blood pressure was observed. Minimal changes were observed in the diastolic blood pressure, maternal and fetal heart rate.

Table No.6: Total duration of prolongation of pregnancy in days

Prolongation of pregnancy (in days)	Study group
Mean	30.41
Minimum	12
Maximum	52

In this study, the average days of prolongation of pregnancy was around 30 days, with a maximum of 52 days

Table No.7: Gestational age at delivery (in weeks) Gestational age at delivery (in weeks)

	Study group	Percentage
<37	21	21
≥37	63	63
Lost to follow up	16	16

Period of gestation at the time of delivery was ≥37 weeks in 63% of the cases. 16 cases were lost to follow up in this study.

Table No 8: Mode of delivery Mode of delivery

	No. of pts	Percentage
Vaginal	60	60
LSCS	24	24
Lost to follow up	16	16

Out of the 84 patients, 60 patients delivered vaginally and 24 patients required caesarean section. 16 cases were lost to follow up

Table No. 9: Perinatal outcome Gestational age at delivery(in weeks)

Mean	37.06
Minimum	33
Maximum	40
Birth wt.(in kgs)	
Mean	2.83
Minimum	3.8
Maximum	1.7
APGAR score	
Apgar score at 1‖	No. of pts
<7	18(21.4%)
>7	66(78.6%)
Apgar score at 5‖	
<7	5(6%)
>7	79(94%)

In the present study the mean birth weight of infants was 2.83 kgs and the mean geatational age at delivery was 37.06 weeks. The apgar scores of >7 at 1‘ and 5‘ mins were 78.6% and 94% respectively maternal hypotension and tachycardia was noted in 2 patients. The most common side effect, facial flushing, developed in about 15 patients. No other serious side effects were in the study group

Table No.10: Maternal side effects

Side effects	No of patients	Percentage
Tachycardia>110 bpm	02	2%
Headache	0	0
Hypotension <90/60	02	2%
Nausea	0	0
Vomiting	0	0
Facial flushing	15	15%

Table No. 11: Neonatal side effects

Side effects	No of patients	Percentage
Tachycardia	15	15%
RDS	0	0

There was no incidence of RDS while fetal tachycardia post nifedipine administration was seen in 15 % of the patients.

Table No. 12: Results of treatment in the study group

Result	No. of patients	Percentage
Success	78	92.8%
Failure	06	7.2%
Total	84	100

In our study, a high success rate of 92.8% and a failure rate of 7.2% was noted. 4 patients in the study group delivered within 48 hours of cessation of therapy. Of the six failure patients, 2 patients had significant fall in blood pressure that necessitated discontinuation of the therapy.

Discussion

Determination of efficacy and safety of tocolytic agents has been a difficult task because of various reasons:

The cause of preterm labour is generally unknown. Therefore therapy cannot be directed to a specific cause.

In about 30 % of the patients with apparent preterm labour, uterine contractions cease spontaneously without treatment. Lack of uniformity in the diagnosis of preterm labour. The diagnosis of preterm labour may be in error as much as 80% of the time.

Also the criteria for the success of tocolysis have been different by different authors.

E.g. delivery delayed > 24 hrs, delivery delayed > 48 hrs, delivery, delayed > 37 weeks, mean days gained in utero etc.

This prospective study was designed to find out the safety, efficacy and perinatal outcome of nifedipine in women with preterm labour. Patients were included into the study group in which uterine contractions continued even after complete bed rest. This could reduce the number of patients in false labour being included in the study.

Since the late 1970's nifedipine has been known to relax the pregnant and non pregnant uterus (Ulmsten, Anderson) (01).The first study of Nifedepine in the management of preterm labour was reported by Ulmsten et al. in 1980.In all patients studied, nifedipine stopped uterine activity and delayed delivery. In second study, Ulmensten showed that Nifidipine was associated with the delayed delivery for more than 3 days in 80% of the study group.

100 antenatal women with singleton pregnancies were enrolled in our study, of which 16 of them were lost to follow up.

Significance of maternal age, gestational age and parity on preterm labour

The patients included in this study were well matched regarding age, antenatal care, gravidity, previous obstetric history and socio economic status with respect other well matched randomized controlled trails conducted by Kedar M G et al. (1990) (02), Kalita D et al. (1998)(03), Rayamajhi R et al.(2003) (04), Read MD and Wellby D E (1986) (05), Murray C et al. (1992) (06), Papatsonis et al. (1997)(07) and Kashanian et al.(2011) (08)

Kedar MG et al, Kalita et al and Rayamajhi R et al have conducted studies about comparison between the efficacy and safety of Nifedipine and Isoxsuprine in the suppression of the preterm labour. Kashanain et al studied the efficacy and adverse effects of nifedipine and indomethacin for the treatment of preterm labor.

Table 13:-Comparative analysis of mean age, gestational age (weeks) at onset of tocolysis and parity at enrolment Clinical parameters

	Kedar et al	Rayamajhi et al	Kashanian et al	Present study
No. of patients	50	32	40	100
Mean age (years)	22±5.5	26	24.7±5.2	23.9±3.81
Gestational age(wks) at the onset of tocolysis	30.5±3.5	32.22	29.5±3.7	32.9±2.01
Parity				
Primigravida	27 (54%)	-	-	49(49%)
Multigravida	23(46%)	-	-	51(51%)

In our study, the patients were well matched regarding maternal age, gestational age and parity with respect to other well matched randomized controlled studies conducted by Kedar M G et al (1990), Rayamajhi R et al (2003) and Kashanian et al (2011). Mean maternal age in our study was 23.9 ± 3.81, while in Kedar et al it was 22±5.5 years and in the Rayamajhi et al study it was 26 years, Kashnaian et al it was 24.7±5.2

Gestational age in weeks at admission in the present study was 32.9 ± 2.01. While in Kedar et al study it was 30 ± 3.5 weeks and in the Rayamajhi et al study it was 32.22 years. It was 29.5±3.7 years in Kashanian et al study. All of the above figures were well matched to the present study.

Table 14:- Comparative analysis of gestational age (weeks) at enrolment.

Study	Gestational age (weeks) at onset of tocolytic therapy
Papatasonis et al	20-33¼
Read & Wellby	20-35
Murray et al	30-35
Kashanian et al	26-33
Present study	28-36

Mean gestation age at enrolment in our study correlated well with other studies. Since all the above studies were in developed countries, lower limit for period of viability has been taken from 20-24 weeks. In developing countries like ours the period of viability is accepted as 28 weeks. The women who participated in our study were between 28 and 36 weeks. In other randomized clinical trails conducted by Papatsonis et.al (1997) and Read and Well by, gestational age at the beginning of tocolysis was taken between 20 – 33¼ and 20 – 35 weeks respectively.

Significance of prenatal care, literacy and socioeconomic status on preterm labour:-

In our study, 26% cases were unbooked and did not have regular antenatal checkups. Booking status or regular antenatal check up did not always protect against preterm labour.

Table 15:- Comparison of tocolytic dosage administrated Study

	Nifedipine dose
Kedar et al	Loading dose – nifedipine 5 mg S/L, repeated every 15 mins, up to a maximum of 8 doses (40mg) during the first two hours of treatment. Maintenance dose – Oral Nifedipine of 10 mg was initiated 3 hrs after the last sublinguial dose. Oral Nifedipine was then continued as 10 mg Q8h for the next 48 hrs. Nifedipine retard tablet 10 mg or 20 mg was then started Q12h and continued till 36 weeks.
Rayamajhi R et al	Loading dose – Nifedipine 10 mg S/L , repeated every 20 mins, up to a maximum of 4 doses (40 mg) Maintenance dose – 4-6 hrs after the last S/L dose, Tab. Nifedipine 10- 20 mg orally, 6-8 hrly, for not more than 7 days.
Kashanian et al	Loading dose :10 mg (1 capsule) of nifedipine was prescribed every 20 minutes up to a maximum of 4 doses. Maintanence dose: 20 mg (2 capsules) was prescribed every 6 hrly for 1st 24 hours;20 mg 8 hrly for the 2nd 24 hours; and lastly, 10 mg 8 hrly for the next 24 hours (total duration of treatment, 3 days).
Present study	Loading dose – Nifedipine 20 mg , tid .maximum of 60 mg/day Maintenance dose - 20 mg tid for three days.

In the present study, Nifedipine dose administered well correlated with Kedar et al, Rayamajhi et al

and Kashanian et al study. Maximum dose of Nifedipine used in our study was 40 mg well correlated with Kedar et al and Rayamajhi et al study. While maintenance dose was continued for 3 days in our study and Kashanian et al study, it was continued for 7 days in Rayamajhi et al study and till 36 weeks in Kedar et al study.

Comparison of prolongation of pregnancy in days Study

	Mean prolongation of pregnancy in days
Kedar et al	22.4±15.6
Rayamajhi et al	25.71
Kalita D et al	31.16±10.2
Tewari et al	39.26±25.5
Present study	30.41±9.4

The mean prolongation of pregnancy in the present study was 30 .41 ± 9.4 days. These results were similar to those reported by Kalita et al study, with mean prolongation of pregnancy being 31.16 ± 10.2 days. Kedar et al reported a mean prolongation of pregnancy as 22.4 ± 15.6 days while Rayamajhi et al noticed a mean 25.71 day prolongation. Tewari et al reported a 39.26 ± 25.5 day mean prolongation of pregnancy

Indian study conducted by Singh S and Gupta K (9)observed that prolongation of pregnancy was more when the period of gestation was less, being 47.44 days at 22-24 weeks and only 10.18 days at 33 – 36 weeks.

Comparative analysis of tocolysis. Parameters

	Rayamajhi et al	Kedar et al	Present study
Successful tocolysis	81.25%	88%	92.8%
Mean birth weight		2383	2830
Perinatal mortality		1 (3.33%)	0

successful tocolysis was achieved in 92.8 % of the cases. These results were similar to those reported by Kedar et al of 88 % success rate.Rayamajhi et al reported a success rate of 81.25 %.

The mean birth weight of the study group was 2830 grams, higher than (2383 grams), as documented by Rayamajhi et al .While perinatal mortality was reported in Rayamajhi et al study, none of the babies have died in our study.

Comparative analysis of maternal side effects

Side effects	Rayamanjhi et al	Kedar et al	Kashania n et al	Present study
Tachycardia	18.75%	23%	7.5%	2%
Hypotension	18.75%	20%	22%	2%
Pulmonary edema	-	-	-	-
Headache	6.67%	30%	7.5%	-
Flushing	3.33%	40%	-	15%
Nausea/vomiting	3.33%	10%	-	-

The maternal side effects profile was less as compared to Kedar et al, Kashanian et al and Rayamajhi et al study. 2 patients in our study group developed significant drop in blood pressure which necessitated cessation of drug therapy. Clinical trails of nifidipine have reported an insignificant drop in blood pressure, which resolves spontaneously in most patients without evidence of prolonged maternal and fetal symptoms.

Conclusion

Prematurity continues to be the major contributor to the perinatal morbidity and mortality. Prevention and treatment of preterm labour is essential to reduce adverse neonatal and infant outcome and to improve survival and quality of life. . Tocolysis remains the predominant modality for the treatment of preterm labour. None of the currently available tocolytic agents are ideal. Calcium channel blocker (Nefidipine) is safer and more effective than other tocolytic agents.

In the present situation, results indicate that a achievable goal of tocolytic therapy is to delay delivery for at least 48 hours, an important interval during which the mother may be transferred to a tertiary centre for, administer corticosteroids to the mother as well as to treat maternal infection present. These measures have shown to reduce neonatal morbidity and mortality. Our study found a favourable outcome with Nifedipine, with a success rate of over 92%.

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