International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 9, September 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.9.2024.13

ORIGINAL RESEARCH

Efficacy and safety of tocolytic therapy with oral nifedipine for the management of preterm labor: Prospective observational study

[1]Dr. Minu Gopy, [2]Dr. Prameeda PR, [3]Dr. Aradhana Radhakrishnan, [4]Dr. Vidyalakshmi R

[1,2,3]Department of Obstetrics & Gynaecology, Sree Gokulam Medical College & Research Foundation, Trivandrum, Kerala, India
[4]Senior Consultant, High Risk Pregnancy & Fetal Medicine, KIMS Hospital, Trivandrum, Kerala, India

Corresponding Author
Dr. Minu Gopy
Assistant Professor, Department of Obstetrics & Gynaecology, Sree Gokulam Medical College & Research Foundation, Trivandrum, Kerala, India

Received: 10July, 2024 Accepted: 11Aug, 2024

ABSTRACT

Objective: To determine the efficacy and safety of oral nifedipine a tocolytic agent in the management of preterm labour and to determine whether nifedipine as a tocolytic can improve neonatal outcome.**Design:**Prospective observational study. **Setting:**Kerala Institute of Medical Sciences, Thiruvananthapuram, a tertiary care hospital in Kerala, South India.**Population:** Women admitted with preterm labour between 24 and 36 completed weeks of gestation. **Methods:**Women admitted with Preterm labour was given Nifedipine 30 mg followed by 10mg 6th hourly for 48 hours. Antenatal steroid coverage with Betamethasone also given.Preterm labour progression monitored with uterine contractions, cervical effacement and dilatation. Maternal parameters-headache, palpitation, dyspnoea, tachycardia, tachypnoea, hypotension and fetal parameters-fetal bradycardia, fetal tachycardia was monitored. Women were then followed up till delivery and duration of pregnancy prolongation noted. Data was collected regarding the neonate- birth weight, Apgar at 5 minutes, need for resuscitation, need for ventilatory support, neonatal complications and duration of hospital stay. The data collected using the predefined proforma was entered into MS Excel and analysis done using the statistical software for social sciences, SPSS version 16.0.All the quantitative data was expressed as mean +/- standard deviation and the qualitative data in frequencies (n) and percentages (%). All the continuous variables were compared using chi square test. A p value of <0.5 was considered significant.**Main Outcome Measures:**Efficacy of nifedipine as an acute tocolytic in preterm labor was assessed in terms ofprolonging pregnancy for 48 hours with antenatal steroid coverage.Safety was assessed in terms of maternal side effects and neonatal morbidity.**Results:**69.2% of cases between GA24-27 weeks, had pregnancy prolongation of >/= 2 days, where as it was 97.4% for GA between 28-32 weeks and 97.1% for GA between 33-36 weeks. A p value of 0.001, showed statistical significance. A total of 52% had their pregnancy prolonged beyond 7 days, 42.7% had their pregnancy prolonged beyond 2 days but within 7 days, 1.3 % delivered between 24hrs and 48 hrs. and 4 % delivered within 24 hrs. of starting the initial dose of nifedipine. The primary objective of prolonging pregnancy >/= 48hrs was achieved in 94.7% of cases.The mean duration of prolongation of pregnancy was 16.41 days.93.3% of cases had antenatal steroid coverage with the standard protocol of betamethasone 12 mg, 2 doses 24 hrs. apart.38.5% of those with GA on admission between 24-27 weeks had GA at birth >34weeks.This was 50% for GA 28-32 weeks.Among the 75 cases, 56% delivered between 35 weeks and 36 weeks, 22% between 33 weeks and 34 weeks, 8% between 31weeks and 32 weeks, 6.7 % between 29 and 30 weeks, only 4% went beyond 36 weeks, and 2.7% between 27 and 28 weeks.The mean gestational age at birth was 35.2 weeks +/- 2.68. Only 46.2 % of GA 24-27 had birth weight >2.5kg.This was 65.8% for GA 28-32 and 85.7% for GA 33-36.P value of 0.018, showed significant association. Apgar at 5 minutes >7 was 69.2% for GA 24-27, 97.4% for GA 28-32 and 100% for GA 33-36 weeks.P value of 0.00, showed significant association.Neonatal hospital stays <4 days was only 38.5% for GA 24-27, 86.8% for 28-32 and 88.6% for 33-36.P value of 0.002 showed significance.No neonatal complication was 53.8% for GA 24-27, 81.6% for GA 28-32 and 85.7% for 33-36.P value of 0.048 showed significant association. 30.8 percent neonates with GA 24-27 required ventilatory support. This was 2.6 percent for GA 28-32 and none in GA 33-36 weeks.**Conclusion:**Nifedipine is a safe and effective drug for acute tocolysis (for 48 hours) in women with preterm labor.The 48 hours gained, is time well spent in achieving antenatal steroid coverage.Nifedipine by prolonging pregnancy probably improves neonatal outcome. This finding has a definite association with gestational age at admission and the more advanced the gestational age at admission, better is the neonatal outcome.

Key words: Preterm labor, oral nifedipine, tocolysis

International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 9, September 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.9.2024.13

INTRODUCTION

The World Health Organization has estimated that 12.9 million births, or 9.6% of all births worldwide, are preterm. Preterm birth accounts for 80% of perinatal morbidity, 60% of perinatal mortality [1] and is one of the leading causes of infant mortality[2].Despite the improvement in survival rates of preterm neonates, they are at increased risk of long-term neurodevelopmental disabilities, and respiratory and gastrointestinal complication.Since uterine contractions are the most frequently recognized symptom and sign of preterm birth, inhibition of uterine contractions with tocolytic agents to prolong pregnancy and reduce neonatal complications has been and continues to be the focus of treatment of preterm labor. Tocolytic agents are intended to arrest uterine contractions during an episode of preterm labor. This approach has not decreased the incidence of preterm birth but can delay delivery long enough to allow administration of antenatal steroids and to transfer the mother and fetus to an appropriate center with neonatal care facilities. These two interventions have consistently been shown to reduce the rates of perinatal mortality and morbidity.

Some authors have proposed that nifedipine, a calcium channel blocker, could be used as a first-line tocolytic agent[3].Nifedipine acts on the L-type calcium channels involved with calcium influx into the cell. They also inhibit release of intracellular calcium from the sarcoplasmic reticulum and increase calcium efflux from the cell. This results in relaxation of the smooth muscle cells.The most recent substantial update of the Cochrane review regarding calcium channel blockers for acute tocolysis in preterm labor included 12 randomized controlled trials (10 using nifedipine) involving 1029patients[4].This review concluded that, when compared with any other tocolytic agent (mainly beta-mimetics), calcium channel blockers (mainly nifedipine) reduce the risk of delivery within 7 days of initiation of treatment and delivery before 34 weeks of gestation with improvement in some clinically important neonatal outcomes such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal jaundice. This trial was performed in 2002. Since that time, additional randomized controlled trials with nifedipine have been published. Therefore, this requires a re-assessment of the efficacy and safety of this agent. The RCOG green top guideline No 1 b also recommends the use of either atosiban or nifedipine as the first line drugs for the management of tocolysis[11].Of the two, cost effectiveness and better neonatal outcome is thought to be more for nifedipine.

As there are not many studies on the use of tocolysis for preterm labor in India, this study aims to find out the safety and efficacy of nifedipine for the management of preterm labor and its perinatal outcome in an Indian population.

AIMS AND OBJECTIVES

To study the efficacy and safety of oral nifedipine as an acute tocolytic in the management of preterm labor and to find out whether tocolysis with nifedipine can improve neonatal outcome

MATERIALS AND METHODS

DESIGN OF STUDY

Prospective observational study

DURATION OF STUDY

April 2014 to May 2015

PLACE

The study is conducted in Kerala Institute of Medical Sciences, Thiruvananthapuram, which is a tertiary care hospital in Kerala, South India.

SAMPLE SIZE

75 cases of women admitted with preterm labor in labor ward, who otherwise had uncomplicated antenatal period.

SAMPLE SIZE CALCULATIONFORMULA

$$N = \frac{(Z_a)^2 XPXQ}{D^2}$$

Where,

Z_a = 1.96 at 95% level of significance
P =Proportion of variable of interest
Q =100-P
D =Allowable error (10% of P)

Therefore,

$$N = \frac{(1.96)^2 X84X16}{70.56} = 73$$

In this study sample size taken was 75.

INCLUSION CRITERIA

1. Women admitted with preterm labor, with gestational age between 24-36 W(weeks).
2. Presence of at least four uterine contractions in 20’ and cervical dilatation>1cm.
3. Singleton/twin gestation.
4. No contraindications in prolonging pregnancy.
5. No antenatal complications.

EXCLUSION CRITERIA

1. Gestational age <24W and >36W.
2. Threatened preterm contractions without cervical change.

DOI: 10.69605/ijlbpr_13.9.2024.13

3. >2 fetus.
4. Already on another tocolytic.
5. Contraindications in prolonging pregnancy.

- Congenital or chromosomal malformation.
- Intrauterine infections.
- Severe preeclampsia.
- Antepartum hemorrhage.
- Advanced cervical dilatation.
- Evidence of fetal compromise.

PRIMARY OUTCOME

Safety and efficacy of nifedipine as an acute tocolytic in preterm labor-prolonging pregnancy for 48 hrs.

SECONDARY OUTCOME

Impact on neonatal complications.

METHOD OF STATISTICAL ANALYSIS

The data collected using the predefined proforma was entered into MS Excel and analysis done using the statistical software for social sciences, SPSS version 16.0.All the quantitative data was expressed as mean +/- standard deviation and the qualitative data in frequencies (n) and percentages (%). All the continuous variables are compared using chi square test. A p value of < 0.5 is considered significant.

OBSERVATIONS AND RESULTS

1) BASELINE CHARACTERISTICS

1. AGE DISTRIBUTION OF PATIENTS

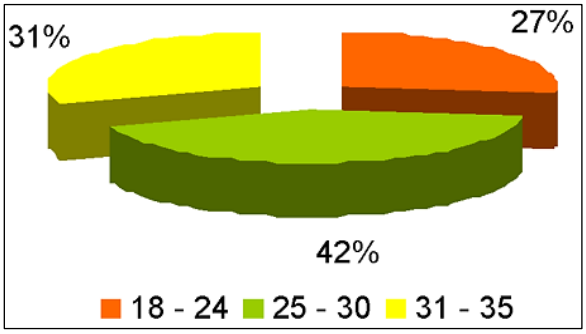

Figure 1: Age distribution of patients

2. OBSTETRIC SCORE OF PATIENTS

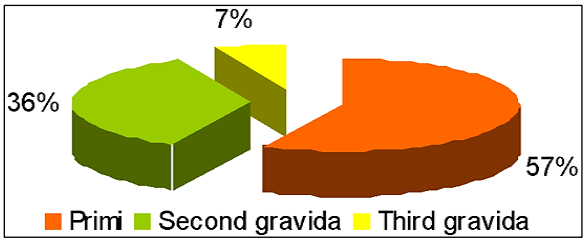

Figure2: Obstetric score of patients

3. NUMBER OF FETUSES

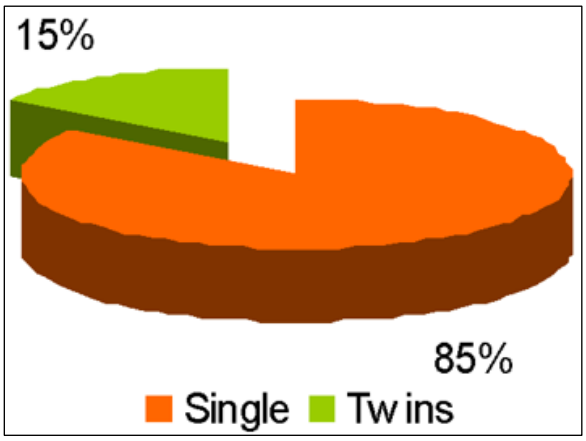

Figure 3: Number of fetuses

DOI: 10.69605/ijlbpr_13.9.2024.13

4. GESTATIONAL AGE AT ADMISSION

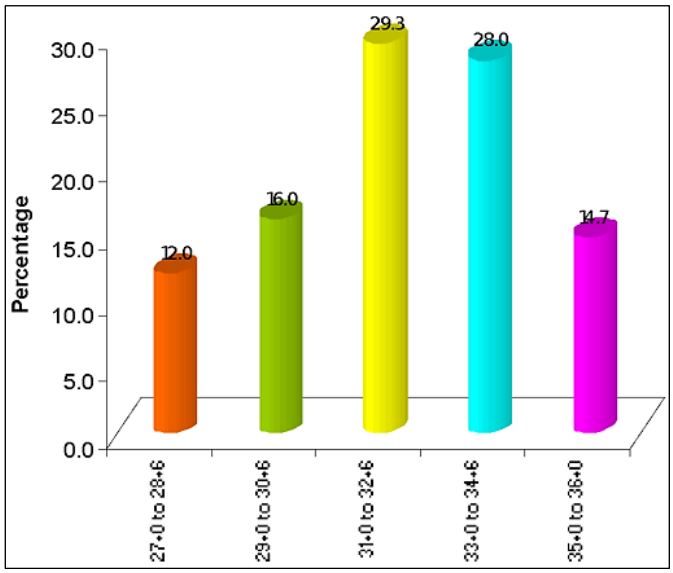

Figure 4: Gestionalage at admission in weeks+days

2)PRIMARY OUTCOME
A)EFFICACY OF NICARDIA
1. PROLONGATION OF PREGNANCY AFTER INITIATION OF TREATMENT WITH NIFEDIPINE

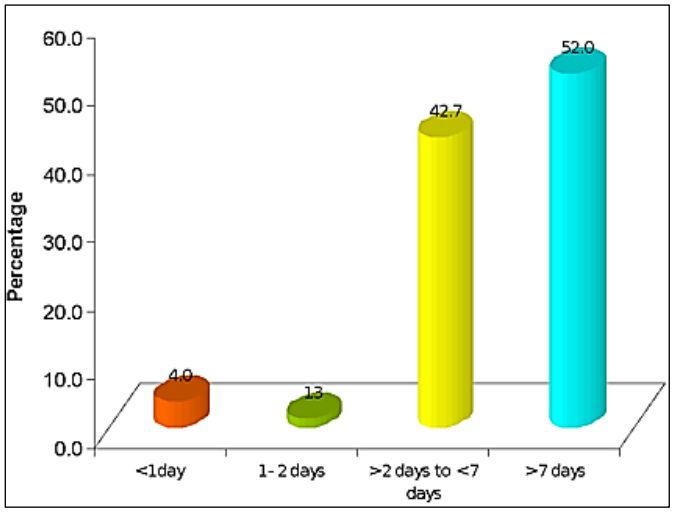

Figure 5: Prolongation of pregnancy in days

Classified into 4 categories.Our objective to prolong pregnancy for 48 hrs was achieved in 94% (n=71) cases.

2. Antenatal steroid coverage

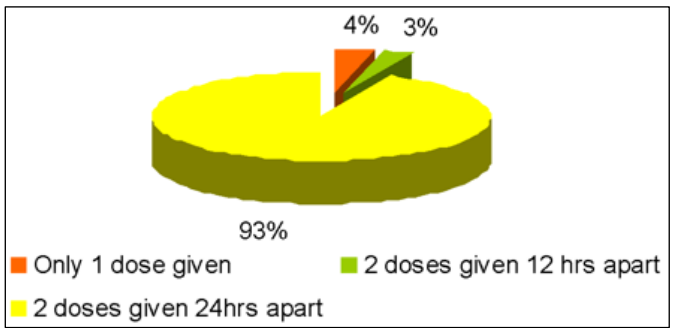

Figure 6: Antenatal steroid coverage

DOI: 10.69605/ijlbpr_13.9.2024.13

3. GESTATIONAL AGE AT BIRTH

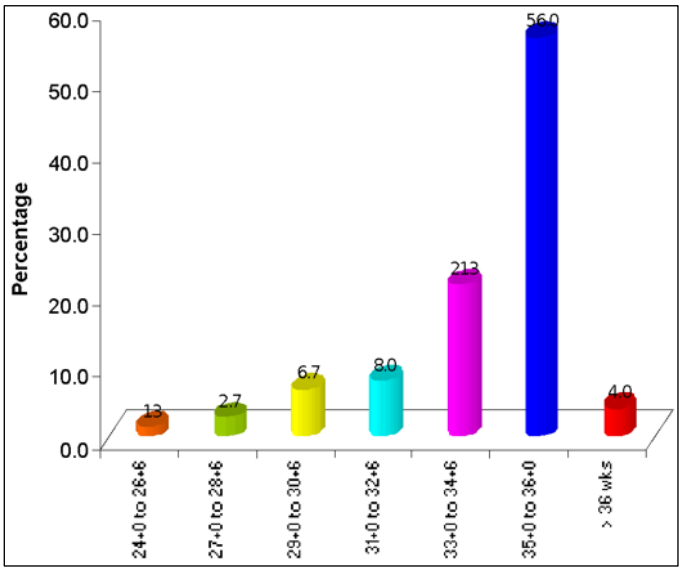

Figure 7: Gestational age at birth in weeks +days

Analyzed as a continuous variable.Mean gestational age at delivery was 35.2W with a standard deviation of 2.68W.

4. NEED TO ADD ANOTHER TOCOLYTIC

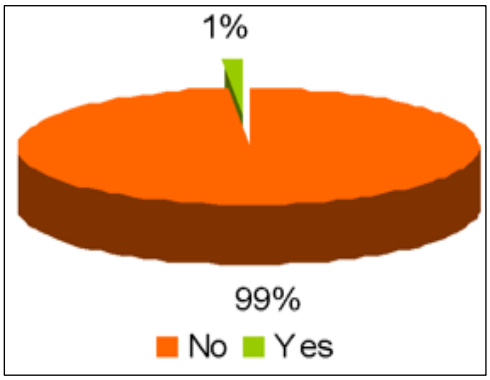

Figure 8: Need to add another tocolytic

In 1% of cases nitroglycerine patch was added.

B)SAFETY OF NIFEDIPINE

1. HEADACHE

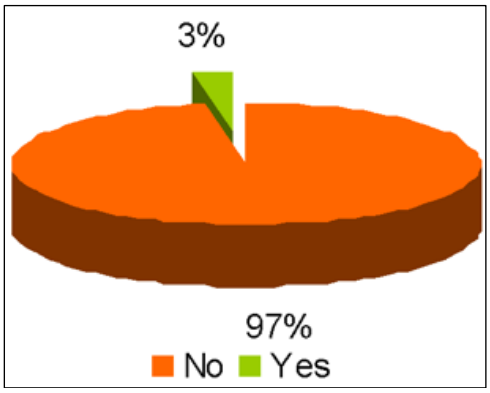

Figure 9: Maternal headache as side effect

DOI: 10.69605/ijlbpr_13.9.2024.13

2. HYPOTENSION

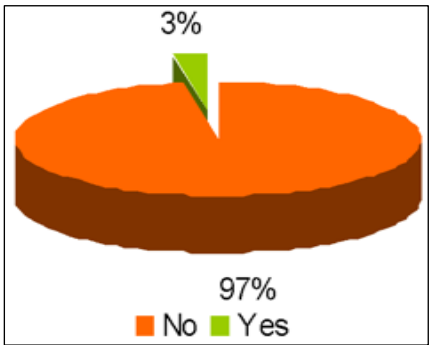

Figure 10: Maternal hypotension as side effect

97.3% (n=73)-no hypotension, 2.7%(n=2) had hypotension.

3. PALPITAION

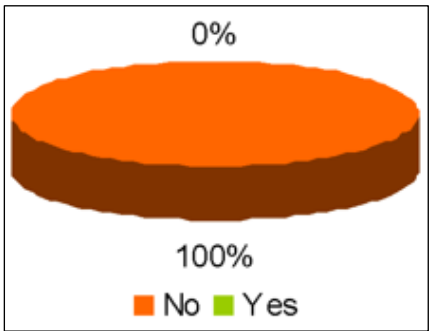

Figure 11: Maternal palpitation as side effect

4. DYSPNOEA

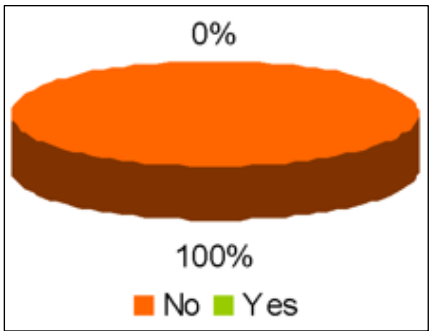

Figure 12: Maternal dyspnoea as side effect

4. FETAL BRADYCARDIA

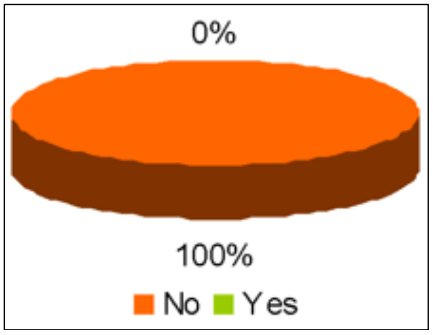

Figure13: Fetal bradycardia as side effect

DOI: 10.69605/ijlbpr_13.9.2024.13

FETAL TACHYCARDIA

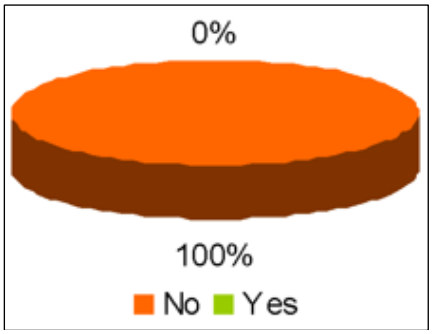

Figure 14: Fetal tachycardia as side effect

6. FETAL BIOPHYSICAL PROFILE(BPP)

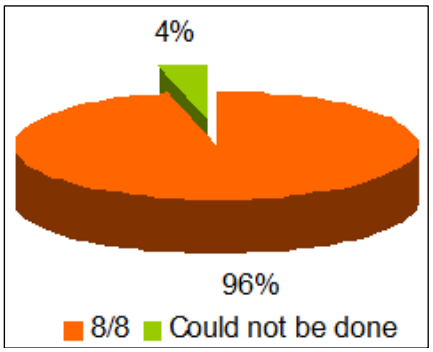

Figure 15: Fetal BPP Score after 48 HRS

In 72 (96%), BPP -8/8 after 48 hrs. rest-delivered

7. NEED TO STOP DUE TO SIDE EFFECTS

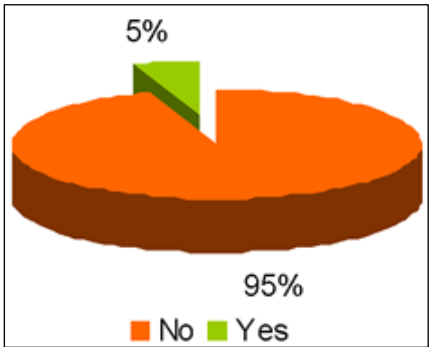

Figure 16: Need to Stop Drug Due to Side Effects

2 had severe headache, 2 had hypotension, that is in 5% (n=4).

3)SECONDARY OUTCOME
1. BIRTH WEIGHT

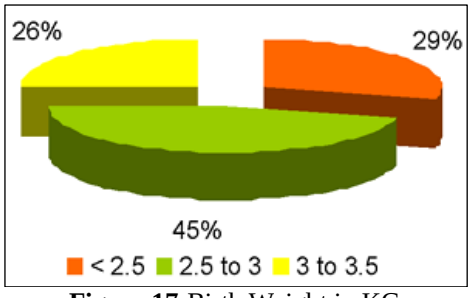

Figure 17: Birth Weight in KG

DOI: 10.69605/ijlbpr_13.9.2024.13

Out of 75 deliveries, 11 were twins-total of 86.29.1% (n=25) < 2.5 kg; 25.6%(n=22)3-3.5kg;45.3% (n=39)2.5-3 kg. Mean birth weight-2.39 KG, standard deviation of 0.56 kilogram.

2. APGAR AT 5'

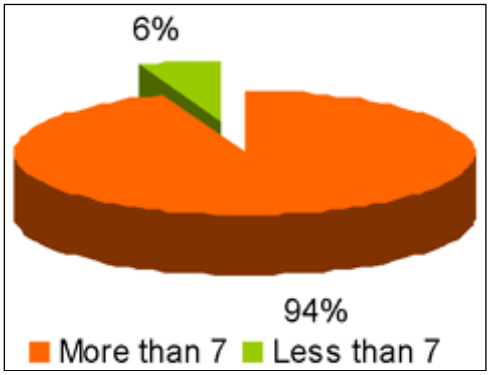

Figure18:APGAR Score at 5Minutes

94.2% (n=81) > 7 at 5';5.8%(n=5) - < 7 at 5'.

3. NEED FOR RESUSCITATION

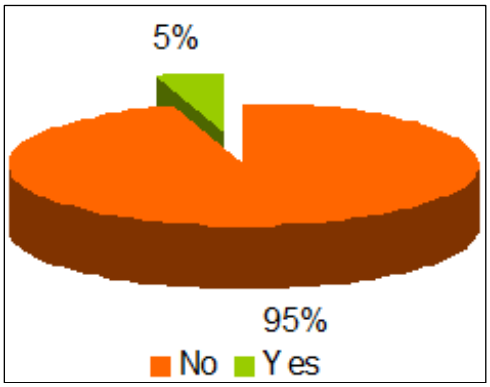

FIGURE 19: Need for Resuscitation

95.3% (n=82)-no resuscitation; 4.7% (n=4)-required.

4. HOSPITAL STAY

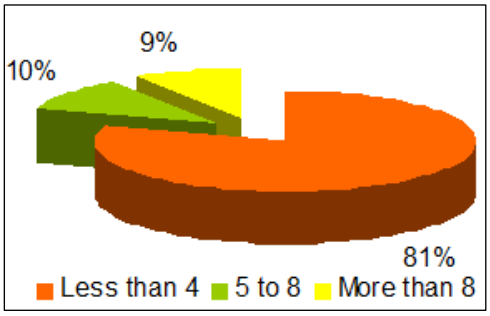

Figure 20: Hospital Stay for Babies in Days

80.2% (n=69), <4 D; 10.5% (n=9) 5 to 8 D; 9.3% (n=8), >8 D.

DOI: 10.69605/ijlbpr_13.9.2024.13

5. NEED FOR VENTILLATION AND SURFACTANT

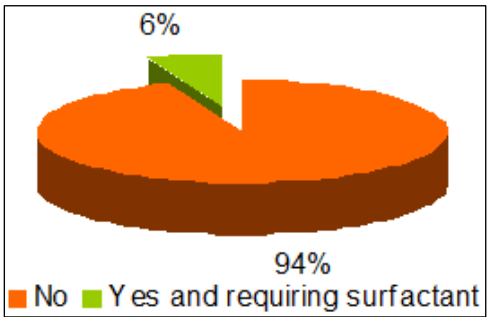

Figure21: Need for Ventilation

5.8% (n=5) -YES, of which 2 babies had respiratory distress syndrome and 3 were given prophylactic ventilatory support for surfactant administration.94.2% (n=81) -NO.

6.NEONATAL COMPLICATION

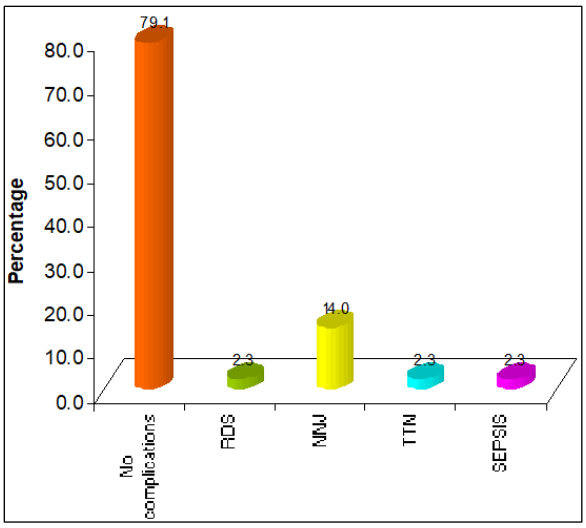

Figure 22: Development of Neonatal Complications

RDS-Respiratory Distress Syndrome; NNJ-neonatal Jaundice;TTn-transient tachypnoea of Newborn.

79.1% (n=68)-NIL; 14% (n=12)-neonatal jaundice; 2.3% (n=20)-respiratory distress syndrome; 2.3% (n=2) - transient tachypnoea; 2.3% (n=2)-sepsis.

ASSOCIATION OF GESTATIONAL AGE AT ADMISSION WITH SELECTED VARIABLES

Table-1:Association of GA at admission and selected variables

Table of Association of GA at admission and selected variables									
		< 28 Weeks		28-32 Weeks		>32 Weeks		χ^2	p
		Count	Percent	Count	Percent	Count	Percent		
Pregnancy prolongation after 1st dose	<= 2 day	4	30.8	1	2.6	1	2.9	13.36**	0.001
	> 2 days	9	69.2	37	97.4	34	97.1		
Gestational age at birth(Weeks + Days)	<= 34+6	8	61.5	19	50.0	12	34.3	3.43	0.180
	>= 35	5	38.5	19	50.0	23	65.7		
Birth Weight(KG)	< 2.5	7	53.8	13	34.2	5	14.3	8.07*	0.018
	>=2.5	6	46.2	25	65.8	30	85.7		
Apgar at 5'	More than 7	9	69.2	37	97.4	35	100.0	17.65**	0.000
	Less than 7	4	30.8	1	2.6	0	0.0		
Resuscitation	No	10	76.9	37	97.4	35	100.0	12.01**	0.002
	Yes	3	23.1	1	2.6	0	0.0		
Hospital stay for baby	Less than 4	5	38.5	33	86.8	31	88.6	16.88**	0.000
	More than 4	8	61.5	5	13.2	4	11.4		

DOI: 10.69605/ijlbpr_13.9.2024.13

Neonatal complications	No	7	53.8	31	81.6	30	85.7	6.08*	0.048
	Yes	6	46.2	7	18.4	5	14.3		
Need for ventilation	No	9	69.2	37	97.4	35	100.0	17.65**	0.000
	Yes and requiring surfactant	4	30.8	1	2.6	0	0.0		

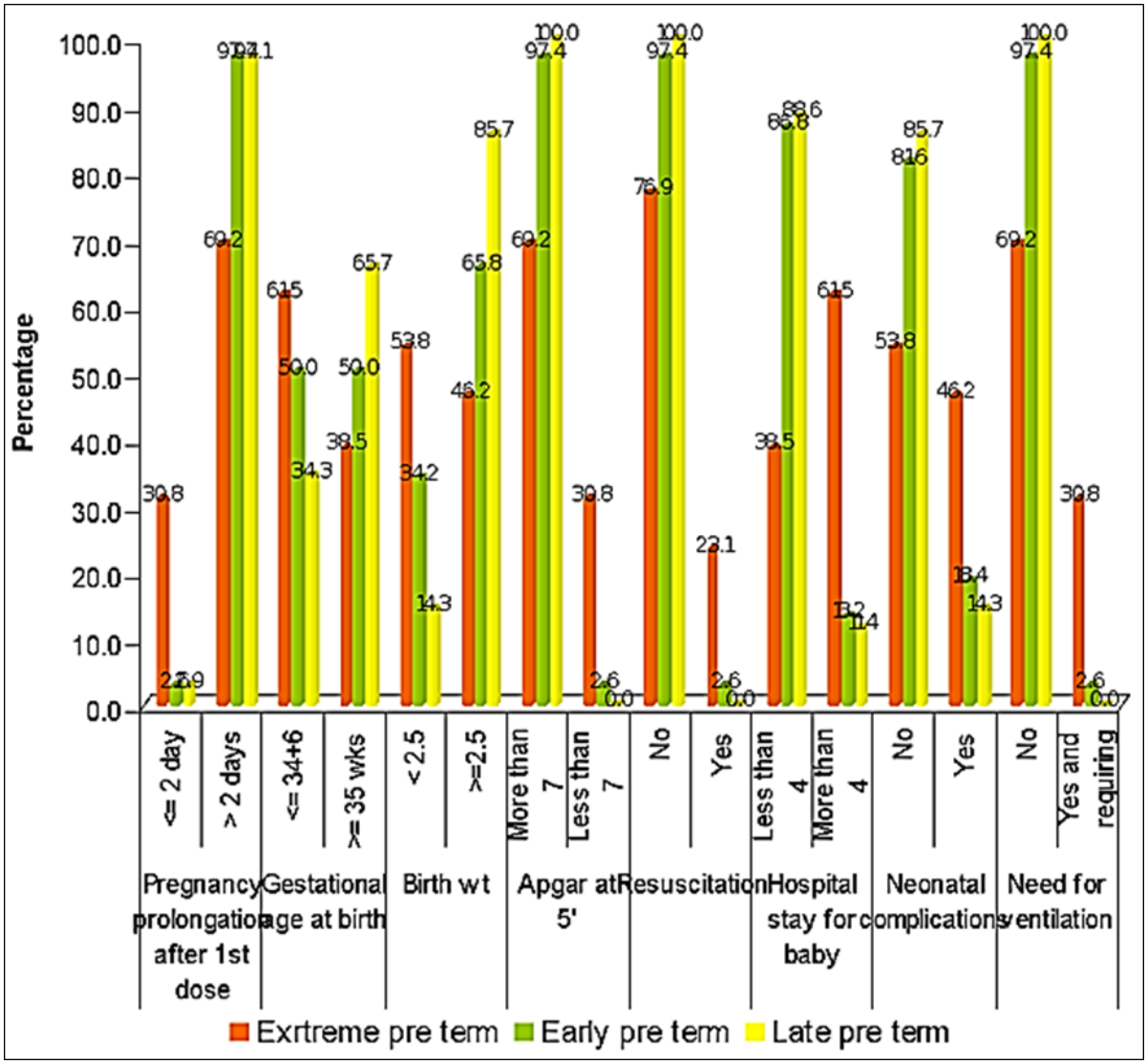

Figure 23: Association of GA at admission and selected variables

For ease GA categorized into 3 categories:

1. 24-28 weeks
2. 28-32 weeks
3. 32-36 weeks

Variables selected

1. Pregnancy prolongation >/= 2 days
2. Gestational age at birth >34weeks
3. Birth weight
4. Apgar at 5 minutes, >7
5. No need for resuscitation
6. Hospital stay <4 days
7. No neonatal complications
8. No need for ventilation

RESULTS FROM ASSOCIATION STUDY

1. Pregnancy prolongation >/= 2 days-69.2%-24-28 W; 97.4%-G 28-32W; 97.1%-32-36W. P = 0.001, showed statistical significance.
2. GA at birth >34W-38.5%-24-28W; 50%-28-32W; 65.7%-32-36W.P = 0.180- not significant.
3. Birth Weight >2.5 Kg-46.2%-24-28W; 65.8%-28-32W; 85.7%-32-36W.P = 0.018, significant association.
4. Apgar at 5 minutes >7-69.2%-24-28W; 97.4%-28-32W; 100%-32-36W.P =0.000, showed significant association.
5. No need for ventilation-76.9%-28-32W; 97.4% 32-36W; 100% 32-36W.P = 0.002 showed significant association.

DOI: 10.69605/ijlbpr_13.9.2024.13

6. Hospital stay <4-38.5%-24-28W; 86.8%-28-32W; 88.6%-32-36W.P = 0.002 showed significance.
7. No neonatal complication-53.8%-24-28W; 81.6%-32-34W; 85.7% 32-36W.P value = 0.048 showed significant association.
8. No need for ventilation-69.2% 24-28W; 97.4% 28-32W; 100%-32-36W.

DISCUSSION

In this study the safety and efficacy of nifedipine as a tocolytic in the management of preterm labor has been studied prospectively.We enrolled 75 patients admitted with preterm labor, between 24-36W, with no history of any obstetric or medical complications.

Of these primigravida were 57.3%, second gravidae (36%) and third gravidae (6.7%).85.3% had singleton pregnancy and 14.7% had twin pregnancy. 42.7% of cases were between 33weeks and 36 weeks, 45.3% were between 29weeks and 32 weeks and only 12% were between 24 weeks and 28 weeks.

PRIMARY OUTCOME

EFFICACY OF NICARDIA

PROLONGATION OF PREGNANCY: 52% had their pregnancy prolonged beyond 7 days, 42.7% had their pregnancy prolonged beyond 2 days but within 7 days, 1.3% delivered between 24hrs and 48 hrs and 4% delivered within 24 hrs of starting the initial dose of nifedipine. That is the primary objective of prolonging pregnancy >/= 48hrs was achieved in 94.7% of cases.This was similar to the study by ***Koks CA***[5] in which, out of55 patients assigned to the nifedipine group, 60%(n=33) had pregnancy beyond 2 days, but less than 7 days, and 47% (n=26) had pregnancy prolonged beyond 7 days.

From the study the mean duration of prolongation of pregnancy was 16.41 days.

Also in our study, 93.3% of cases had antenatal steroid coverage with the standard protocol of betnesol 12 mg, 2 doses 24 hrs apart.For 4% of cases only one dose could be given and 2.7% had 2 doses covered 12 hrs apart.

Among the 75 cases, 56% delivered between 35 weeks and 36 weeks, 22% between 33 weeks and 34 weeks, 8% between 31weeks and 32 weeks, 6.7% between 29 and 30 weeks, only 4% went beyond 36 weeks, and 2.7% between 27 and 28 weeks.This was similar to the study by Lyell*et al*. [6] in which, for the nifedipine group of patients, 57% had delivery between 34 weeks and 37 weeks.

In our study the mean gestational age at birth was 35.2 weeks +/- 2.68, compared to the study by Jannet*et al*.[7],where the mean gestational age at birth was 38.4 +/- 1.7.

SAFETY OF NICARDIA

Of the 75 patients, 2.7% had severe headache and another 2.7% had hypotension. In these 4 patients the regimen was stopped. The rest experienced no side effects. After 48 hours bio-physical profile was found to be 8/8 in 96% and in the rest 4% BPP could not be done since they either delivered or the regimen was stopped.

This proves nifedipine to be a safe drug from maternal and fetal aspects.Studies by ***FlenadyV*** *et al*. [4], ***Koks CA****et al*. [5]**,** ***Nikolov A*** *et al*.[8], ***Mawaldi L****et al*. [9] also found similar results.

SECONDARY OUTCOME

Of the 86 babies followed up,

- 45.3% had birth weight between 2.5kg and 3 kg, 29.1% had birth weight less than 2.5 kg, and 25.6% had birth weight between 3 and 3.5kg.
- Birth weight of babies born, had a mean weight of 2.39 kilogram +/- 560 gram in our study.In comparison, the study by Jannet*et al*.(41) had shown a mean birth weight of 3.131 kilogram +/- 488 grams.
- 94.2% had Apgar at 5 minutes of >7 and only 5.8% had Apgar at 5 minutes <7
- 95.3% required no immediate resuscitation, while 4.7% required immediate resuscitation.
- 80.2% had a hospital stay of <4 days, 10.5% stayed between 5 to 8 days, and 9.3% had to stay for more than 8 days
- 94.2% needed no ventilatory support and 5.8% required ventilatory support and administration of surfactant.

Of the neonatal complications reported most was for neonatal jaundice, which was 14%; 2.3% had RDS, 2.3% had TTN and another 2.3% had culture positive sepsis.

The data shows low risk for neonatal complications for tocolysis with nifedipine.Similar studies by Nancy D Berkman [52], Koks CA [54], and Lyell DJ [59] also showed low risk for neonatal complications with use of nifedipine as a tocolytic.

INFERENCE FROM ASSOCIATION STUDY BETWEEN GESTATIONALAGE AT ADMISSION AND SELECTED PARAMETERS

Tocolysis does not treat the cause of preterm labor.The time gained by tocolysis gives an opportunity for antenatal steroid administration.Although this can lessen the neonatal complications, the more preterm a patient presents with preterm labor, more is her chance of delivering a premature baby, with low birth weight and neonatal complications.

CONCLUSION

Nifedipine is a safe and effective drug for acute tocolysis (for 48 hours) in women with preterm labor.The 48 hours gained, is time well spent in achieving antenatal steroid coverage

Nifedipine by prolonging pregnancy probably improves neonatal outcome. This finding has a definite association with gestational age at admission

DOI: 10.69605/ijlbpr_13.9.2024.13

and the more advanced the gestational age at admission, better is the neonatal outcome.

RECOMMENDATIONS

1) Tocolysis should be offered to women with suspected preterm labor between gestational age (24 – 34 wks.), when they have had an otherwise uncomplicated pregnancy and if there are no contraindications to prolong pregnancy.
2) Only acute tocolysis for a period of 48 hours should be advised. There is no role for maintenance tocolysis.
3) Oral nifedipine is a safe and effective tocolytic with comparatively lesser side effects, cost effectiveness & better neonatal outcome.
4) The time gained should be used for administration of antenatal steroids and for transferring the patient to a center with neonatal intensive care.
5) Available evidence should be discussed with the patient and her partner before advising tocolysis.

LIMITATIONS OF THIS STUDY

- It was an observational study.A placebo-controlled trial, or a comparative study with another tocolytic could have yielded more substantial results.
- The data is insufficient to determine the wide range and severity of adverse effects that can be attributed with the use of nifedipine.

ACKNOWLEDGEMENTS

The authors are thankful to all the patients in this study.

FUNDING

No funding sources.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Committee.

REFERENCES

1. Beck S, Wojdyla D, Say L.The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ.2010; 88:31–8.
2. Heron M, Sutton PD, Xu J, Ventura SJ, Strobino DM, Guyer B. Annual summary of vital statistics, Pediatrics.2010; 125:4–15.
3. Tsatsaris V, Papatsonis D, Goffinet F, Dekker G, Carbonne B. Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. Journal of Obstet Gynecol. 2001; 97:840–7.
4. King JF, Flenady V, Papatsonis D, Dekker G, Carbonne B. Calcium channel blockers for inhibiting preterm labour; a systematic review of the evidence and a protocol for administration of nifedipine. Aust N Z J ObstetGynaecol.2003; 43:192–8.
5. Koks CA, Brölmann HA, de Kleine MJ,Manger PA. A randomized comparison of nifedipine and ritodrine for suppression of preterm labor. EurJObstetGynecolReprod Biol. 1998Apr;77(2):171-6.
6. Lyell DJ, Pullen K, Campbell L, Ching S, Druzin ML, Chitkara U *et al*. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial.Obstet Gynecol.2007 Jul; 110(1):61-7.
7. Jannet D, Abankwa A, Guyard B, Carbonne B, Marpeau L, Milliez J. Nicardipine versus salbutamol in the treatment of premature labor. A prospective randomized study. European Journal of Obstetrics Gynecology and Reproductive biology. 1997; 73(1):11-16.
8. Nikolov A, Markov D, Dimitrov A, Ivanov S, Diavolov V.Treatment of preterm delivery with calcium channel blockers-Nifedipine.AkushGinekol(Sofiia). 2007; 46(9):18-22.
9. Mawaldi L, Duminy P, Tamim H.Terbutaline versus nifedipine for prolongation of pregnancy in patients with preterm labor.Int J Gynaecol Obstet.2008 Jan;100(1):65-8
10. Berkman ND, Thorp JM, Lohr KN *et al*. Tocolytic treatment for the management of preterm labour.American Journal of Obstetrics and gynecology. 2003 Jun; 188(6): 1648-59.
11. RCOG-Royal College of obstetrics and Gynecology. Tocolysis for women in preterm labour. 2011 Feb; green-top guideline No.1b