ORIGINAL ARTICLE

Role of Nifedipine in Preterm Labour

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Abstract:
Objective: The objective of the study was to assess the efficacy of Nifedipine for suppression of preterm labour.
Study Design: Quasi experimental study.
Setting & duration: The study was conducted at Department of obstetrics and Gynaecology unit II, Civil Hospital Karachi from november, 2004 - October 2005.
Methadology: 65 singleton pregnancies with preterm labour occurring between 28 and 34 weeks of gestation were selected. Patient presenting with Preterm labour, having cervical dilatation <3cm with intact membrane included in the study. Nifedipine was used as a tocolytic agent.
Results: Successful tocolysis was achieved in 70% (45 /65) of patients, while in remaining 30% (20/65) tocolysis was not achieved
Conclusion: Nifedipine effectively suppressed uterine contractions and delayed delivery for >48hours, a period which is sufficient for the effect of corticosteroid or inutero transfer.

Key words: Preterm labour, Tocolysis, Nifedipine.

Introduction:
Preterm labour is defined as labour which occurs from viability of the fetus (currently defined in the UK as 24 completed weeks of gestational age from the date of the last menstrual period, assuming a 28 days menstrual cycle) until the completion of the 37th week of gestation.[1] Preterm Birth is a major contributor of perinatal mortality and morbidity in industrialized world.[2]

In Europe, the incidence of preterm birth is 5.8% which accounts for approx. 400, 000 preterm birth each year and it is estimated that around 100, 000 of these are potentially preventable.[2]
Perinatal mortality rate of Pakistan is 96 per 1000 live births, it is significantly higher when compared to the developed countries while not comparable to the developing world (India 48.6, Burma 57.2, Indonesia 45 and Thailand 28.3).[3]
The perinatal mortality and morbidity associated with preterm birth decreases with increasing gestational age. Of babies born at 24 weeks gestation, only 20% survive and by 30 weeks gestation survival increases to 90%. Between the gestational age of 23 and 27 weeks, neonatal survival increases in a linear fashion at a rate of approximately 3% per day with a concomitant reduction in neonatal morbidity. The prevalence of handicap decreases with gestational age from 31% at 23 weeks to 7% at 27 weeks.[4] Some 15% to 20% of extremely preterm or extremely low birth weight survivors may have severe neurological impairments or disabilities and approximately half may have more subtle deficits in hearing or intellectual performance. Cerebral palsy in particular has been studied. Its prevalence has increased in preterm infants, but it is not clear whether the cause increased survival of perinatally damaged infants or perinatal sequelae of preterm birth.[5]

In the USA, the short term cost of neonatal intensive care is estimated to be US$ 10, 000 per

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baby per week, resulting in an annual cost of approximately US$5 Billion[5]. The high rates of mortality and morbidity arising from preterm birth and low birth weight impose a immense burden on the health care and social services and on families.[6]

Prematurity often results in significant immediate and long term morbidity and mortality related to sepsis, intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis and retinopathy of prematurity.[7]

The interval from administration of antepartum glucocorticoids to delivery has an effect on neonatal outcome. Although there is a trend towards reduction in the development of RDS after an interval of 24-48 hours, a significant reduction is only obtained if delivery can be postponed more than 48 hours[4]. It is therefore desirable that pharmacological treatment of PTL delays preterm delivery for at least 48 hours.

A wide variety of agents have been advocated as suppressing uterine contraction. Those in current use include β-agonists, Calcium channel blockers, prostaglandin synthetesis inhibitors, Nitric oxide donors and oxytocin receptor antagonists[8]. The use of these drugs is associated with a number of side effects. Tocolytics which have been most widely tested are the β-mimetics. These have a high frequency of unpleasant some times severe maternal side effects including tachycardia, hypotension and a range of biochemical disturbances. β-mimetic have been associated with maternal deaths mainly from pulmonary edema[9]. Myocardial infarction has been reported in women receiving β-mimetic tocolytic therapy.[7]

There is a need therefore of an effective tocolytic agent with less side effect. The dihydropyridine group of calcium channel blockers (Type II) and specifically nifedipine are considered relatively safe for use in pregnancy. They are more effective tocolytics. These agents also results in improvement in some clinically important neonatal outcomes including fewer cases of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, jaundice, and risk of admission to neonatal intensive care unit. They have little teratogenic or fetotoxic potential. These are also associated with marked reduction in the frequency of adverse maternal side effects. There are few patients, who have to discontinue nifedipine because of side effects.[10]

Recent meta analysis suggest that calcium channel antagonists are more effective and much better tolerated than β-agonists.[11] If the decision is made to use a Tocolytic drug, ritrodine no longer seems to be the best choice. Alternatives such as atosiban or nifedipine appear to have comparable effectiveness in delaying delivery for a few days with few maternal adverse effect and less risk of rare serious adverse events.[8]

Atosiban -- oxytocin anatagonist, is considered as a first line tocolytic agent in Europe as it has few maternal side effects. It is licensed in the UK for treatment of threatened preterm labour. The purchase price of atosiban is substantially higher than alternatives such as nifedipine or the β-agonist. Drug cost for a 19 hours treatment are £240 (June 2000 Price), compared with £40-80 for an equivalent length of treatment with ritrodine and £17-25 for nifedipine[8]. Nifedipine has the advantage of oral use and it is cheap.[8]

The rationale for the use of tocolytic therapy is to prolong pregnancy long enough until growth and maturation is complete. Even a short term delay in delivery is helpful to permit administration of antepartum glucocorticoids, which may result in a significant reduction in respiratory distress syndrome and neonatal death. Corticosteroid has proven efficacy that they promote pulmonary maturation. A short term delay also enable in-utero transfer to a center with neonatal intensive care unit facilities. The main aim of this study is to demonstrate the effect of nifedipine as a tocolytic agent in preterm labour.

Material and methods

The study was conducted at Dow Medical College and Civil Hospital Karachi Gynae Unit. The latter being a tertiary center with a capacity of

1700 beds and receives patients from all over Sindh and Balochistan. This study was carried out at Gynae Unit II Civil Hospital Karachi from November 2004-October 2005 and total number of patients included in this study were 65. It was non-probability convenience sampling. Patients presented with preterm labour between 28 and 34 weeks of gestation with singleton pregnancy having regular uterine contraction, cervical dilatation of <3 cm with intact membrance were included in the study. The frequency of contractions had to be 1 or more per hour and the duration 30s or more. Efficacy of drug was checked by comparing the mean number of uterine contractions before and after Nifedipine and by determining mean number of days gained after nifedipine treatment.

Patient with fetal malformation or fetal death in utero, suspecting fetal compromise as determined by ultrasound or CTG warranting delivery, placental abruption or preeclampsia, chorioamnionitis. significant maternal cardiac disease, hepatic dysfunction or hypotension, concurrent use of intravenous beta mimetics or anti hypertensive medication, allergy to Nifedipine were excluded.

Patients admitted in the labour room via emergency or out patient department fulfilling the inclusive and exclusive criteria of the study were included in the study. The purpose, risks and benefits ratio were explained to them and informed consent was taken. All the women selected for the study had continuous monitoring of fetal heart rate and uterine contractions. Fetal heart rate was monitored by Fetoscope while uterine contractions by palpatory method (as CTG was not available for each patient).

Initially 5% dextrose–saline (or lactated ringers solution) at a rate of 200ml/hr was given upto 500ml. During an observational period of at least 60 minutes, physical examination was carried out. Blood samples were taken for complete blood count, serum electrolytes, urea, creatinine and blood sugar. Urine for detailed report and cervical cultures were also obtained. All patient had an abdominal obstetrical ultrasound for the confirmation of viability and estimation of gestational age. Long acting variety of Nifedipine in tablet form was administered per orally.

Nifedipine tocolysis was initiated with a Tab. Adalat Retard (20mg) given orally. If uterine contractions persisted after 30 minutes, a similar dose was repeated at interval of 30 minutes. If contractions were not suppressed after the second dose a third dose of 20mg was repeated at interval of 30 minutes, up to a maximal total dose of 60mg during the first hour of treatment. After the third dose, patients were put on Tab. Adalat Retard (20mg) 3-8 hourly for 48 to 72 hours as indicated. The maximum dose given during study was 160 mg /day. Maternal blood pressure, pulse, uterine contractions, fetal heart rate were checked before treatment and after the initiation of treatment, charting was done, half hourly for the first hour, then hourly upto 4 hours and there after 4 hourly observation for 24 hrs. All patient received steroids to promote fetal lung maturation and they remained in hospital for at least 72 hrs. Women in whom uterine quiescence was maintained after this period were discharged and instructed to continue with bed rest. Tocolysis was considered successful if delivery was deferred for at least 48 hours.

Results:

The mean number of uterine contractions before nifedipine treatment was 3.29±2.2 (per 10 minutes) while after treatment it was recorded as 0.12±0.494 (per 10 minutes) which is statistically significant (p<0.01).For frequency of uterine contractions refer to Table -1.

The mean delay in delivery for <2 days was

Table 1: *Frequency of uterine contractions before and after nifedipine treatment per 10 minutes (n=65)*

Frequency of uterine contractions	Before	up to 24 hours	up to 48 hours
0	-	43(66.2%)	43(66.2%)
1	-	-	-
2	17(26.2%)	3(4.6%)	2(3.0%)
3	29(44.6%)	-	-
4	19(29.2%)	19(29.2%)	-

Table 2: *Gain in days after nifedipine treatment (Delay in delivery) [n=65]*

Duration in Days	N	%	mean ±SD	P-Value
< 2 days	20	30%	1.0±0.2	0.009
> 2 days	45	70%	4.9±10.0	

The value is statistically significant.

1.0±0.2 days while delay for >2 days was 4.9±10 days which is statistically significant (p<0.009). Therefore the mean gain in days after treatment was 4.9±10 days. For delay in delivery refer to Table 2.

Successful tocolysis was achieved in 70% (45 /65) of patients, while in the remaining 30% (20/65) tocolysis was not achieved. The mean pulse rate before nifedipine treatment was 83.0±4.0 while after treatment was 92.9±3.9, which shows a difference of increase in pulse rate of 9b/min that is statistically insignificant.

The mean systolic blood pressure before treatment was 114.4±5.3 while after treatment was 100.1±3.6 which shows a decrease is systolic BP of 14 mmHg that is statistically significant.The mean diastolic blood pressure before treatment with nifedipine 75.5±5.4 while after treatment was 67.4±4.9. This decrease in blood pressure was significant but was not accompanied with any clinical symptoms of hypotension. There was no change noticed in respiratory rate, fetal heart rate before and after treatment with nifedipine that is statistically significant. For base line information refer to Table 3.

Discussion:

The study was carried out in a population of patients of low socioeconomic class. These patients also have poor antenatal care.In this study 46% of patients were booked and 54% were unbooked. Maximum number of patients were primigravida.A great number of drugs and other interventions have been used to inhibit PTL, but unfortunately, none has been completely effective (ACOG95)[12] Marriam Malik at Allama Iqbal Hospital, Lahore observed the effect of glyceryl trinitrate in PTL. Side effect reported were headache and palpitation that required removal of patches.[13] Further studies are required to confirm that glyceryl trinitrite is safe in PTL.

In a study, conducted at King Edward Hospital Lahore, effectiveness of ritrodine was demonstrated in which delivery were delayed for 72 days in 88.2% but the drug was withheld in 9 women due to unwanted side effects, that could have cause maternal fetal jeopardy.[14]

In another study conducted at Institute of Baqai Medical University, Karachi, polytheraphy was instituted i.e. multiple tocolytic agents were used inspite of single agent.[15] Their result suggested that polytheraphy is more effective than monotheraphy but, this requires confirmation.

Potential maternal complications of tocolytic drugs emphasized by the American College of obstetricians and Gyneocologists (1995).[12] Their importance can not be under estimated. For example, tocolysis was the third most common cause of adult respiratory distress syndrome and death in pregnant women during a 14 year period in Jackson, Mississippi.[16] The tocolytic drugs most frequently used in the United States are the β-Sympathomimetic agents, usually Terbutaline or Food and Drug Administration approved ritrodine.Intravenous administra-

Table 3: *Mean comparison between before treatment (baseline information) and after treatment effects (n=65)*

	Baseline Pretreatment Mean±SD	After treatment mean±SD	P Value
Systolic Blood Pressure (mmHg)	114.4±5.3	100.1±3.8	< 0.01*
Diastolic Blood Pressure (mmHg)	75.5±5.4	67.4±4.9	< 0.01*
Pulse (beats/min)	83.0±4.0	92.9±3.9	0.791
Respiratory Rate (per 10 min)	18.8±1.0	18.8±1.0	< 0.01*
Fetal Hear Rate (per 10 min)	145.4±3.6	141.3±23.2	< 0.01*
Uterine Contractions (per 10 min)	3.29±2.23	0.1277±0.494	< 0.01*

tion of these drugs has a rapid tocolytic effect. The β-mimetic drugs however, have significant and potentially serious maternal and fetal side effects e.g. pulmonary edema, cardiac ischemia and fetal cardiotoxicity. Less serious side effects are tachycardia, tremors, anxiety, palpitations and insomnia. Maternal intolerance of these side effects often requires reduction in dosage or discontinuance of theraphy. [15, 16]

Nifedipine, a calcium channel blocking agent has emerged as a potentially safer and better tolerated tocolytic agent.[17] Successful treatment of PTL with nifedinpine has been reported.
The current study was conducted to study the effectiveness of nifedipine as a tocolytic agent and to determine gain in days or weeks after nifedipine treatment. In this study nifedipine effectively suppressed uterine contractions without causing any side effects and delivery was delayed for >48hrs and >72hrs in 19% (12/65) and 51% (33/65) of cases respectively. Failure of tocolysis occurred in 30% (20/65) of patients who were delivered within 48 hrs.

Success of tocolysis was defined as deference of labour for 48 hours, to allow enhancement of fetal lung maturity with glucocorticoids and to allow inutero transfer to tertiary center. Using these criteria, successful tocolysis was achieved in 70% of the women treated with nifedipine. Those patients who delivered on the same day, came with the maximum uterine contractions of 3 to 4 per 10 minutes and with cervical dilatation of 3cm and effacement of 70%. Those patients whom quiescence of uterine contraction was achieved admitted with mild uterine contractions less cervical dilatation and effacement compared with those who delivered.

In this study Nifedipine was administrated as a single course of 20mg followed by 20mg orally if needed, maximum of 60 mg in first hour , followed by 20 mg orally at 8 hours interval for 3 days.

In subsequent randomized studies, Ferguson et al[16], Meyer etal and Kupferminc et al[18] all found nifedipine to have a tocolytic efficacy similar to that of ritrodine. Kupferminc et al[18] gave an initial loading dose of 30 mg of nifedipine and a maximum maintenance dose of 20 mg every 8 hours.

The decrease in blood pressure which we observed after oral administration of nifedipine, although statistically significant, was unlikely to be of clinical importance.[19] In this study, increase in maternal heart rate was found following each dose, but this was transient and less pronounced. No significant changes were noted in the fetal heart rate. Different dosages of nifedipine were used ranging from 60 to 160 mg per 24 hours. In most of the studies, nifedipine was started with a sublingual dose.[20] But in this study we gave nifedipine in oral form in order to avoid the side effects that are reported with the use of sublingual (short acting) nifedipine. In our study, only minor side effects were observed including headache experienced in 10 patients while flushing in 15 patients. These side effects subsided after few hours, and did not necessitate any special measures.

In this study, there were no perinatal deaths reported and those babies who delivered after 48 hours of tocolytic treatment & who received steroids cover born with good Apgar and did not need NICU admission. NICU admission were required only in those babies who born within 24 hours. Previous clinical studies did not detect any major adverse neonatal effect attributable to nifedipine. Four studies reported no significant difference in neonatal outcome in the two treatment groups; i.e. (Nifedipine & Ritrodine), although in two other studies significantly larger infants were found in the group of women treated with nifedipine.[20] Nifedipine would appear to be among the more efficacious and safer tocolytics available to use when properly indicated.

Conclusion:

Nifedipine effectively suppressed uterine contractions and delayed delivery for >48hours, a period which is sufficient for the effect of corticosteroid or inutero transfer.

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