Assessment of safety and efficacy of Nifedipine in Preterm Labor Patients and its effect on Neonates: An Observational Study

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Abstract

Background: *The health of the neonates is compromised in case of preterm delivery. The risk of neonatal death is high in preterm delivery. Nifedipine is a widely used tocolytic drug. This study focuses on learning safety and efficacy of Nifedipine as tocolytic agent.*

Objective: *The primary objective is to study efficacy and safety of Nifedipine as well as maternal and neonatal outcomes.*

Methods: *This study is a prospective observational single centre study and conducted in Labor ward, Department of Obstetrics and Gynaecology, Government Cuddalore Medical College and Hospital, Chidambaram-608002. This study includes inpatients. Filling Proforma (Preformed data collection form) by reviewing case sheets and face to face interaction with patients. Means and Standard Deviations are determined for continuous variables and Percentages for categorical variables.*

Results: *The most common adverse drug reaction found in our study was headache (6.2%) which was followed by nausea (4.6%), facial puffiness (3.1%), vomiting 3.1%) and facial flushing (3.1%). Tachycardia and palpitations were present in 1.5%. In our study 22% were presented with pedal edema which was followed by burning micturition (9.2%), cold and cough (7.7%), vulval edema (3.1%) and abdominal wall edema (3.1%). Perinatal depression was found in 3.1%. In our study, majority (75.4%) of the patients gave birth within 5 days of administering nifedipine. The mean delay in pregnancy was 4 days and 10 hours and the median was found to be 48 hours.*

Conclusion: *The observational study on nifedipine as a tocolytic agent in preterm labor presents promising findings. It demonstrates effectiveness in delaying preterm labor with the mean of 4 days, thereby offering a valuable intervention like antenatal corticosteroids to enhance fetal lung maturation, prolong pregnancy and reduce neonatal morbidity and mortality. While some minor adverse effects were observed, they were generally well-tolerated and transient, posing minimal risk to mothers. No serious maternal and neonatal adverse drug reactions were evident in this study. No post-partum complications were identified.*

Keywords: *Preterm labor, Nifedipine, Tocolysis, Maternal outcome and Neonatal outcome.*

1. Introduction

Preterm is the global burden and it is unanticipated. It is the prime reason for neonatal mortality (below 5 years of age). Preterm birth results in long-term physical, neurodevelopmental, and socioeconomic effects[1]. Preterm Birth may be born spontaneously or non-spontaneously (Induced)[2]. Respiratory distress is the major complication of preterm.

Preterm Premature Rupture of Membranes (PPROM), cervical dilation and uterine contractions (natural) comes under spontaneous preterm births. Preterm birth is clinically proposed due to complications during pregnancy such as hypertensive states, hemolysis, increased liver enzymes, low platelet count syndrome, worsening of fetal condition and placental disorders[3].

Half of long-term morbidity and three fourth of mortality are caused by Preterm deliveries. The newborns born out of preterm are highly susceptible to suffer from respiratory, gastrointestinal, and cognitive disorders in spite of their survival. Elevated indicated preterm births are main reason for the singleton preterm birth rate[4].

Preterm birth has been corelated with a broad range of maternal or fetal characteristics, including the maternal demographics, history of pregnancy, current status of pregnancy, psychological traits, negative behaviors, infection, nutritional status, uterine contractions, creatinine clearance & biochemical and genetic markers[4].

2. Materials and Method

This is a single center prospective cross sectional observation study, carried for 6 months. Selection of subjects is based on inclusion and exclusion criteria. Study proforma (Data collection form) is designed to collect all the details like inpatients number, name, age, chief complaints, history of present illness, past medical and medication history, drug chart details, prescribed dosage, frequency, route of administration and clinical diagnosis.

A thorough medical history, including the patient's obstetric, menstrual, family, and personal histories, was obtained at the time of admission. The patient's gestational age was also noted. An extensive menstruation history was obtained in order to rule out incorrect dates. A thorough physical examination was conducted, and the results of a full serial obstetric examination were documented. Estimated fetal weight was recorded. Assessment of the fetal growth was noted. A per speculum and per vaginum examination findings were noted to determine cervical conditions and bishop score was noted. Abnormal laboratory findings were noted.

The present study was carried among the preterm labor patients prescribed with nifedipine under guidance from the department of O/G, Government Cuddalore Medical College and Hospital.

Symptoms, risk factors, hemodynamic changes (Pre and Post administration of drugs), APGAR score, birth weight, Neonatal Intensive Care Unit (NICU) admissions, maternal and neonatal side effects, mode of delivery, gestational age at delivery, calculation of medical expenses and any adverse drug reactions are intended to be collected.

2.1. Inclusion Criteria

1. Patients, who are in the third trimester stage of gestation (28 – 35 weeks).
2. Patients with regular uterine contractions ≥2/10 minutes and last for at least 15 – 25 s.
3. Patients with cervical dilation ≤3 cm.
4. Patients with cervical effacement 75% with intact membrane.

2.2. Exclusion Criteria

1. Patients who are not willing to join.
2. Patients with fluid discharge.

2.3. Sample Size and Power

As per World Health Organization (WHO) data, the estimated prevalence of preterm births in India ranges from 13% to 17%. Hence, considering an average of 15% an error of 10%, the sample size was estimated by using the following formula: $N=4\rho q/d^2$. A minimum sample size of ~ 51 participants were required. Sample of 65 participants had been collected.

3. Observation and Results

The mean maternal age of patients with preterm labor was found to be 24 years. The lowest maternal age at the time of admission was 18 years and 37 was the highest age. The patient's immunization status in our study showed that majority (93.8%) of the pregnant females were booked for immunization and vaccination. BMI value of the patients demonstrated that majority (44.6%) of the patients came under the normal healthy weight.

The gravidity status of the admitted patients demonstrated that 55.4% were primigravida which means that these patients were pregnant for the very first time and 6.6% had multiple pregnancies. Majority of patients underwent left medio-lateral episiotomy procedure. 50.8% patients were admitted between 33 and 35 weeks of gestation, about 95% had normal cephalic presentation. All the 65 patients had intact membranes at the time of admission but 23% developed PPROM post admission.

Taking the maternal comorbidities into consideration, it was found that about half (53.85%) of the admitted patients had anemia. These women had hemoglobin levels less than 12 g/dl. Gestational hypertension was found in 15.38%. 15.38% had oligohydramnios and 9.23% had polyhydramnios. In our study, 55.4% had bishop score range of 4-7 at the time of admission which indicates that it is unlikely that the labor may be starting soon. The mean prolongation of delivery in these patients was 2 days & 7 hours. 18.5% had bishop score of 8 & above which indicates that labor might start soon. The mean prolongation was 9 hours in these women.

In our study about 30.8% had risk factors for preterm labor. 21.5% had major risk factors like polyhydramnios (9.2%), multiple gestation (6.2%), two or more second trimester abortion (3.1%) and bicornuate uterus (1.5%). 9.3% had minor risk factors like more than two first trimester abortion (6.2%) and one second trimester abortion (3.1%). 12.3% had previous Lower Segment Cesarean Section (LSCS).

In our study, almost all the babies born needed NICU admission. The maximum number of days the neonate had been stayed in the NICU was 11 days for the condition called fetal distress. The mean NICU stay in our study was found to be 5.5 days. About 52.1% were admitted in NICU because of RDS. 44% needed NICU admission because of low birth weight (<2kg).

4 babies out of 69 were died. The reasons for neonatal mortality were sepsis and Disseminated Intravascular Coagulation (DIC). 2 babies died in the uterus. The reason for Intrauterine Fetal Death (IUFD) is unknown. However, it has been speculated that maternal conditions might have contributed to the fetal demise. One of the mothers of the in-utero dead fetus had chronic hypertension and the other one had polyhydramnios with increased utero-placental perfusion. No fetal anomalies were found in the babies born.

Among the 69 babies born, majority (68%) of the babies weighed between 1.5 kg and 2.5 kg. 9% belonged to the very low birth weight category of 1-1.5 kg. Only 23% were born with the normal weight of 2.5-4 kg. In our study, no babies were born with the weight more than 4 kg. The lowest birth weight was 1 kg and it belonged to a female baby. 2.7 kg was the maximum birth weight and it belonged to a male baby.

APGAR score which evaluates the baby's clinical condition demonstrates that about 58% were moderately depressed as they had their APGAR score between 4 and 5 at 1 minute interval. Only 30.4% had their scores between 7 and 10. Almost 11.6% were severely depressed. However, at 5 minutes, 66.7% had normal APGAR score and about 8.7% had low APGAR score of 0-3 and were considered severely depressed. The mean APGAR score was 5 and 6 at 1 minute and 5 minutes respectively.

In our study, majority (75.4%) of the patients gave birth within 5 days of administering nifedipine. The mean delay in pregnancy was 4 days and 10 hours and the median was found to be 48 hours. Only 7.7% had their deliveries at 37 weeks of gestation. About 72.3% delivered babies before 35 weeks of gestation. The mean gestational age at the time of delivery was found to be 33 weeks. The

minimum and the maximum gestational age at the time of delivery was 27 weeks and 37 weeks respectively.

The most common adverse drug reaction found in our study was headache (6.2%) which was followed by nausea (4.6%), facial puffiness (3.1%), vomiting 3.1%) and facial flushing (3.1%). Tachycardia and palpitations were present in 1.5%. There are no new ADRs found among participants.

Table 1. General Characteristics of Patients

Attributes		No of Patients	Percentage
Patient age (Years)	15 – 19	14	21.5
	20 – 30	45	69.2
	> 30	6	9.0
Gestational age at admission (Weeks)	< 32 Weeks	18	27.7
	32 – 33 Weeks	14	21.5
	33 – 35 Weeks	33	50.8
Gravida Status	Primigravida	36	55.4
	G2	14	21.5
	≥ G3	15	23.1
Pregnancy type	Singleton Pregnancy	61	93.8
	Multiple Pregnancy	4	6.2
Blood Group	O^+	25	38.5
	A^+	11	16.9
	AB^+	4	6.3
	B^+	19	29.3
	O^-	2	3
	A^-	2	3
	B^-	2	3
Immunization	Booked	61	93.8
	Not Booked	4	6.2
Menstruation	Irregular	27	41.5
	Regular	38	58.5
BMI (kg/m^2)	<18.5 (Underweight)	12	18.46
	18.5-24.9 (healthy weight)	29	44.62
	25-29.9 (overweight)	14	21.54
	30 and above (obesity)	10	15.38
Consanguinity	NCM	50	76.9
	CM	15	23.1

Table 2. Clinical Characteristics of Patients

Attributes		No of Patients	Percentage
Mode of Delivery	Normal	12	18.5
	Episiotomy	35	53.8
	Elective LSCS	5	7.7
	Emergency LSCS	13	20.0
Gestational age at delivery (Weeks)	< 35	47	72.3
	35	10	15.4
	36	3	4.6
	37	5	7.7
AFI (cm)	< 5	10	23.2
	5 – 25	49	68.1
	> 25	6	8.7
Presentation	Cephalic	62	95
	Breech	3	5

Position	Anterior placenta	36	55.4
	Posterior placenta	29	44.6
Membrane	Intact membrane	50	77
	Rupture of membrane	15	23

Table 3. General Characteristics of Neonates

Attributes		No of Neonates	Percentage
Gender	Male	32	46.4
	Female	37	53.6
Birth Weight (kg)	Normal (2.5 – 4)	16	23
	Low birth weight (1.5 – 2)	47	68
	Very low birth weight (1 – 1.5)	6	9
Mortality	Alive	65	94.2
	Dead	4	5.8
Nature of Mortality	Sepsis	1	1.53
	IUFD	2	3.07
	DIC	1	1.53

Table 4. Clinical Characteristics of Neonates

Attributes		No of Neonates	Percentage
APGAR Score (At 1 min)	0 – 3 (Severely Depressed)	8	11.6
	4 – 6 (Moderately Depressed)	40	58
	7 – 10 (Normal)	21	30.4
APGAR Score (At 5 min)	0 – 3 (Severely Depressed)	6	8.7
	4 – 6 (Moderately Depressed)	17	24.6
	7 – 10 (Normal)	46	66.7
NICU Stay	0 – 5 Days	34	52.3
	5 – 10 Days	25	38.5
	10 – 15 Days	6	9.2
Reason for NICU Stay	Low Birth weight	44	63.8
	Respiratory Distress Syndrome	5	7.2
	Fetal Distress	2	2.8

Table 5. Efficacy Profile of Nifedipine

Delay in Delivery		No of Neonates	Percentage
0 – 5 Days		49	75.4
6 – 10 Days		6	9.2
11 – 15 Days		6	9.2
16 – 20 Days		4	6.2
Bishop Score	**Mean prolongation of delivery in days**	**No of Patients**	**Percentage**
1 to 3	17	11.70	26.1
4 to 7	36	2.26	55.4
8 and above	12	0.37	18.5
Difference between predicted and actual delivery date		**No of Patients**	**Percentage**
20-30 Days		6	9.23
31-40 Days		26	40
41-50 Days		14	21.54
51-60 Days		13	20
61-70 Days		5	7.70
71-80 Days		1	1.53

Table 6. Safety Profile of Nifedipine		
Adverse Drug Reactions	**No of Patients**	**Percentage**
Facial puffiness	2	3.10
Nausea	3	4.60
Vomiting	2	3.10
Facial flushing	2	3.10
Tachypnea	1	1.50
Palpitations	1	1.50
Tachycardia	1	1.50
Headache	4	6.20

Table 7. Comorbidities of Patients		
Comorbidities	**No of Patients**	**Percentage**
Anemia	35	53.85
GHTN	10	15.38
Oligohydramnios	10	15.38
pre-eclampsia	6	9.23
Polyhydramnios	6	9.23
Hypothyroidism	5	7.69
eclampsia	3	4.62
GDM	3	4.62
UTI	3	4.62
Class-II obesity	2	3.08
Bronchitis	2	3.08
Vulvovaginitis	2	3.08
Typhoid	2	3.08
Thrombocytopenia	2	3.08
Hyperthyroidism	1	1.54
PCOS	1	1.54
PCOD	1	1.54
Seizure	1	1.54

Table 8. Concomitant Medications of Patients		
Medications	**No of Patients**	**Percentage**
Ampicillin	4	6.15
Gentamicin	4	6.15
Metronidazole	7	10.77
Cefotaxime	13	20
Dexamethasone	63	96.92
Labetalol	16	24.62
Levothyroxine	5	7.69
Tramadol	4	6.15
Amoxicillin	4	6.15
Propyl Thiouracil	1	1.54
Metformin	2	3.08
Ceftriaxone	2	3.08
Mgso4	3	4.62
Cefixime	1	1.54

4. Patient Outcome

4.1. Primary outcome

The primary outcomes of interest are delivery within 48 hours and 7 days of treatment for tocolysis, delivery before 34 and 37 weeks of gestation, perinatal death, admission to NICU, neurodevelopmental impairment at two years of age and severe maternal adverse drug reactions. In our study, the mean delay in pregnancy was found to be 4 days and 48 hours. The mean gestational age at the time of delivery was 33 weeks. These results are in par with the study done by Agustín Conde-Agudelo *et al.,* (2011)[5]. The percentage of mortality was found to be 5.8%. No serious maternal or fetal adverse drug reactions were found in this study[6].

4.2. Secondary outcome

The secondary outcomes include evaluation of APGAR scores and birth weight of the neonates. In our study, the mean APGAR score at 1 and 5 minutes were 5 and 6 respectively. It is considered to be normal. The mean birth weight was found to be 1.76 kg which comes under low-birth-weight category.

5. Discussion

Study by Ghina Mumtaz *et al.,* (2010)[7] found that compared to babies of unrelated parents, consanguineous parents' offspring had increased risk of being born at less than 33 weeks' gestation. In our study 23.1% had consanguineous marriage. Taking into account the gender of the babies born in preterm labour, our study noted that majority of the babies born were females (53.4%). 46.4% of the babies born were males. This is in contradiction with the study done by Myrthe J.C.S *et al.,* (2016)[8] which states that male fetuses are more likely to be preterm than female fetuses. However, *Teoh P J et al.,* (2018)[9] states that gender need not be integrated into high-risk management protocols for preterm birth.

A study by Shumalia Zia (2013)[9] evaluated the association between placental location and feto-maternal outcome of pregnancy. This study found that women with posterior placenta have a greater risk of preterm delivery. However, in our study we found that majority (55.4%) of the pregnant women had anterior placenta.

In our study, about 96.9% were prescribed dexamethasone along with nifedipine. Among the concomitantly administered medicines, nifedipine may interact with tramadol, metformin, magnesium sulphate, labetalol and dexamethasone. Tramadol's effects and blood levels may be increased by nifedipine. This may increase side effects like low blood pressure, nausea, constipation, dizziness, and drowsiness. 6.2% patients who were prescribed tramadol along with nifedipine in our study did not show any such side effects. Nifedipine may increase the effects of metformin which can cause weakness, sleepiness, slow heart rate, muscle pain, shortness of breath, stomach pain and fainting. In our study, only 3.1% were prescribed metformin along with nifedipine and no such interaction effects were noted. Concomitant use of nifedipine with magnesium sulphate may occasionally cause low blood pressure. 4.6% who received both magnesium sulphate and nifedipine had no significant changes in their blood pressure. Labetalol and Nifedipine may have additive effects and lower blood pressure which may cause headache, dizziness, lightheadedness, fainting, and changes in pulse rate. No significant hypotensive effects were noted when labetalol was administered with nifedipine[10].

A study by Florent Fuchs *et al.,* (2018)[11] showed that preterm birth and maternal age followed U shaped distribution and patients of maternal age 31 – 34 years showed least risk for preterm birth. In our study, majority of the patients belonged to the age group of 20-30 years (68.23%) which was followed by the age group of 15-19 years (21.53%) with the least belonging to the category of above 30 years. This is similar to our study.

BMI value of the patients demonstrated that majority (44.6%) of the patients came under the normal healthy weight category of 18.5-24.9 kg/m^2. 21.54% were overweight (25- 29.9 kg/m^2) and 15.38% were obese (30 kg/m^2). A study by R P Cornish *et al.,* (2024)[12] showed that women with lower and higher BMI are at an increased risk for preterm.

A study by Cande V Ananth *et al.,* (2007)[13] showed that Primiparous women are at increased risk of both preterm birth. In our study, the gravidity status of the admitted patients demonstrated that 55.4% were primigravida which means that these patients were pregnant for the very first time, 44.6% were multigravida. Among multigravida, 21.5% were secundigravida or those who were pregnant twice and 23.1% had been pregnant more than twice. This was similar to our study.

A study by Tiril Tingleff *et al.,* (2022)[14] showed that preterm birth was more prevalent in multiple pregnancies than in singleton pregnancy. This is contradicted to our study which showed that singleton pregnancies were more common in preterm labor when compared to multiple pregnancies. About 93.4% had singleton pregnancies and 6.6% had multiple pregnancies. Only twins were born in multiple pregnancies.

Among the 69 babies born, majority (68%) of the babies weighed between 1.5 kg and 2.5 kg. 9% belonged to the very low birth weight category of 1-1.5 kg. Only 23% were born with the normal weight of 2.5-4 kg. In our study, no babies were born with the weight more than 4 kg. The lowest birth weight was 1 kg and it belonged to a female baby. 2.7 kg was the maximum birth weight and it belonged to a male baby. Low birth weight is the complication of preterm birth and this is supported by the study done by Clare L Cutland *et al.,* (2017)[15].

It has been found that about 52.1% required NICU admission for the condition called respiratory distress syndrome. 45.8% were admitted due to low birth weight and 2.1% were admitted due to fetal distress. In our study, 4 babies out of 69 were expired. The reasons for neonatal mortality were sepsis and DIC. A study by Yograj Sharma *et al.,* (2023)[16] showed at respiratory distress was the major reason for NICU admission. Similar results were observed in our study.

5.1 Descriptive Statistical Analysis

5.1.1. Impact of nifedipine on gestational age:

For t = 6.7638 at 64 degrees of freedom, p value is less than 0.0001 showed that the difference between Gestational age in days before treatment minus Gestational age in days after treatment was statistically significant.

5.1.2. Impact of nifedipine on maternal diastolic BP:

For t = 4.8506 at 64 degrees of freedom, p value is less than 0.0001 showed that the difference between diastolic BP before treatment and after treatment was statistically significant.

5.1.3. Impact of nifedipine on maternal systolic BP:

For t = 2.0891 at 64 degrees of freedom, p value equals 0.0407 showed that the difference between systolic BP before treatment and after treatment was statistically significant.

5.1.4. Impact of nifedipine on maternal pulse rate:

For t = 2.7842 at 64 degrees of freedom, p value equals 0.0070 showed that the difference between maternal pulse rate before treatment and after treatment was statistically significant.

5.1.5. Impact of nifedipine on fetal pulse rate:

For t = 0.3553 at 64 degrees of freedom, p value equals 0.7233 showed that the difference between fetal pulse rate before treatment and after treatment was not statistically significant.

Table 9. Descriptive statistical analysis - Before and After Treatment

Parameters	Gestational Age (Weeks)		Maternal DBP		Maternal SBP		Maternal PR		Fetal PR	
	Before	After	Before	After	Before	After	Before	After	Before	After
Mean	32.26	33.23	74	69.23	117.38	114.46	89.03	92.35	142.06	142.57
Median	33	33	70	70	110	110	86	90	143	143
Mode	34	34	70	70	110	100	80	110	146	140

Std. Deviation	1.91	2.18	11.43	9.89	19.39	16.3	13.55	12.24	11.24	3.04
Minimum	27	27	40	40	80	90	50	72	80	132
Maximum	35	37	100	100	180	160	130	120	195	148
Range	8	10	60	60	100	70	80	48	115	16
Skew	-0.65	-0.49	0.38	0.46	1.06	0.8	0.35	0.14	-1.09	-0.87
95% Confidence interval of Mean	31.8; 32.73	32.7; 33.76	71.22; 76.78	66.83; 71.64	112.67; 122.1	110.5; 118.42	85.74; 92.33	89.38; 95.33	139.33; 144.79	141.83; 143.31

6. Conclusion

We should frame systematic investments to prevent preterm births and follow evidence-based quality care to treat preterm births. Proper maintenance of records and regular update of preterm cases to the regulatory authority plays a crucial role in the management of the preterm births. The collection of the WHO minimum perinatal dataset for every new born (including gestational age, sex, and birthweight) will ensure proper reporting[1].

Preterm labor must be prevented and appropriately treated in order to lower perinatal morbidity and mortality and enhance perinatal quality of life. A perfect tocolytic agent should delay birth at a reasonable cost without causing adverse effects to the mother or the fetus. In conclusion, the observational study on nifedipine as a tocolytic agent in preterm labor presents promising findings. Nifedipine demonstrates effectiveness in delaying preterm labor with the mean of 4 days, thereby offering a valuable intervention like antenatal corticosteroids to enhance fetal lung maturation, prolong pregnancy and reduce neonatal morbidity and mortality.

The safety profile of nifedipine offers promising results in preterm labor management. While some minor adverse effects were observed, they were generally well-tolerated and transient, posing minimal risk to mothers. No serious maternal and neonatal adverse drug reactions were evident in this study. No post-partum complications were identified. Overall, the findings suggest that nifedipine holds considerable promise as a valuable tool in the management of preterm labor, offering clinicians a safe and effective option to improve outcomes for both mothers and their babies.

However, more investigation is needed to fully understand the long-term safety and effectiveness profile of nifedipine, especially with regard to optimal dosage regimens and how it impacts neonatal outcomes. Further investigation is necessary to confirm our results in a wider range of patient populations and healthcare environments.

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