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Research Article

A Comparative Evaluation of Nifedipine, Ritodrine & Isoxsuprine As A Tocolytic

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ABSTRACT

Background: *Preterm birth is a leading cause of neonatal mortality & morbidity in India. The goal of tocolysis is to cause cessation of uterine contractions in preterm labour. Main objectives of this study was to compare tocolytic effect of Nifedipine, Isoxsuprine & Ritodrine .*

Methods: *This prospective study conducted in the Department of Obstetrics & gynaecology, J.K Lon Hospital, Kota. After taking Written and informed consent 150 cases with inclusion and exclusion criteria were selected & divided into 3 groups: A (Nifedipine), B (Ritodrine) &C (Isoxsuprine) All the patients received Injection Betamethasone. The babies were evaluated & shifted to NICU if needed.*

Results: *The prolongation of pregnancy upto 48 hours seen more in Nifedipine . Prolongation of pregnancy till 37 weeks was seen in 20% patients in Nifedipine, 18% in Ritodrine and 10% in Isoxsuprine.The side-effect with Nifedipine was predominantly headache(12%). Hypotension(10%) and fetal tachycardia(10%) with Ritodrine. The side effects in Isoxsuprine were Palpitation (16%) followed by hypotension(10%) and fetal tachycardia(6%) .Side effects in nifedipine group were 20%,28% in Ritodrine & 32 % in Isoxsuprine. Number of NICU admissions was 26% both in Nifedipine and Ritodrine & 40% in Isoxsuprine . Perinatal deaths were 24% in Isoxsuprine, 20% in Ritodrine and 18% in Nifedipine group.*

Conclusions: *In this study we conclude that oral Nifedipine is a cheaper and effective tocolytic alternative and has fewer and less serious side effects when compared with I.V Ritodrine and I.V. Isoxsuprine .*

Keywords: *Preterm labour , Tocolytics*

Introduction

Preterm birth is a leading cause of neonatal mortality and morbidity in India. According to Global estimates (2001), 24% of neonatal deaths are due to complications of prematurity.

Incidence of preterm birth is approximately 6-7% of all births. Incidence in India 24 %,USA is 11.5%, in Europe - 5.8 % [1], & in Turkey - 5.6%.

Preterm labour pain defined as one where 4 regular uterine contraction in 20 minutes or 8 in 60 minutes causes cervical dilation greater than 1cm starting before 37th completed weeks.

Tocolysis means pharmacological inhibition of uterine contractions. The goal of tocolysis is to cause cessation of uterine contractions in patient with preterm labour. There by reducing neonatal

morbidity, mortality and cost of neonatal care due to prematurity. Tocolytics are used to gain sufficient time for to enhance fetal lung maturation by concommitent use of corticost-eroids and to gain time for in utero transfer enabling premature infant to be delivered in care of high risk pregnancies and with supportive neonatal intensive care facilities.

ACOG has recommended tocolysis when there are regular uterine contractions 4 in 20 minutes or 8 in 60 minutes plus progressive changes in cervix, cervical dilatation greater than 1cms, cervical effacement of 80% or greater[2]

Historically nonpharmacologic treatments to prevent preterm births included bed rest, abstention from intercourse, and hydration either orally or parenterally. Currently a variety of pharmacological agents are available to treat preterm labour .The incidence of troublesome side-effects and debatable efficacy prompt to search for the better drug.

In 1961, first betamimetic agent Isoxsuprine was proposed as tocolytic to prevent preterm labour pain. It can be used parentrally as well as orally.

Beta mimetics like Ritodrine, a phenyl ethylamine derivative which was developed for obstetrics use in 1971, is approved by Food and Drug Administration for tocolysis,[3] being effective orally and parentrally

Nifedipine is a calcium channel blocker, which inhibits the influx of calcium ions into myometrial and other cells and thereby reduces muscle contractility. It reaches peak plasma levels within 45 to 60 minutes after being taken orally and has a plasma half-life of 2 to 3 hours. It has been shown in vivo and in vitro to be an effective tocolytic agent for suppressing uterine activity with low toxicity and no teratogenicity. Its ability to suppress preterm labour was first reported in 1980. A recommendation has been made by the Royal College of Obstetricians and Gynecologists (RCOG) to use nifedipine or atosiban as the first line treatment in preference to betamimetics. While The American College of Obstetricians and Gynecologists (ACOG) stated in a 2003 guideline (reaffirmed in 2008) that no optimal first-line agent for tocolysis has been identified.

This study was undertaken to compare the efficacy of Nifedipine, Ritodrine and Isoxsuprine in the treatment of preterm labour.

Aims and Objectives

1. To compare tocolytic effect of Nifedipine, Isoxsuprine and Ritodrine
2. Efficacy and Adverse effects of drugs
3. Neonatal outcome.

Methods

This prospective study was conducted in the Department of Obstetrics and gynaecology, Jay Kay Lon Hospital, Kota.

150 cases with inclusion and exclusion criteria were selected during the study period.

Inclusion criteria

- Singleton pregnancy
- Gestational age between 28-36 weeks
- Intact membranes

Exclusion criteria-

- Maternal Medical Disorders
- Pregnancy induced hypertension
- Advanced labour
- Suspected chorioamnionitis
- Antepartum haemorrhage
- Intrauterine growth retardation with abnormal colour Doppler
- Congenital anamolies
- Multiple pregnancy
- Polyhydramnios

Complete history was taken regarding age, occupation, socioeconomic status, and any history of infections, obstetric history, and history of previous preterm deliveries, abortions, history of any medical disorder. Period of gestation was calculated from Naegeles rule in patients with known last menstrual period, otherwise assessed by clinical examination and ultrasound. Patient's general physical examination was done. Vitals

were recorded. Cardiovascular system and respiratory system examined.

Abdominal examination- uterine heights, presentation, position, lie of the fetus, liquor volume, fetal heart rate were recorded. Uterine contractions were evaluated with respect to frequency and duration.

Per speculum examination- speculum was introduced into the vagina any discharge /leak /bleed noted. Presence or absence of herniation of membranes noted.

Per vaginal examination –the consistency, position, effacement, dilatation of cervix, status of membranes, and station of presenting part noted.

Routine investigations like Hb%, total count, differential count, E.S.R, Urine for albumin, sugar and microscopy, blood grouping & Rh typing, HIV, HBsAg, ultrasound examination, non stress test, urine for culture and sensitivity were sent after satisfying the above mentioned criteria and after excluding the contraindications. Written and informed consent was taken from the participants.

Group - A 50 patients received Nifedipine. Loading dose of 30 mg orally and after 1 ½ hours 20 mg orally which was followed by 20 mg 8th hourly for acute tocolysis. Maintenance dose of 10 mg 12 hourly was given till 37 weeks or till delivery whichever occurs early.

Group - B 50 patients received 2 ampoules of Ritodrine (100 mg) in 500 ml (preparation contains 200 mcg/ml) of Ringer Lactate. The infusion was started at the rate of 100 mcg/min (7-8 drops). It was increased every 10 min by 50 mcg/min (3-4 drops/min) until the contractions stopped. Maximum dose is 350 mcg/min (26-28 drops/min). This was maintained for 24 hrs after the contractions stopped. Oral tablet was given ½ hour before stopping I.V drip.

Incidence of preterm deliveries found to be 13%

Oral Ritodrine–10mg/6th hourly for first 24 hours, as long as pulse rate did not exceed 120/min and the maintenance of 10mg 8th hourly till 37 weeks or till delivery whichever occurs early.

Group C- 50 patients received I.V. infusion of Isoxsuprine 40mg in 500ml Ringer lactate @ 0.08 mg/min increasing infusion rate upto 0.24 mg/min depending upon uterine contractions and side effects . After discontinuation of IV infusion, patients were maintained on oral Isoxsuprine 10mg 8hourly for up to 7 days.

All the patients received Injection Betnesol 12 mg 2 doses 24 hours apart.

After delivery placenta was examined and the neonate was evaluated for gestational age, birth weight, congenital anamolies, APGAR score at 1 and 5 minutes. The babies were shifted to NICU if needed. These babies were followed up for perinatal complicatons during the hospital stay

Results

The observations made in this present study were:

Incidence of preterm delivery

- Age wise distribution
- Parity wise distribution
- Gestational age at treatment
- Mean prolongation of pregnancy
- Comparison of side effects
- Neonatal side effects

There were 170 cases, out of these 20 cases were lost in follow up and were excluded from further analysis.

Table 1 : Incidence of preterm deliveries

Total number of deliveries	Incidence of preterm labour	Total number of preterm deliveries
14374	13%	1868

Table 2: Age group distribution

Age group	Nifedipine(50)	Ritodrine(50)	Isoxsuprine(50)
16-20 yrs	10 (20%)	7 (14%)	10 (20%)
21-25 yrs	30 (60%)	27 (54%)	23(46%)
26-30 yrs	8 (16%)	11 (22%)	12 (24%)
31-35 yrs	2 (4%)	4 (8%)	4 (8%)
36-40 yrs	-	1 (2%)	1 (2%)

Majority of cases were between 21 and 25 years. 60% in Nifedipine group, 54% in Ritodrine group and 46% in Isoxsuprine group .Mean age was 24 years in Nifedipine group and Isoxsuprine group and 25 years in Ritodrine group.

Table 3: - Distribution parity wise

Gravida	Nifedipine(50)	Ritodrine(50)	Isoxsuprine(50)
Primi	24(48%)	19(38%)	18(36%)
Multi	26(52%)	31(62%)	32(64%)

Multi gravida were in majority in both the groups. 64% of patients were seen in Isoxsuprine group and 62% in Ritodrine group,52% in Nifedipine group.

Table 4: - Distribution based on gestational age at tocolysis

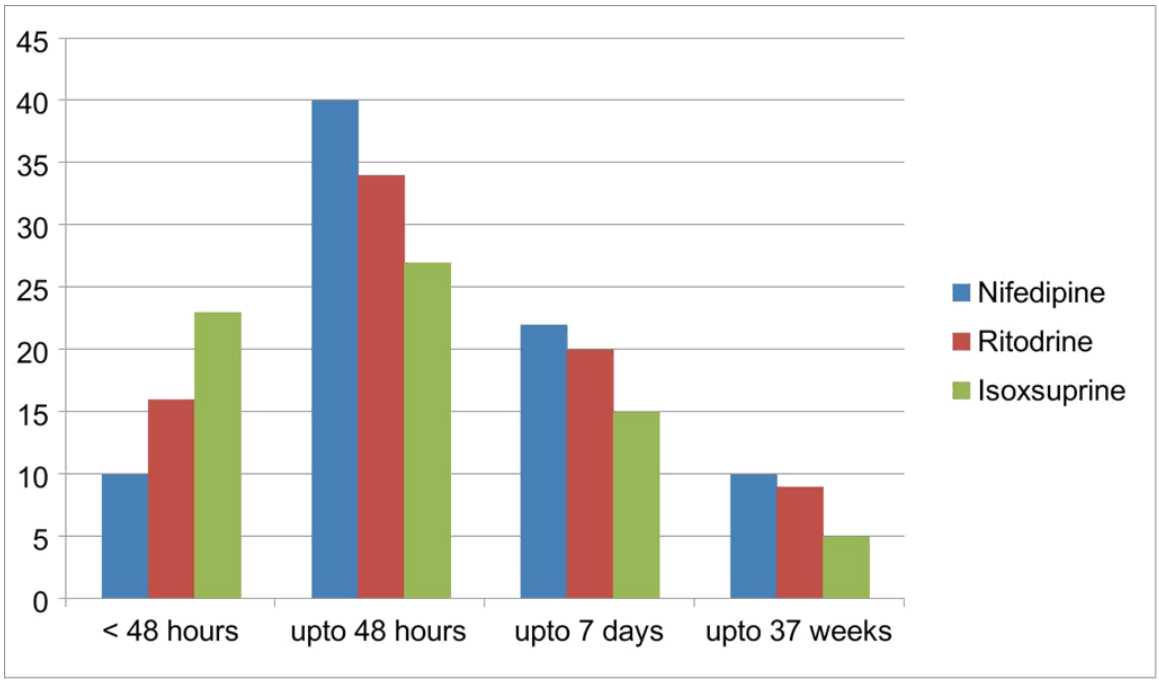
Gestational age (weeks)	Nifedipine (n=50)	Ritodrine (n=50)	Isoxsuprine(n =50)
28-30 weeks	10(20%)	8(16%)	7(14%)
31-33 weeks	15(30%)	20(40%)	19(38%)
34-36 weeks	25(50%)	22(44%)	24(48%)

More number of patients was between gestational age of 34 and 36 weeks being 50 percent in Nifedipine group, 44 percent in ritodrine group and 48 percent in Isoxsuprine group. Mean gestational age at tocolysis was 32 weeks in all the three groups.

Table 5: - Mean prolongation of pregnancy

No of days	Nifedipine (n=50)	Ritodrine (n=50)	Isoxsuprine(n=50)
<48 hours	10 (20%)	16 (32%)	23 (46%)
Up to 48 hours	40 (80%)	34 (68%)	27 (54%)
Up to 7 days	22 (44%)	20 (40%)	15 (30%)
Up to 37 weeks	10 (20%)	9 (18%)	5 (10%)

Graph 1: - Mean prolongation of pregnancy



The prolongation of pregnancy was up to 48 hours seen more in Nifedipine group when compared with Ritodrine group or Isoxsuprine group. This shows that Nifedipine was more successful in delaying delivery for 48 hours which would enhance fetal maturity by concomitant use of corticosteroids. The prolongation of pregnancy up to 7 days was comparable in the groups. Prolongation of pregnancy till 37 weeks was seen in 20 percent patients in Nifedipine group, 18 percent in Ritodrine group and 10 percent in Isoxsuprine group.

Table 6 Pregnancy outcomes in treatment groups

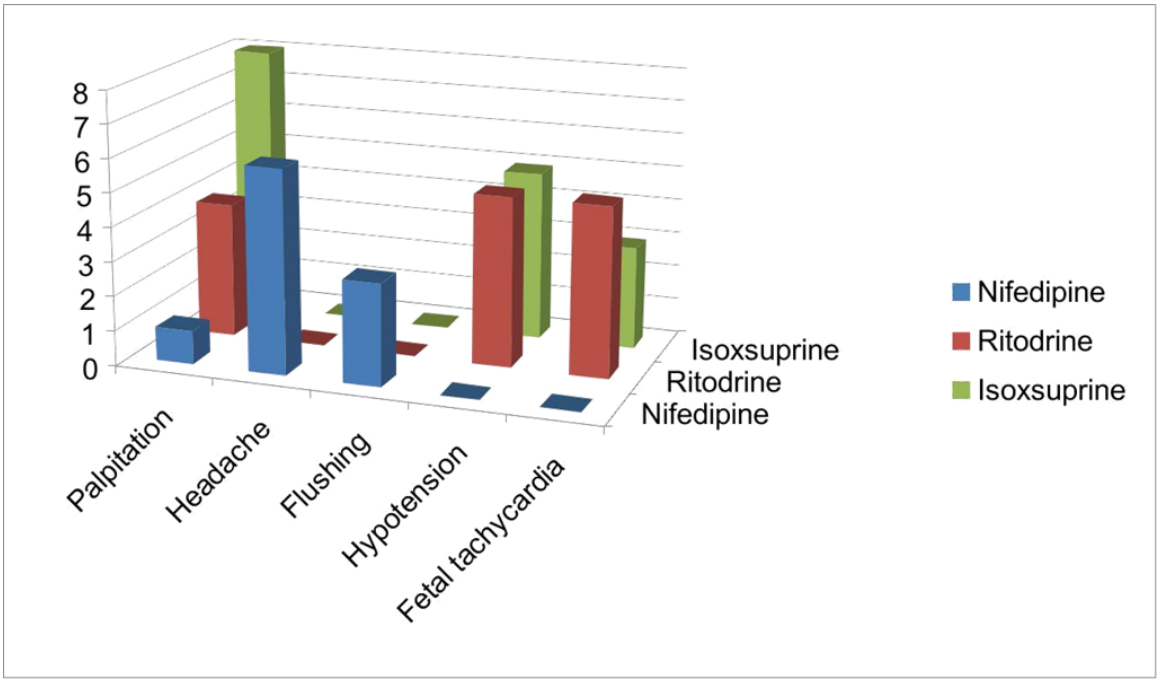
	Success n (%)	Failure n (%)
Nifedipine	40 (80%)	10 (20%)
Ritodrine	34 (68%)	16 (32%)
Isoxsuprine	27 (54%)	23(46%)

This analysis shows that at 48 hrs, which is relevant because it permits use of steroids to promote fetal lung maturation, 80% of nifedipine patients remained undelivered compared to 68% in Ritodrine group and 54% in Isoxsuprine group.

Table 7: - Comparison of side effects

Side effects	Nifedipine (n=50)	Ritodrine (n=50)	Isoxsuprine(n=50)
Palpitation	1	4	8
Headache	6	-	-
Flushing	3	-	-
Hypotension	-	5	5
Fetal tachycardia	-	5	3

Graph 2 Comparison of side effects



The side effects noted in Nifedipine group was predominantly headache (12%) followed by hot flushes (6%) as clearly represented by the Graph 2. These complications were not seen in patients who received Ritodrine and Isoxsuprine. Hypotension(10%) and fetal tachycardia(10%) were significant side effects seen in patients who received Ritodrine. The side effects in Isoxsuprine were Palpitation (16%) followed by hypotension(10%) and fetal tachycardia(6%).

Side effects in nifedipine group were 20 percent (10 patients) as compared to 28 percent (14 patients) in Ritodrine group and 32 percent (16 patients) in Isoxsuprine group.

The side effects were more frequent and were more troublesome with Ritodrine and Isoxsuprine when compared to Nifedipine. 5 patients in both Ritodrine and Isoxsuprine group had pronounced fall in diastolic blood pressure. Nausea and vomiting were successfully treated with antacids and antiemetics.

In nifedipine group there was decrease in systolic blood pressure that was lower than base line after administration of second dose. The fall in the blood pressure was 10 –20mm of Hg seen in 20 patients. The fall in the diastolic blood pressure was 10mm Hg which was seen in 24 patients of Nifedipine group after the administration of second dose of the drug. This decrease in the blood pressure in the Nifedipine group did not necessitate any treatment. Other side effects were headache, seen in 6 patients and flushing, seen in 3 patients. These side effects subsided after few hours and did not necessitate any special measures.

Table 8: Side effects

Drugs	Side effects
Nifedipine	10 (20%)
Ritodrine	14 (28%)
Isoxsuprine	16 (32%)

Isoxsuprine followed by Ritodrine are associated with significantly more side effects than Nifedipine.

Table 9: Neonatal outcomes

Parameters	Nifedipine (n=50)	Ritodrine (n=50)	Isoxsuprine (50)
Gestational age at birth (weeks)	34 weeks	33 weeks 4 days	33 weeks 1day
Birth weight (grams)	2209	2194	2150
NICU admission	13(26%)	13(26%)	20 (40%)
Perinatal death	9 (18%)	10 (20%)	12 (24%)
Respiratory distress syndrome	6 (12%)	9 (18%)	13(26%)

The mean gestational age at birth was not significantly different, in Nifedipine group was 34 weeks, in Ritodrine was 33 weeks 4 days and in Isoxsuprine was 33 weeks 1 day. The mean birth weight in Nifedipine group was 2209 grams, in Ritodrine group was 2194 grams and in Isoxsuprine group was 2150 grams.

Number of admissions to NICU was 26% both in Nifedipine group and Ritodrine while it was 40% in Isoxsuprine group. Perinatal deaths were 12 (24%) in Isoxsuprine group, 10 (20%) in Ritodrine group and 9 (18%) in Nifedipine group. Respiratory distress syndrome was 6 (12%) in Nifedipine group, 9 (18%) in Ritodrine group and 13(26%) in Isoxsuprine group. Neonatal outcomes were comparable in these groups.

Discussion

Preterm labour remains one of the unconquered frontiers in the present era of Obstetrics. Throughout the years a variety of drugs with different pharmacologic principles are used to suppress preterm labour. The choice is limited by their efficacy, safety and side effects.

Currently, the most commonly used tocolytic agents are beta sympathomimetics. However the incidences of troublesome side effects have led to continuous search for other alternatives.There is growing evidence that Nifedipine is effective, potentially safer and better tolerated agent with no fetal side effects.

This study compares the efficacy, safety of Nifedipine, Ritodrine and Isoxsuprine in the suppression of preterm labour.

Table 10: Comparison of Incidence of preterm labour with different authors

Authors	Percentage
James E Ferguson (1996)[4]	9.6 %
M Kupferminc (1992)[5]	7-9 %
Vijay Roy (2006)[6]	5-10%
Present study (2014)	13%

The incidence of preterm labour in the study population is comparable to other study groups.

Table 11: Comparison of efficacy of Nifedipine

Delay of delivery	Kupferminc *et al.* N(30)	Carolien A M Koks[7] (55)	Present study N(50)
48 hours	24 (80%)	33 (60%)	40(80%)
7 days	20 (67%)	26 (47%)	22(44%)
Up to 36 weeks	15 (50%)	21 (38%)	10(20%)

The efficacy of Nifedipine in the present study population in prolongation of pregnancy at 48 hours and 7 days was comparable with other study groups however it was lower at 36 weeks when compared to other study groups.

The mean prolongation of pregnancy with Nifedipine

- up to 48 hours was 80 per cent
- up to 7 days was 44 per cent
- up to 36 weeks was 20 per cent.

Table 12: Comparison of efficacy of Ritodrine

Delay in delivery	Kupferminc *et al.* N(30)	Carolien A M Koks N(47)	Present study N(50)
48 hours	25 (83%)	31 (66%)	34 (68%)
7 days	20 (67%)	21 (45%)	20 (40%)
Up to 36 weeks	15 (50%)	11 (23%)	9 (18%)

The efficacy of Ritodrine in the present study was comparable to study by Carolien A M Koks in prolongation of pregnancy, but the number of patients who remained undelivered was lower when compared to Kupferminc *et al*. study group.

The mean prolongation of pregnancy with Ritodrine

- up to 48 hours was 68%
- up to 7 days was 40 %
- up to 36 weeks was 18 %.

Table 13: Comparison of efficacy of Isoxsuprine

Delay in delivery	Vijay Roy et al. N (25)	Present study N(50)
48 hours	2 (8%)	27 (54%)
7 days	4 (16%)	15 (30%)
Up to 36 weeks	9 (36%)	5 (10%)

The efficacy of Isoxsuprine in the present study population in prolongation of pregnancy at 48 hours and 7 days was higher, however it was lower at 36 weeks when compared to other study group.

The mean prolongation of pregnancy with Isoxsuprine

- up to 48 hours was 54%
- up to 7 days was 30 %
- up to 36 weeks was 10 %.

Table 14: Comparison of side effects

Study	Nifedipine	Ritodrine	Isoxsuprine
Kupferminc *et al.*	8 (27%)	23 (77%)	-
Ferguson *et al.*	5 (15%)	18 (55%)	-
Vijay Roy *et al.*	-	14 (56%)	16 (64%)
Present study	10 (20%)	14 (28%)	16 (32%)

The side effects of Nifedipine in the present study were comparable to the results of Kupferminc *et al*. while those of Ritodrine and Isoxsuprine were less than other studies.

In this study the significant difference in the tocolytic effect between Ritodrine, Isoxsuprine and Nifedipine could be demonstrated. The survival analysis shows that at 48 hours, which is relevant because it permits use if steroids to promote fetal lung maturation. 80 percent of Nifedipine patients remain undelivered compared to 68 per cent in Ritodrine group and 54 percent in Isoxsuprine group. The prolongation of pregnancy till term was seen in 20 per cent in Nifedipine group, 18 per cent in Ritodrine group and 10% in Isoxsuprine group.

Nifedipine caused fewer side effects which subsided after few hours and did not necessitate

any special treatment whereas Isoxsuprine and Ritodrine group had more frequent and more serious side effects.

Calcium channel blockers are known to have vasodilatory effects hence the hemodynamic side effects were evaluated. Our study showed that there was reduction in both systolic and diastolic blood pressure following oral administration of second dose of Nifedipine. However these changes were statistically not significant and were less when compared to decreased blood pressure associated with Ritodrine and Isoxsuprine. These changes in the blood pressure were considered unlikely to be of physiological importance. Other side effects seen in Nifedipine group were headache 12 per cent, flushing 6 percent.

Ritodrine and Isoxsuprine caused decrease in blood pressure in 10 percent cases in each group. Other side effects seen were palpitation (8 % in Ritodrine group and 16% in Isoxsuprine group) and fetal tachycardia (10%in Ritodrine group and 6% in Isoxsuprine group).

The neonatal outcomes between all the three groups were comparable.

Conclusion

In this study it was found that oral Nifedipine has fewer and less serious side effects as compared to I.V Ritodrine and I.V. Isoxsuprine. Moreover I.V Ritodrine requires intensive monitoring of the patients. The Nifedipine drug was more successful in delaying the delivery for 48 hours which would enhance fetal lung maturity by use of corticosteroids. The mean prolongation of gestation was higher for Nifedipine when compared to Ritodrine and Isoxsuprine. The neonatal outcome was comparable in both the groups.

Nifedipine has the ease of oral administration. Other advantages are lack (relative) of influence on maternal cardiac and carbohydrate metabolism in contrast with Ritodrine and Isoxsuprine.

In addition Nifedipine does not interfere with the interpretation of fetal heart rate tracings as does Ritodrine.

Hence we conclude that oral Nifedipine is a cheaper and effective alternative and has fewer and less serious side effects when compared with I.V Ritodrine and I.V. Isoxsuprine for suppression of preterm labour.

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Declarations

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