# Comparative Study of Oral Nifedipine Versus Intravenous Isoxsuprine in Arresting Preterm Labour

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## ABSTRACT

**Introduction:** The purpose of the study was to compare the efficacy of Isoxsuprine and Nifedipine as tocolytic agent on preterm labour and to compare the Obstetrical outcome following Isoxsuprine and Nifedipine therapy as a tocolytic agent. Study aimed to compare the tocolytic efficacy of parenteral and oral Isoxsuprine with oral Nifedipine in the suppression of preterm labor. Maternal side effects and neonatal outcome were also evaluated.

**Material and methods:** The study which was randomised prospective study, comprised of 100 patients with preterm labor, admitted in antenatal ward of Chalmeda Anand rao institute of medical sciences, bommakal, Karimnagar during the period of June 2019 to june 2020. The Patients who fulfilled the inclusion criteria for the study were divided into 2 groups; group-A consisted of 50 patients, treated with Nifedipine for tocolysis, the group-B consisted of 50 patients, who received isoxsuprine for tocolysis, and were monitored throughout the course of treatment.

**Results:** Successful tocolysis was achieved by Nifedipine in 92% of the case as compared to 76% with the isoxsuprine treated cases. And Nifedipine prolonged pregnancy for 20.16±14.09 days while Isoxsuprine prolonged pregnancy for 13.98±11.03 days.

**Conclusion:** Nifedipine is more effective tocolytic agent, as compared to Isoxsuprine. The neonatal outcome with respect to maternal complications, neonatal complications and perinatal death were better in the cases treated with nifedipine as compared


**Keywords:** Isoxsuprine, Nifedipine, Preterm Labour.

## INTRODUCTION

Preterm birth, defined by WHO as the onset of labour prior to the completion of 37 weeks of gestation, in a pregnancy beyond 20 weeks of gestation.[1] Preterm Labour is defined as initiation of regular uterine contraction with increase in frequency and magnitude with progressive cervical dilation and effacement (unless inhibited by tocolysis) culminating in delivery of the preterm infant. Prematurity also contributes significantly to mental retardation, visual and hearing impairment and cerebral palsy.[2]

There are no accurate recent worldwide data but estimates of preterm birth range from a relative stable 5-10%[3] in developed countries to as high as 25% in some of the worst hit developing countries. The global annual incidence of preterm birth in 2005 was reported by WHO world health organization to be 9.6% of all live births. Preterm labour and delivery is one of the biggest challenges for obstetricians and so are the preterm babies for the pediatricians.[4]

Increasing rates of preterm labor could be due to artificial reproductive techniques, psychosocial stress or medically induced prematurity.[4] Preterm delivery affects 11%in US[5] or even greater in developing countries(23.3%) in India.[6] 12% of child mortality under 5 years of age are due to complications of prematurity; making it one of the four major killers of this age group.[1] Even though there has been a lot of research and attempt to diagnose and predict women at risk of developing preterm labour, But the definitive causative factor is still elusive, and the obstetrician has to manage preterm labour.

However, tocolysis should be considered if few days gained would be used for completing a course of corticosteroids which will help in lung maturity thereby preventing respiratory distress syndrome in the new-born if delivery occurs within 7 days of steroid administration or in utero transfer to higher medical centre where adequate NICU facilities can be provided to the neonate as and when required.[7-8] Nifedipine is a calcium channel blocker. It works by affecting the movement of calcium into the cells of the heart and blood vessels. As a result, nifedipine relaxes blood vessels and increases the supply of blood and oxygen to the heart while reducing its workload. Isoxsuprine hydrochloride is a beta-adrenergic agonist that causes direct relaxation of uterine and vascular smooth muscle. Its vasodilating actions are greater on the arteries supplying skeletal muscle than on those supplying skin.[7-9]

Efforts are directed towards finding alternatives that are safer, better tolerated, as well as efficacious in prolonging pregnancy.[9] Both nifedipine and isoxsuprine have been shown to be effective in preterm labour. However only a few studies have directly compared the safety and efficacy of nifedipine with isoxsuprine as tocolytic in preterm labour.[10] This study was done to compare the tocolytic efficacy of nifedipine and isoxsuprine in the suppression of preterm labour and to evaluate the maternal side effects and neonatal

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outcome of the two drugs.

## MATERIAL AND METHODS

This was a prospective study of 100 antenatal women conducted in the department of obstetrics and Gynaecology, Chalmeda Anand Rao Institute of Medical Sciences, Bommakal, Karimnagar. Written informed consent was taken from the patients included in this study. Antenatal women between 28 to 36 weeks of gestation with painful intermittent contractions are considered for study. They were evaluated thoroughly by detailed history, clinical examination and USG if not done before. Amniotic membrane status was noted in vaginal examination.

**Inclusion criteria**

1. Gestational age between 28 to 37 weeks
2. Presence of regular uterine contractions 4 in 20 minutes or 8 in a period of 1 hour
3. Cervical changes - cervical effacement >80% or dilatation of >1 cm with intact membranes
4. No previous administration of tocolytics.

**Exclusion criteria**

1. Systemic diseases like diabetes mellitus, cardiac diseases, liver or renal diseases, hypotension
2. Obstetric complications like hypertensive disorders of pregnancy, antepartum haemorrhage, ruptured membranes, dilatation of >4 cm
3. Foetal complications like chorioamnionitis, IUGR, congenital anomaly, foetal distress,
4. Multifoetal gestation.

Patients will be monitored from the time of admission to the time of discharge. Group A constituted subjects who were given 20 mg oral nifedipine initially followed by 10 mg 12$^{th}$ hourly for 1 week. If contractions persisted at 90 min, the first 10 mg dose was started at the same time.

Group B constituted subjects who were given injection isoxsuprine 20 mg intravenous infusion with 4-5 microdrops per minute for 48 hours. Followed by oral 10mg 8$^{th}$ hourly for 1week.In both groups subjects were strictly monitored for uterine contractions, maternal pulse rate, palpitation and fetal heart rate. In case of any serious side effects as progression of labor, the respective drug was stopped.

All women with preterm labor were investigated for infection by complete hemogram, urine and vaginal swab culture. Antibiotics were provided to cases having significant pathogen count in urine or vaginal culture accordingly. Women with gestational age less than 34 completed weeks were given 12 mg betamethasone intramuscularly that was repeated after an interval of 24 hours. Goal of tocolysis was to delay delivery for 48 hours in patients with ruptured membranes and through 36 completed weeks of gestation in patients with intact membranes. Tocolysis was considered failed if uterine quiescence was not achieved despite maximum dose and delivery occurred within 48 hours. Patients, in whom delivery was delayed for at least 48 hours, were taken as cases of primary success. Patients were followed till delivery and data was recorded about side effects that patients developed during the treatment, time interval between admission and delivery and neonatal outcome.

## RESULTS

Out of 100 women with singleton pregnancies who enrolled for study, 50 were assigned to isoxsuprine group and 50 to nifedipine group after randomization. In this study, patients distributed according to gestational age, majority of patients were between 28 to 32 weeks of gestation in nifedipine group and isoxsuprine group respectively. There is no significant difference in gestational age in both study groups.

Table 1 shows that most of the preterm presenting patients were between 20-30 years age group. The two groups were age matched with p=0.384, Student t test. Cluster of preterm presenting patients were primi and gravida 2 in both the groups.

Table 2 shows that in both the groups maximum number of patients presented in between 31-33.6 weeks of gestation, with $x^2$ =37.45, p<0.00001.

Table 3 depicts that most patients in group A delivered between 34 to 36.6 weeks and in group B >37weeks, but in group A patients delivered <33.6 weeks were less compared to group B, with $x^2$ – 28.1 and p value of <0.00001 making the result significant.

Table 4 shows that prolongation of pregnancy (days) is significantly more in group A compared to group B (20.16 days vs 13.98 days) with p=0.016, significant, student t test.

It is clear from table 5 that more patients had successful tocolysis in group A compared to group B and vice versa more failure in group B compared to group A. With $x^2$=9.5, p=0.002.

Table 6 shows the distribution of mode of delivery is statistically similar in two groups with $x^2$=0.35, p=0.55.

Table 7 shows that the Apgar score at 1 minute were statistically similar in both groups, at 5 min group B babies had less Apgar score than group A. Mean Apgar score in two groups were almost similar statistically.

Table 8 shows that the mean birth weight is statistically

| Age in years | Group A | | Group B | | Parity | Group A | | Group B | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | | No. | % | No. | % |
| <20 | 14 | 28 | 15 | 30 | PRIMI | 24 | 48 | 23 | 46 |
| 21-30 | 32 | 64 | 33 | 66 | G2 | 16 | 32 | 19 | 38 |
| 31-40 | 4 | 8 | 2 | 4 | G3 | 4 | 8 | 4 | 8 |
| Total | 50 | 100 | 50 | 100 | >/=G4 | 6 | 12 | 4 | 8 |
| Mean±SD | 23.74±4.64 | | 23.00±3.70 | | | | | | |

**Table-1:** Distribution of sample according to age and parity

| GA at weeks (no. of weeks) at Presentation | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| 28-30.6 | 14 | 28 | 8 | 16 |
| 31-33.6 | 27 | 54 | 29 | 58 |
| 34-36.6 | 9 | 18 | 13 | 26 |
| Total | 50 | 100 | 50 | 100 |

**Table-2:** Distribution of the sample according to Gestational age at presentation

| GA at weeks (no. of weeks) at Delivery | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| 28-30.6 | 0 | 0 | 4 | 8 |
| 31-33.6 | 10 | 20 | 14 | 28 |
| 34-36.6 | 32 | 64 | 15 | 30 |
| 37+ | 8 | 16 | 17 | 34 |
| Total | 50 | 100 | 50 | 100 |

**Table-3:** Distribution of the sample according to gestational age at delivery

| Prolongation of pregnancy in days | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| <2 | 4 | 8 | 12 | 24 |
| 3-7 | 21 | 42 | 11 | 22 |
| 8-14 | 6 | 12 | 9 | 18 |
| 15-21 | 6 | 12 | 5 | 10 |
| 22-28 | 5 | 10 | 8 | 16 |
| 29 days or more | 8 | 16 | 5 | 10 |
| Total | 50 | 100 | 50 | 100 |
| Mean±SD | 20.16±14.09 | | 13.98±11.03 | |

**Table-4:** Prolongation of pregnancy in days in both the groups

| Prolongation of pregnancy in days | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Failure <2 days | 4 | 8 | 12 | 24 |
| Success ≥2 days | 46 | 92 | 38 | 76 |
| Total | 50 | 100 | 50 | 100 |

**Table-5:** Outcome of prolongation of pregnancy in both the groups

| Mode of delivery | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| VD | 32 | 64 | 34 | 68 |
| LSCS | 18 | 36 | 16 | 32 |
| Total | 50 | 100 | 50 | 100 |

**Table-6:** Mode of Delivery in both the groups

| APGAR score | Group A | | Group B | | P value (Fischer Exact Test) |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| 1 MIN.; <7 | 32 | 64 | 32 | 64 | 1.000 |
| 1 MIN.; ≥7 | 18 | 36 | 18 | 36 | |
| 5 MIN.; <7 | 0 | 0 | 7 | 14 | 0.012 |
| 5 MIN.; ≥7 | 50 | 100 | 43 | 86 | |

**Table-7:** Apgar Score at different times

| Birth weight (kg) | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| 1-1.49 | 2 | 4 | 1 | 2 |
| 1.5-1.99 | 12 | 24 | 18 | 36 |
| 2-2.49 | 18 | 36 | 14 | 28 |
| 2.5+ | 18 | 36 | 17 | 34 |
| MEAN±SD | 2.27±0.49 | | 2.24±0.49 | |

**Table-8:** Birth weight in both the groups

| Neonatal Complications | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Nil | 34 | 68 | 24 | 48 |
| Yes | 16 | 32 | 26 | 52 |
| NICU | 8 | 16 | 17 | 34 |
| PNM | 5 | 10 | 5 | 10 |
| RDS | 3 | 6 | 4 | 8 |

**Table-9:** Neonatal Complications in both the groups

| Maternal side effects | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Nil | 37 | 64 | 25 | 50 |
| Yes | 13 | 26 | 25 | 50 |
| Flushing | 0 | 0 | 1 | 2 |
| Headache | 7 | 14 | 4 | 8 |
| Hypotension | 2 | 4 | 6 | 12 |
| Nausea | 1 | 2 | 2 | 4 |
| Skin rash | 0 | 0 | 0 | 0 |
| Tachycardia | 3 | 6 | 12 | 24 |

**Table-10:** Maternal Side effects in both the groups

similar in two groups with p=0.752, Student t test.

Table 9 shows that neonatal complications were significantly less in group A (34.0%) compared to group B (52.0%) with $x^2 = 8.21$;P = 0.004, with more NICU admissions in group B compared to group A.

Table 10 shows the Incidence of maternal side effects is significantly more in Group B with $x^2 = 12.2$;P=0.0004, with headache and tachycardia being common in group A compared to hypotension and tachycardia in group B.

## DISCUSSION

Efficacy and safety of tocolytic agents in pre term labor has been a difficult task because the cause of preterm labor is generally unknown and therapy cannot be directed to a specific cause. This prospective study was designed to find out the safety, efficacy and perinatal outcome of Isoxsuprine and Nifedipine in women with preterm labour.[11-13]

Cochrane review on preterm labor concludes that tocolysis is definitely indicated before 34 weeks gestational age.[11] Patients were included into the study group in whom uterine contractions continued even after complete bed rest to reduce the number of patients in false labour being included in the study. The patients in both groups were well matched regarding age, antenatal care, gravidity, previous obstetric history and socio economic status.

This is supported by well matched randomized controlled trials conducted by Kedar M G et al (1990)[14] Kalita D et al (1998),[15] Rayamajhi R et al (2003)[10], singh nisha(2009).[4] Nifedipine has been known to relax the pregnant and non pregnant uterus Since the late 1970's (Ulmsten, Anderson KE)[13] Most of the studies so far conducted have compared the efficacy and safety between Nifedipine and Ritodrine. Only few studies have been done between Nifedine and Isox- suprine. Kedar M G et al[14], Kalita D et al[15], Rayamajhi R et al[10] and singh nisha et al[4] have conducted studies about comparison between the efficacy and safety of Nifedipine and Isoxsuprine in the suppression of preterm labor.

India study conducted by Singh S et al, observed that the prolongation of pregnancy was more when the period of gestation was less.[16] The mean prolongation of pregnancy in the present study was 20.16+14.09 days with Nifedipine and 13.98+11.03 days with Isoxsuprine. These results were similar to those reported by Kalita D et al[15] study. Kalita et al reported mean prolongation of pregnancy as 31.16±10.2 days with Nifed- ipine and 23.06 days with Isoxsuprine. Kedar et al[14] report- ed mean prolongation of pregnancy as 22.4 ± 15.6 days with Nifedipine and 16.5 ± 14.5 days with Isoxsuprine. Rayamajhi et al[10] reported mean prolongation of pregnancy as 25.71 days with Nifedipine and 19.18 days with Isoxsuprine. Tewari et al[17] reported mean prolongation of pregnancy as 39.26 ± 25.5 days with Nifedipine and 25.5 ± 15.75 days with Isoxsuprine. Nisha S et al reported successful tocolysis with isoxsuprine in 68% of the patient.[18] Bankatlal JP et al found 68.3% with ritodrine.[19]

Indian study conducted by Singh S and Gupta K[16] observed that prolongation of pregnancy was more when the period of gestation was less, being 47.44 days at 22-24 weeks and only 10.18 days at 33-36 weeks of gestation. We infer that prolongation of pregnancy depends not only on the gestational age at the time of tocolysis, duration of tocolysis but also the dose given for tocolysis.

In the present study, successful tocolysis was achieved in 92% with Nifedipine group and 76% with Isoxsuprine group. These results were similar to those reported by Kedar et al, 88% with Nifedipine and 76% with Isoxsuprine group. Rayamajhi et al reported 81.25% successful tocolysis with Nifedipine and 70% with Isoxsuprine group. The maternal side effects observed in our study were less as compared to Kedar et al Rayamajhi et al study. No significant change in BP was observed with Nifedipine group in our study that necessitated discontinuation of therapy, as Nifedipine exhibits greater selectivity for inhibition of uterine activity relative to cardiovascular effects. This may be attributed to the use.[17-19]

The RCOG, recommends that if tocolysis drug is to be used, Atosiban and nifedipine appear to be preferable as they have fewer side effects and seems to have comparable effectiveness. The "choice" of tocolysis agent, which could improve neonatal outcome with no maternal or neonatal side effect, has not yet surfaced.[20,21]

## CONCLUSION

The approach which prevent and treat preterm labor will have great impact on society and long-term public health care costs. Our study found a favorable outcome with Nifedipine in this aspect (92% vs 76%). In the view of increasing evidence of efficacy, safety and its ease of administration, Nifedipine will play an expanded role in the suppression of preterm labour.

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