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A study of Nifedipine in the Treatment of Preterm Labor of South Indian Origin

Ragunath MP[1]*, Sasmal D[1], Mitra Dhanaraj[2]

[1]*Department of Pharmaceutical Sciences, Birla Institute of Technology. Mesra, Ranchi -835215, India.*

[2]*CSI Kalyani Multi Speciality Hospital and Research, RK Salai Mylapore, Chennai 600004, India.*

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ABSTRACT

The first line Treatment of preterm labour at CSI Kalyani hospital Chennai was hydration and bed rest followed by tocolytics, the hospital followed a treatment protocol with nifedipine. A total of 48 patients with singleton pregnancies at a gestational age between 28-36 weeks were selected according to the protocol to receive nifedipine. The meta analysis showed similarities with respect to the age at preterm labor, status of gravid, suppression of preterm labor, prolongation of pregnancies, adverse events, neonatal outcomes by apgar scores. The results confirmed that nifedipine is a growing calcium channel blocker as a safe and potential drug in the treatment of preterm labor especially in situations where a woman needs a full course of corticosteroids for fetal lung maturation or transfer to hospital that can provide neonatal intensive care.

KEYWORDS

Nifedipine, Preterm labor, Tocolytics

INTRODUCTION

Preterm birth is the primary determinant of any adverse infant outcome. Many researches have shown that the use of tocolytics during preterm significantly prolongs the delivery thereby helps in completing a course of corticosteroids or in utero transfer. Drugs play an important role in improving human health and promoting well-being. However, to produce the desired effect, they have to be safe, efficacious and have to be used rationally. In pregnancy, drug treatment presents a special concern due to the threat of potential teratogenic effects of the drug and physiologic adjustments in the mother, in response to pregnancy. However, it has been documented that congenital abnormalities caused by human teratogenic drugs accounts for less than 1% of total congenital abnormalities[1].

About 8% of pregnant women need permanent drug treatment due to various chronic diseases and pregnancy-induced complications. Calcium channel blockers (CCBs)were originally developed in the early sixties for angina pectoris, but due to new insights in their action mechanism the number of indications has expanded[2,3]. Calcium channel blockers are now used for angina pectoris, hypertension, supraventricular arrhythmias, subarachnoid hemorrhage, and myocardial infraction[4]. In recent years CCBs have found their way in obstetrics and gynaecology, especially in the management of preterm labor and preeclampsia[5]. Their popularity in the management of preterm labour is atleast partially based on the absence of tachyphylaxis and low incidence of side effects in comparission with betamimetics[6,7]. The women most likely to benefit from tocolysis are those who are still very preterm, those needing transfer to a hospital that can provide neonatal intensive care or those who have not yet completed a full course of corticosteroids to promote fetal lung maturation. In recent years there has therefore been considerable interest in identifying a safe alternative with equal, or

***Address for Correspondence:**
M.P.Ragunath,
Department of Pharmaceutical Sciences,
Birla Institute of Technology,
Mesra, Ranchi, India. – 835215
Phone: +91 – 651 – 2275444/896
E-Mail Id:masilaragunath@gmail.com

greater, effectiveness and fewer adverse effects. There are many drugs which are studied as tocolytics such as nitric oxide donors (primarily glyceryl trinitrate), ritodrine, magnesium sulphate, atosiban, indomethacin and nifedipine. There was insufficient evidence for any conclusions about the effect on neonatal mortality. It is unclear whether they have any substantive advantage in terms of fetal or neonatal outcome. There is insufficient evidence for reliable conclusions about more substantive effects on prenatal or infant mortality or on serious neonatal morbidity. Despite much research on various pharmacological agents for the treatment of preterm labor, the ideal tocolytic has yet to be developed. The present study was carried out in view for the scope of providing safety data on the maternal and neonatal outcomes in the use of nifedipine as a tocolytic agent for the clinical research society.

MATERIAL AND METHODS

The study period was from March 1, 2009 - December 30, 2011. Patients above 18 years old with singleton pregnancies and cervical dilatation not more than 4cm and intact membranes who were admitted for preterm labor at CSI Kalyani Multi Speciality hospital at 28 and 36 weeks' gestation were considered eligible for the study. The gestational age was estimated according to the last menstrual period and ultrasonographic examination. Preterm labor was diagnosed on the basis of regular uterine activity, defined as regular uterine contractions 4 per 20 min, each lasting 30 s, and cervical dilatation of 0–3 cm for nulliparous and 1–3 cm for multiparous with cervical effacement of 50%. The institutional review board approved the study, and written informed consent was obtained from the entire patient prior to their enrollment in to the study.

Maternal exclusion criteria included obstetric or medical indication for delivery, known exposure to tocolytic agents during the study pregnancy, abruptio placentae, documented intrauterine infection, cervical incompetence, or any contraindication to the use of the study medications, such as renal insufficiency, hepatic insufficiency, myasthenia gravis, or preeclampsia. Maternal hypotension, defined as a blood pressure <90/50 mm Hg, was also cause for exclusion. Patients with cervical dilatation ≥4 cm were excluded from the study.

Fetal exclusion criteria included nonreassuring fetal status, intrauterine growth restriction, and congenital fetal anomalies. A sonogram was obtained before inclusion to assess amniotic fluid volume, to screen for fetal anomalies, and to confirm gestational age. After informed consent was obtained, the patient was assigned to the nifedipine with an initial oral loading dose of 30 mg (10 mg sublingual and 20 mg oral) and a maintenance oral dose of 20 mg every 6 h until tocolysis is achieved. Treatment was discontinued if no uterine contractions occurred within a 48 h period and was switched to indomethacin 25-50 mg every 6 hours, with a maximum daily dose 200 mg, for 48 hours. If spontaneous rupture of membranes occurred within 48 hours of treatment, delivery was considered. To enhance fetal lung maturation, all the patients were given head low position and injection dexamethasone 12 mg im 12 hrly for two doses followed by weekly injections up to 36 weeks and Antibiotic prophylaxis was given in the form of erythromycin to patients. Rest and hydration for half an hour was applied as first line management in all cases, Normal saline infusion at a rate of 100-150ml/hr after an initial bolus of 200ml was given for hydration.

An electrocardiogram was obtained from each woman before and after 24hr of treatment and then 24hr till 7 days of drug treatment. Maternal blood pressure oral temperature, heart rate and pulse were monitored at the screening and before the start of therapy and every 15min after starting the therapy for 2hrs and thereafter 8hr till 7days of drug treatment. Uterine contractions; were confirmed by an external tocodynamometry and was performed every 15min for the first 2hrs and hourly for the next 22hrs,then twice daily thereafter when uterine quiescence has been achieved. Fetal Heart rate measurement was done every 15min for the first 2hrs then hourly for the next 22hrs then twice daily thereafter when uterine quiescence had

been achieved. Clinical signs and symptoms of intolerance to nifedipine used was assessed every 6hr. Several neonatal parameters, such as weight, apgar score, umbilical arterial and vein PH values and presence of hyperbilirrubinemia was determined, neonatal complications such as hemorrhage or infections were recorded.

Tocolysis was considered to have been achieved when uterine activity decreased to <4 contractions/h with the absence of cervical change. If patients continued to have uterine activity after 6 hours or had cervical dilatation >2 cm after admission examination, they could be switched to another tocolytic regimen. Study outcomes included time in hours until the arrest of labor, failure of tocolysis, time gained in weeks from the onset of preterm labor to delivery, and recurrence of preterm labor. Tocolytic failure was defined as delivery <48 hours after the initiation of a study agent. All patients were placed on a home uterine activity monitor (Tokos Medical Corp, Encino, Calif) at hospital discharge. Uterine activity was monitored twice daily. These data were telephonically transmitted to the research nurses. Recurrence of preterm labor was as previously defined. The CSI Kalyani Multi Specialty Hospital pharmacy supplied all maintenance oral medications. All patients were followed up weekly in the outpatient research clinic until delivery. At each clinic visit the degree of cervical dilatation was determined, monitor recordings were reviewed. If a patient was readmitted because of preterm labor, tocolytic therapy was initiated with again with nifedipine, previously demonstrated to be effective for that particular patient.

Tocolytic outcome and Safety outcomes were analyzed by descriptive statistics and qualitative analysis for all emergent adverse events, measured after initial and after the treatments by SPSS graph pad prism software. And a Meta - analysis was performed with other research outcomes of tocolysis.

RESULTS

During the course of the study, 208 patients were screened for enrollment. Twenty-four patients refused to participate in the study. One hundred thirty six patients were excluded because they met exclusion criteria or failed to meet inclusion criteria as defined in the Material and Methods section. The reasons for exclusion included (1) failure to meet study definition of preterm labor (n = 26), (2) estimated gestational age <28 weeks or >36 weeks (n = 41), (3) rupture of membranes (n = 20), (4) cervical dilatation ≥4 cm (n = 29), and other contraindications to tocolytic therapy or study tocolytic agents (n = 24). During the study period 160 patients were enrolled; 48 patients were subjected to nifedipine therapy A Total of 40 patients data were taken for statistical considerations as 8 patient required alternate therapy for tocolysis.

In the present study preterm labour was more common in patients of younger age group that is below 25 years of age (67.5%) and in primi gravidas (45%) comparatively Griswold Cavang[8] (1996) was 50% In primi and 2nd gravid however the studies of Kaltreider and Kohl[9] (1980) also confirmed with our present study with more number of cases in primigravida. There is an association of preterm labour with low socioeconomic status and poverty as seen in this study, where majority of cases belong to upper and lower middle class (78.5%). It might be due to lack of ANC care, anemia, malnutrition, reproductive excess, general infection, local genital and urinary tract infection and low education levels. It was also confirmed by Barden[10] (1980) were the common cases of preterm labour was of socio economic deprivation and Meis & Colleagues[11] (1955) found that preterm labour associated with poverty, low maternal weight gain. In the present study majority of the cases were educated upto matriculation (66.25%) this was contraindicated with Fredrick Anderson[12] (1976) and Creasy[13] (1980) reported that less educated were associated with Preterm labour. Though majority of cases in this study were house wives (90%) they were not leading a sedentary life style as they belonged mostly to middle class. Majority of the patients belonged to 33-36 weeks of gestation (65%) the time when lower

segment is forming. There is increased association of preterm labour with previous history of abortion (23.75%) and previous history of preterm delivery (12.5%) which was seen in this study. In the present study successful tocolysis was achieved in 90% of nifedipine and was more successful in suppressing labour for 7 days to 21 days and more than 21 days. However nifedipine successfully suppressed labour when dialatation was less than 1.5cm and effacement less than 50%. Mean prolongation of pregnancy in days as compared to gestational age and gestational age at the time of delivery at different weeks of gestation was more in in the present study. The mean prolongation of pregnancy was 13.7 days with nifedipine in the present study. The mean gestational age at delivery was 34.4 weeks in the present study.

Tachycardia 52.5% , hypotension 12.5% were the common side effects in the present study and Tachycardia 18.75% and 46% were reported by Rayamajhe et al.[14] (2003) and Kedar et al.[15] (2004) respectively. Hot flushes and headache were seen in the present study that is 5% and 7.5% respectively however a 3.30% and 40% was reported by Rayamajhe et al.[14] (2003) and Kedar et al.[15] (2004) respectively. Nifedipine in the present study was better able to suppress labour when cervical dialatation was 1.5 to 3cm and effacement was more than 50% i.e. 89.4% .

The neonatal outcome in terms of mode of delivery was similar in all the studies. However mean birth weight was more in the present study as compared to other studies which might be due to longer prolongation of pregnancy in nifedipine group. Perinatal mortality was almost similar in all the studies. The details of Nifedipine in the present study and other similar studies with respect to Mode of Delivery.

CONCLUSION

In the present situation, the results of meta analyses indicate that a more 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 center for delivery, administer corticosteroids to the mother as well as treat maternal infection when present. These measures have been shown to reduce neonatal morbidity and mortality and aggressive pursuit of these achievable goals may be expected to lead to further improvements in neonatal outcome. The present study found that nifedipine has better tocolytic efficacy, less side effects and better tolerability. However the significance could be accountable only when a comparative study is done with other tocolytics. In view of the increasing evidence of its efficacy and safety combined with its ease of administration, it appears likely that Nifedipine will play an expanded role in the suppression of preterm labor.

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