

# Study to Determine the Efficacy of Nifedipine in Inhibiting Preterm Labor

SHAISTA HABIB<sup>1</sup>, SHAZIA SADARUDDIN<sup>2</sup>, SHAKEELA YOUNUS GILL<sup>3</sup>

<sup>1,3</sup>Consultant Gynecologist, Department of Obstetrics & Gynecology, Dr Sulaiman Al-Habib Hospital, Buraidah Al-Qassim Saudi Arabia

<sup>2</sup>Department of Obstetrics & Gynecology, Sulaiman Al-Habib Hospital, Buraidah Al-Qassim Saudi Arabia

Correspondence to: Dr Shaista Habib, PH 00966-0541962181 sh\_habib73@yahoo.com

## ABSTRACT

**Aim:** The aim of the study was to evaluate the effectiveness of nifedipine in inhibiting preterm labor.

**Study design:** A Quasi-experimental study.

**Place and duration:** The study was conducted at the Department of obstetrics & Gynecology

Dr Sulaiman Al-Habib Hospital, Buraidah Al-Qassim Saudi Arabia for one-year duration from April 2019 to April 2020.

**Methodology:** 75 single pregnancies with preterm labor between 28 and 34 weeks of pregnancy were selected. A patient with preterm labor, dilation of the cervix <3 cm and an intact membrane was enrolled in the study. Nifedipine was used as a tocolytic agent.

**Results:** While effective tocolysis was achieved in 73.33% (55/75) of patients, tocolysis was not achieved in the remaining 27.7% (20/75).

**Conclusion:** Nifedipine successfully inhibited uterine contractions and delayed labor by > 48 hours; sufficient time for an intrauterine or corticosteroid transfer effect.

**Key words:** Preterm labor, Tocolysis, Nifedipine.

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## INTRODUCTION

Preterm labor is defined as delivery that occurs from viability of the fetus (currently defined in the UK as 24 full weeks of gestation from the date of the last menstrual period, assuming a 28-day menstrual cycle) to the end of the 37th week of pregnancy<sup>1-2</sup>. Preterm delivery is one of the most important contributors to perinatal mortality and morbidity in the industrialized world.

In Europe, the prevalence of preterm births is 5.8%, corresponding to around 400,000 preterm births per year, and it is estimated that around 100,000 are potentially preventable. The perinatal mortality in Pakistan is 96 per 1000 live births, it is much higher compared to developed countries, although not comparable to developing countries (India 48.6, Burma 57.2, Indonesia 45 and Thailand 28.3)<sup>3-4</sup>. Perinatal mortality and the morbidity associated with preterm labor decrease with gestational age. Only 20% of babies born at 24 weeks of gestation survive, and the survival rate at 30 weeks increases to 90%. Between 23 and 27 weeks of gestation, neonatal survival increases linearly by about 3% per day, while the incidence of newborns is reduced. The incidence of disability decreases with gestational age from 31% at 23 weeks to 7% at 27 weeks. Between 15% and 20% of survivors born prematurely or with very low birth weight may have severe neurological impairment or disability, and about half may have more subtle hearing or intellectual deficits<sup>5-6</sup>. Cerebral palsy has been studied in particular. Its incidence is increased in premature babies, but it is unclear whether it is intended to increase the survival rate of infants with perinatal injury or have the perinatal consequences of preterm delivery.

The time from prenatal glucocorticoid administration to delivery affects the outcome of the newborn. Although there is a tendency to reduce the development of RDS after a 24-48-hour interval, significant reduction is only achieved if delivery may be delayed by more than 48 hours.

Therefore, it is desirable that pharmacological treatment of PTL should delay preterm labor by at least 48 hours<sup>8-9</sup>.

Many different agents have been proposed to inhibit uterine contractions. Currently used include  $\beta$  agonists, calcium channel blockers, prostaglandin synthesis inhibitors, nitric oxide donors, and oxytocin receptor antagonists. The use of these drugs is associated with a number of side effects. The most widely tested tocolytic agents are  $\beta$ -mimetics. They have a high frequency of unpleasant and sometimes serious maternal side effects, including tachycardia, hypotension, and various biochemical abnormalities<sup>10-11</sup>. Mimetics have been associated primarily with maternal deaths from pulmonary edema. Myocardial infarction has been reported in women receiving tocolytic mimetic therapy.

Therefore, there is a need for an effective tocolytic agent with fewer side effects. Calcium channel blockers of the dihydropyridine group (type II), especially nifedipine, are considered relatively safe for use in pregnancy. They are more effective tocolytics<sup>12</sup>. These drugs also improve some clinically important neonatal outcomes, including fewer cases of respiratory distress syndrome, intraventricular bleeding, necrotizing enteritis, jaundice, and the risk of neonatal intensive care unit admission. They have little teratogenic or fetotoxic potential. They are also associated with a marked reduction in the incidence of maternal adverse events. Few patients should discontinue nifedipine due to side effects<sup>13-14</sup>.

## MATERIALS AND METHODS

The study was conducted at the Department of obstetrics & Gynecology, Dr Sulaiman Al-Habib Hospital, Buraidah Al-Qassim Saudi Arabia for one-year duration from April 2019 to April 2020. The total number of patients included in this study was 75. The sampling method was non-probability convenience sampling. The study included patients with preterm labor between 28 and 34 weeks of gestation with a

single pregnancy with regular uterine contractions, cervical dilatation less than 3 cm with an intact membrane. The contractions should have a frequency of 1 or more per hour and a duration of 30 seconds or more. The effectiveness of the drug was confirmed by comparing the mean number of uterine contractions before and after nifedipine and determining the mean number of days obtained after nifedipine treatment.

A patient with a fetal malformation or fetal death in the uterus, suspected fetal damage justifying delivery by ultrasound or CTG, placental abruption or pre-eclampsia, amniotic membranes, significant maternal heart disease, liver dysfunction or hypotension, concomitant use of beta-agonists or intravenous antihypertensive drugs, and allergy to nifedipine were excluded.

The study included patients who came to the delivery room via the ambulance service or outpatient clinic and met the inclusion and exclusion criteria. The reasons for the purpose, risks and benefits were explained to them and informed consent was obtained. Fetal heart rate and uterine contractions were continuously monitored in all women selected for the study. Fetal heart rate and uterine contractions were monitored by CTG.

Initially, 5% dextrose saline (or lactated Ringer's solution) was used at a rate of 125 ml / hr. The physical examination was performed for a minimum observation period of 60 minutes. Blood samples were taken for blood counts, serum electrolytes, urea, creatinine, and blood glucose. Urine was also collected for detailed report and high vaginal swab cultures. All patients underwent an obstetric ultrasound examination to check viability and to assess the gestational age and cervical length. The long-acting variant of nifedipine was administered as an oral tablet.

Nifedipine tocolysis was started with Tab. Adalat Retard (20 mg) is administered orally. If uterine contractions continued after 30 minutes, a similar dose was repeated every 30 minutes. If contractions were not stopped after the second dose, a third dose of 20 mg was repeated at 30-minute intervals up to a maximum total dose of 60 mg during the first hour of treatment. After the third dose, the patients were switched to tab. Adalat Retard (20 mg) every 3 to 8 hours for 48 to 72 hours as indicated. The maximum dose administered in the study was 160 mg / day. Before treatment, maternal blood pressure, heart rate, uterine contractions, fetal heart rate were monitored and every half hour for the first hour after starting treatment, then hourly up to 4 hours, and then 24 hours of observation. All patients received steroids to support fetal lung maturation and remained in hospital for at least 72 hours. After this period, women with persistent uterine inactivity were discharged and instructed to continue bed rest. Tocolysis was considered successful if delivery was delayed by at least 48 hours.

## RESULTS

While the mean number of uterine contractions before nifedipine treatment was  $3.29 \pm 2.2$  (10 minutes), it was recorded as  $0.12 \pm 0.494$  (10 minutes) after treatment, which was statistically significant. ( $p < 0.01$ ). The frequency of uterine contractions is given in Table 1.

Table 1: Frequency of uterine contractions before and after nifedipine treatment per 10 minutes (n=75)

Frequency of uterine contractions	Before	up to 24 hours	up to 48 hours
0	-	47(62.7%)	51(68.0%)
1	-	-	-
2	19(25.3%)	5(6.7%)	4(5.3%)
3	33(44.0%)	-	-
4	23(30.7%)	23(30.7%)	-

The delay to delivery <2 days was  $1.1 \pm 0.3$  days, and the delay > 2 days -  $5.0 \pm 10.1$  days, which was statistically significant ( $p < 0.009$ ). Therefore, the mean gain in days after treatment was  $5.0 \pm 10.1$  days. See Table 2 for delays in delivery.

Table 2: Gain in days after nifedipine treatment (Delay in delivery) [n=75]

Duration in Days	N	%	mean $\pm$ SD	P-Value
< 2 days	20	27%	$1.1 \pm 0.3$	0.009
> 2 days	55	73%	$5.0 \pm 10.1$	

While effective tocolysis was achieved in 73.33% (55/75) of patients, it was not achieved in the remaining 30% (20/65). While the mean heart rate before nifedipine treatment was  $84.0 \pm 4.1$ , after treatment it was  $93.9 \pm 4.0$ , indicating a heart rate increase of 9b / min that is not statistically significant.

The mean systolic blood pressure before treatment was  $115.4 \pm 5.4$ , and after treatment it was  $101.1 \pm 3.9$ , which indicates a statistically significant decrease in systolic BP by 14 mmHg. While the mean diastolic blood pressure before nifedipine treatment was  $76.5 \pm 5.5$ , after treatment it was  $68.4 \pm 5.0$ . This reduction in blood pressure was significant but was not associated with any clinical signs of hypotension. There was no statistically significant change in respiratory rate and fetal heart rate before and after treatment with Infoline. Basic information is presented in Table 3.

Table 3: Mean comparison between before treatment (baseline information) and after treatment effects (n=75)

	Baseline Pretreatment	After treatment	P Value
	Mean $\pm$ SD	Mean $\pm$ SD	
Systolic Blood Pressure (mmHg)	$115.4 \pm 5.4$	$101.1 \pm 3.9$	< 0.01*
Diastolic Blood Pressure (mmHg)	$76.5 \pm 5.5$	$68.4 \pm 5.0$	< 0.01*
Pulse (beats/min)	$84.0 \pm 4.1$	$93.9 \pm 4.0$	0.791
Respiratory Rate (per 10 min)	$19.8 \pm 1.1$	$19.8 \pm 1.1$	< 0.01*
Fetal Hear Rate (per 10 min)	$146.4 \pm 3.7$	$142.3 \pm 23.3$	< 0.01*
Uterine Contractions (per 10 min)	$4.29 \pm 2.33$	$0.1287 \pm 0.504$	< 0.01*

## DISCUSSION

The study was conducted on a population of patients from Buraidah Al-Qassim Saudi Arabia. Prenatal care for these patients is also poor. In this study, 46% of patients were booked and 54% were not. The maximum number of patients was primary. Many drugs and other interventions have been used to inhibit PTL, but

unfortunately none have been fully effective (ACOG95). Mariam Malik from Allama Iqbal Hospital in Lahore observed the effect of glyceryl trinitrate on PTL. The reported side effects were headache and palpitations which required removal of the patches. More studies are needed to confirm that glyceryl trinitrate is safe in PTL<sup>15, 16</sup>.

In a study at King Edward Hospital in Lahore, ritodrine was shown to be effective, delaying labor by 72 days in 88.2%, but 9 women stopped the drug because of side effects. This could endanger the mother and the fetus.

Another study conducted at the Karachi Baqai Medical University Institute established polytherapy, that is, despite one measure, many tocolytic agents were used. Their results suggested that polytherapy is more effective than monotherapy, but requires consent<sup>17</sup>.

Possible maternal complications caused by tocolytic drugs indicated by the American College of Obstetricians and Gynecologists (1995). Its importance cannot be underestimated. For example, tocolysis was the third leading cause of adult respiratory distress syndrome and death in pregnant women over a 14-year period in Jackson, Mississippi. The most commonly used tocolytic drugs in the United States are sympathomimetic agents, usually terbutaline or ritodrine, approved by the Food and Drug Administration. Intravenous administration of these drugs produces a rapid tocolytic effect<sup>18</sup>. However, -mimetic drugs have significant and potentially serious maternal and fetal side effects, e.g., for example, pulmonary edema, cardiac ischemia, and fetal cardiotoxicity. Less serious side effects include increased heart rate, tremors, anxiety, palpitations, and insomnia. Maternal intolerance to these side effects often requires dose reduction or treatment discontinuation<sup>19</sup>.

Although statistically significant in the blood pressure we observed following oral administration of nifedipine, it was unlikely to be of clinical significance. In this study, there was an increase in the mother's heart rate after each dose, but this was transient and less pronounced. There was no significant change in the fetal heart rate. Various doses of nifedipine were used, ranging from 60 to 160 mg after 24 hours. In most studies, nifedipine was started with a sublingual dose<sup>20</sup>. However, in this study, we administered nifedipine orally to avoid the side effects reported with sublingual (short-acting) nifedipine. In our study, only minor side effects were seen, including a headache. These side effects disappeared after a few hours and did not require any special measures.

There were no perinatal deaths in this study, and children who gave birth after 48 hours of tocolytic treatment and were treated with steroids were born with good Apgar scores and did not require admission to the ICU. Admission to the neonatal intensive care unit was only required for babies born within 24 hours. Previous clinical studies did not reveal any significant adverse effects associated with nifedipine in neonates. Four studies found no significant difference in neonatal outcomes between the two treatment groups; namely (nifedipine and ritodrine), but two other studies found significantly larger neonates in the group of women treated with nifedipine. Nifedipine appears to be one of the most effective and safest tocolytic agents available for use when properly indicated.

## CONCLUSION

Nifedipine was effective in inhibiting uterine contractions and delayed labor for > 48 hours; sufficient time for corticosteroid effect and intrauterine transfer to hospital with neonatal care facilities.

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