TO ASSESS THE EFFICACY OF NIFEDIPINE IN THE TREATMENT OF PRETERM LABOUR IN COMPARISON TO ISOXSUPRINE

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ABSTRACT

BACKGROUND

Preterm labour and delivery remains a major cause of prenatal morbidity and mortality.[1] Numerous drugs and interventions have been used to prevent and inhibit the preterm labour but none have been found to be completely effective with the choice being further limited by troublesome side effects. Tocolysis, the pharmacologic inhibition of uterine contractions, is currently the principal preterm birth preventive measure. The aim of this study was to compare the tocolytic efficacy of Isoxsuprine and Nifedipine in the treatment of preterm labour. Maternal side effects and neonatal outcome were also evaluated.

MATERIALS AND METHODS

This is a prospective randomised study. 120 antenatal cases with 28-36 weeks of gestation with painful intermittent uterine contractions were considered for the study. Subjects were randomly allotted into two groups-Group A (Isoxsuprine) and Group B (Nifedipine) 60 patients each. Main outcomes include prolongation of pregnancy, maternal side effects and neonatal outcome were compared.

RESULTS

Baseline characteristics were well matched in both study groups. Success rate with Nifedipine was found to be 96% as compared to Isoxsuprine which was 75%. Maternal side effects like hypotension (13.33%) and tachycardia (6.66%) were common in Isoxsuprine group, while facial flushing was seen in 16.66% patients in Nifedipine group. Neonatal outcome was similar in the both groups.

KEYWORDS

Preterm labour, Tocolysis, Isoxsuprine, Nifedipine.

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BACKGROUND

"Preterm" is defined as a gestational age less than 259 days from the first day of the last menstrual period.[2] with the presence of regular uterine activity which produces cervical effacement & dilatation prior to 37 completed weeks of gestation.[3] In terms of gestational age, the following definitions have been proposed: mildly preterm 32 to 36 weeks, very preterm less than 32 weeks, and extremely preterm, less than 28 weeks.[4] Chorioamnionitis is 20-30% cause for preterm labour.[5] (Figure 1) and previous history of pregnancies with placenta previa or abruption increases risk of preterm labour in current pregnancy.

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The presence of FFN in vaginal or cervical secretions before 35 weeks and after 21 weeks is a moderately good predicator of preterm delivery.[6] Cervical length of 35 mm or less at 28 to 30 weeks was associated with a significantly increased incidence of preterm birth.[7] Maternal administration of corticosteroids causes a reduction in neonatal death, respiratory distress syndrome, necrotising enterocolitis and intraventricular haemorrhage in babies born preterm.[8] Timing of therapy is crucial. The best neonatal respiratory results come after a complete course of 2 doses of Betamethasone 12 mg, 24 hours apart or 4 doses of Dexamethasone 6 mg, 12 hours apart.[8]

Isoxsuprine

It has both β 1 & β 2 activity and has potent inhibitory effect on vasculature and uterine smooth muscle. Beta adrenergic agonist act by activating the enzyme adenylate cyclase, by binding with beta adrenergic receptor which catalyses the conversion of adenosine tri-phosphate to c- AMP which results in inhibition of myosin light chain kinase (MLK) and subsequent smooth muscle contraction, by decreasing free calcium concentration available to activate calmodulin.[9,10,11]

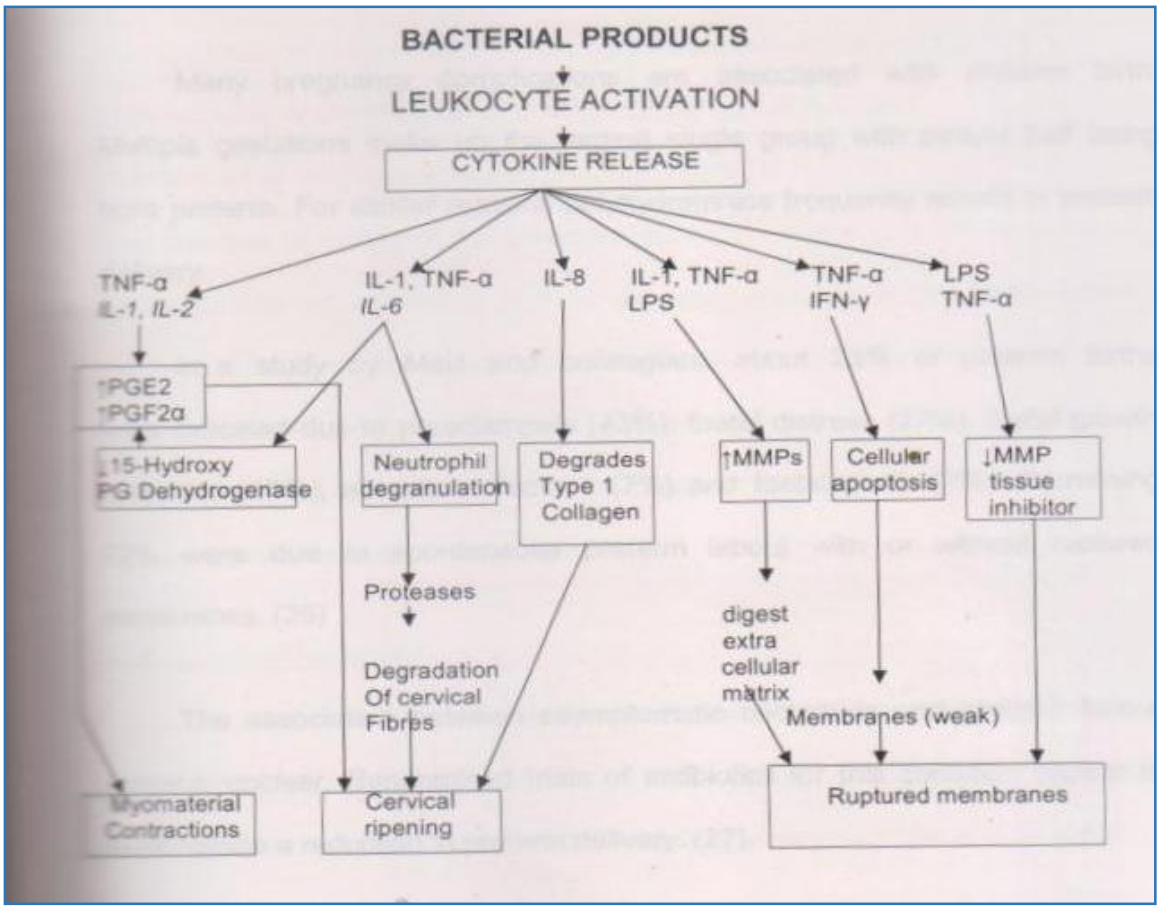

Figure 1.

Side effects of Isoxsuprine: Maternal effects are Hypotension, tachycardia, Pulmonary oedema, hyperinsulinemia, hypokalaemia, lactic acidosis. Foetal effects are Foetal tachycardia, Hypocalcaemia, Hypoglycaemia, Paralytic ileus, Hypotension, Neonatal death.

Nifedipine

It is a powerful uterine relaxant. The drug is characterised by the ability to inhibit calcium influx through voltage dependent calcium channels in myometrial cells. Maternal effects of nifedipine are tachycardia, palpitation, headache, cutaneous flushing, hypotension, hypocalcaemia, fluid retention, pulmonary oedema, drug induced hepatitis. Foetal and neonatal risks are foetal tachycardia, Altered utero-placental blood flow decreased foetal arterial oxygen content.

MATERIAL AND METHODS

Source of Data

This is a prospective study, carried out in the department of Obstetrics and Gynaecology of Katuri Medical College, Chinakondrupadu, Guntur, over a period of 18 months- from July 2013 to August 2015. 120 antenatal cases with 28-36 weeks of gestation with painful intermittent uterine contractions are considered for the study, after which they were randomly allotted into two groups- Group-A (Isoxsuprine) and Group-B (Nifedipine).

Inclusion Criteria

Gestational age between 28-36 weeks, with 1-2 regular uterine contractions occurring in 10 min, each lasting for 30 seconds and cervical effacement of more than 80% and with dilatation of less than 3 cms. with intact membranes with no previous administration of tocolytics.

Exclusion Criteria

Systemic diseases like diabetes mellitus, cardiac diseases, liver or renal diseases. Obstetric complications like severe pre-eclampsia, eclampsia, antepartum haemorrhage, hydramnios, hyperthyroidism. Foetal complications like chorioamnionitis, IUGR, congenital anomaly, foetal distress, oligoamnios and multifoetal gestation.

Method of Collection of Data

All pregnant women admitted to labour ward were taken in this study as per inclusion and exclusion criteria. A detailed history, complete physical and obstetric examination and routine investigations were done for all the patients. Patients were monitored from the time of admission to the time of discharge.

Method of Study

Patients were taken up for the study based on inclusion criteria. They are randomly allotted into two groups-Group A (Isoxsuprine) and Group B (Nifedipine).

RESULTS

Treatment was considered successful, if there was abolition of uterine contractions, no progression of cervical dilatation, and also if contractions did not recur within 48 hrs of cessation of therapy. Treatment was deemed failure, despite maximal dose mentioned for both groups, if uterine relaxation was not achieved or patient or foetus developed some significant side effects that necessitated discontinuation of therapy. Data regarding efficacy of the drugs in terms of arrest of preterm labour, prolongation of pregnancy and the days gained in-utero were noted. Details of mode of delivery, gestational age at the time of delivery, baby's sex, birth weight and Apgar score were noted.

OBSERVATION AND ANALYSIS

Out of the 120 women with singleton pregnancies who enrolled for the study, 60 were assigned to Isoxsuprine group and 60 to Nifedipine group after randomization. In the present study, patients were between 18-33 years of age. About 80% of the patients were less than or equal to 26 years. Mean age being 23.7 years in Isoxsuprine group and 24 years in Nifedipine group. Minimum and maximum age in Isoxsuprine group is 19 and 33 years respectively and in Nifedipine group is 18 and 31 years respectively. (Table 1).

Age in Years	Isoxsuprine Group	Nifedipine Group
18-20	14	08
21-23	18	20
24-26	18	20
27-29	02	04
>30	08	08
Total	60	60
Mean Age	23.7	24
Minimum Age	19	18
Maximum Age	33	31
SD	3.79	3.41

Table 1. Age Wise Distribution of the Patients

More than 60% of the study population were illiterates in both groups (63.34 vs 66.67). (Table 2). Majority of the patients in the present study came from low socioeconomic status families in both groups (73.33 vs 70). (Table 3). In the present study, primigravidae were more in Isoxsuprine group (56.67%) as compared to Nifedipine group (46.67%). (Table 4). Majority of the patients in the present study were between 28-32 weeks of gestation (70% vs 63.33%) in Isoxsuprine group and Nifedipine group respectively. The mean gestational age in Isoxsuprine group and Nifedipine group is 31.62 weeks and 31.9 weeks respectively. There is no statistically significant difference in both study groups with respect to gestational age. (Table 5). Commonest and most significant risk factor in Isoxsuprine and Nifedipine groups was anaemia (53.33 vs 63.33 respectively), followed by substance abuse (Tobacco) - 43.33 vs 33.33, physical and psychological stress (36.67 vs 50) and infections (20.00 vs. 13.33).

Out of 60 patients in Isoxsuprine group, who showed evidence of infection, 8 patients had UTI, 1 had upper respiratory tract infection and other had acute gastroenteritis. In Nifedipine group out of 8 patients, 3 had UTI and other had upper respiratory tract infection. (Table 6). In our study, prolongation of pregnancy was more in Nifedipine group 31.68 days when compared to Isoxsuprine group 27.54 days. The prolongation is statistically significant P being ≤ 0.001 and it depended on the gestational age at the onset of tocolytic therapy and the time from the onset of therapy to delivery. (Table 7). Period of gestation at the time of delivery was ≥37 weeks in 66.68% of cases in Nifedipine group when compared to Isoxsuprine group (46.67%). 06 patients in Isoxsuprine and 05 patients in Nifedipine group have lost to follow up.

In our study, hypotension was noted in 04 patients of Isoxsuprine group as compared to Nifedipine group where none of them had hypotension. While other side effects like facial flushing noted in 5 patients of Nifedipine group and tachycardia in 2 patients of Isoxsuprine and 1 patient of Nifedipine group. (Table 8).

	Isoxsuprine Group		Nifedipine Group	
	No. of Patient	Percentage	No. of Patients	Percentage
Illiterates	38	63.34	40	66.67
Literates	22	36.64	20	33.33
Total	**60**	**100**	**60**	**100**

Table 2. Distribution of the Patients According to Literacy

Socioeconomic Status	Isoxsuprine Group		Nifedipine Group	
	No. of Patients	Percentage	No. of Patients	Percentage
Low	44	73.33	42	70
Middle	14	23.33	18	30
High	02	3.34	00	00
Total	**60**	**100**	**60**	**100**

Table 3. Distribution of the Patients According to Socioeconomic Status

Parity	Isoxsuprine Group		Nifedipine Group	
	No. of patients	Percentage	No. of patients	Percentage
Nulliparous	34	56.67	28	46.67
Multiparous	26	43.33	32	53.33
Total	**60**	**100**	**60**	**100**

Table 4. Distribution of the Patients According to Parity

Gestational Age (weeks)	Isoxsuprine Group		Nifedipine Group	
	No. of Patients	Percentage	No. of Patients	Percentage
28-30	16	26.66	18	30.00
31-32	26	43.34	20	33.33
33-36	18	30.00	22	36.67
Total	**60**	**100**	**60**	**100**
Mean	31.62		31.9	
Minimum	28		28	
Maximum	35		36	
SD	1.91		1.93	

Table 5. Distribution of the Patients According to Gestational age at admission

Risk Factor	Isoxsuprine Group		Nifedipine Group	
	No	Percentage	No	Percentage
Previous Preterm	01	3.33	03	10.00
Abortions	04	13.33	07	23.34
Evidence of Infection	06	20.00	04	13.33
Previous D & E	04	13.33	04	13.33
Physical & Psychological Stress	11	36.67	15	50.00
Multiple Pregnancies	-	-	-	-
Coitus During Pregnancy	01	3.33	02	6.67
Substance Abuse	13	43.34	10	33.33
Anaemia	16	53.33	19	63.33
Uterine Malformation	-	-	-	-
Cervical Incompetence	-	-	-	-
No Risk Factor Found	11	36.67	10	33.33

Table 6. Risks Factors for Preterm Delivery

Prolongation of Pregnancy (Days)	Isoxsuprine Group (n=24)	Nifedipine Group (n=25)	P value
Mean	27.54	31.68	0.047
Minimum	15	18	
Maximum	42	47	

Table 7. Total Duration of Prolongation of Pregnancy in Days

Gestational Age at Delivery (weeks)	Isoxsuprine Group		Nifedipine Group	
	No	Percentage	No	Percentage
<37	20	33.33	10	16.66
≥37	28	46.67	40	66.68
Lost to followup	12	20	10	16.66
Total	**60**	**100**	**60**	**100**

Table 8. Gestational Age at Delivery in Weeks

DISCUSSION

Preterm labour complicates 5-10% of pregnancy and leading cause of neonatal mortality and morbidity worldwide. It is a major health problem in terms of loss of life and long term disability (Cerebral Palsy, Blindness, Deafness, Chronic Lung Diseases). Unfortunately the incidence of preterm labour has changed very little over last 40 years. Tocolytics are pharmacological agents that relax the uterine myometrium and inhibit contractions leading to abolition of preterm labour. They act by various mechanism to decrease the availability of intracellular calcium ion leading to inhibition of actin-myosin interaction. Though tocolytics usage is controversial, it definitely helps in for continuation of corticosteroids or in-utero transfer and is currently the principal preterm birth preventive measure and will remain so until the aetiology of preterm labour is better understood.

Many therapeutic agents have been investigated for efficacy and safety in tocolysis. The tocolytic drugs most frequently used are β- sympathomimetic agents. The incidence of troublesome side effects, debatable efficacy, and low uterine specificity of these agents prompt the search for better drugs. 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 randomised controlled trials conducted by Kedar M G et al (1990).[12] Kalita D et al (1998).[13] Rayamajhi R et al (2003).[14]

Clinical Parameters	Kedar et al		Rayamajhi et al		Present Study	
	N	I	N	I	N	I
No. of Patients	30	30	32	30	60	60
Mean Age (years)	22±5.5	23.4±4.6	26	25.12	24±3.41	23.7±3.29
Gestational Age (wks.) at the Onset of Tocolysis	30.5±3.5	31.4±2.8	32.22	32.64	31.9±1.91	31.62±1.93
Parity						
Primigravida	27 (54%)	24 (48%)	-	-	14 (46.67%)	17 (56.67%)
Multigravida	23 (46%)	26 (52%)	-	-	16 (53.33%)	13 (43.33%)

Table 9. Comparative Analysis of Mean Age, Gestational Age (weeks) at Onset of Tocolysis and Parity at Enrolment

N- Nifedipine Group I- Isoxsuprine Group

In our study, the patients in both groups were well matched regarding maternal age, gestational age and parity. This is supported by well-matched randomised controlled trials conducted by Kedar M G et al and Rayamajhi R et al. Mean maternal age in our study, in Nifedipine and Isoxsuprine group was 24±3.41 and 23.7±3.29 yrs. respectively. While in Kedar et al study it was 22±5.5 yrs. in Nifedipine group and 23.4±4.6 yrs. in Isoxsuprine group and Rayamajhi R et al study it was 26 yrs. in Nifedipine group and 25.12 yrs. in Isoxsuprine group. Gestational age in weeks in the present study, in Nifedipine group was 31.9±1.91 and 31.62±1.93 in Isoxsuprine group. While in Kedar et al study it was 30.5±3.5 wks. In Nifedipine group and 31.4±2.8 wks. In Isoxsuprine group and Rayamajhi R et al study it was 32.22 wks. in Nifedipine group and 32.64 wks in Isoxsuprine group. Meis et al (1995) in an invariable analysis of demographic risks factors, found parity to be in U shaped relationship with preterm birth, with both high and low parity showing increased rates. In our study, about half of them were primigravidae and half of them were multigravidae in both groups. This was well correlated with Kedar et al study.

Study	Gestational Age (wks.) at onset of Tocolytic Therapy
Papatasonis et al	20-33⅓
Read & Wellby	20-35
Murray et al	30-35
Present study	28-36

Table 10. Comparative Analysis of Gestational Age (weeks) at Enrolment

Significance of Prenatal Care, Literacy and Socioeconomic Status on Preterm Labour

There was no difference in antenatal care in both groups in our study, 30% cases were unbooked and did not have regular antenatal check-up. Most of them came from rural areas (Nearly 65%). Many studies have demonstrated a higher incidence of prematurity in the lower socioeconomic groups. In our study also, majority (70%) of the patients belonged to low socioeconomic status. The factors responsible for this difference are hard to dissect. Nutrition would appear to be an obvious factor. Most of these women are malnourished and anaemic. In our study, almost 50% of the patients had Hb% of less than 10 mg/dl in both groups. In the present study, maximum loading dose of nifedipine is 30 mg. while maintenance dose was continued for 7 days in our study as in Rayamajhi R et al. In Kedar et al study maintenance dose of nifedipine was continued till 36 weeks (Table 11).

Study	Nifedipine Dose	Isoxsuprine Group
Kedar et al	**Loading Dose**: Nifedipine 5 mgs/L, Repeated every 15 mins, up to a maximum of 8 doses (40 mg) during the first two hours of treatment. **Maintenance Dose**: Oral Nifedipine of 10 mg was initiated 3 hrs after the last sublingual dose. Oral Nifedipine was then continued as 10 mg 8 hrly. for next 48 hrs. Nifedipine retard tablet 10 mg or 20 mg was then started 12 hrly and continued till 36 weeks.	60 mg of Isoxsuprine was added in 5% Dextrose and was initially started at the rate of 0.5 mg/min and increased up to 10 mg/min and after cessation of uterine activity drip was continued for 12 hours. Subsequently patients Received Isoxsuprine Injectable 1 mg IM 8 hrly for 48 hrs followed by oral 10-20 mg, 8 hrly till 36 weeks.
Rayamajhi R et al	**Loading dose**:- Nifedipine 10 mgs/L, repeated every 20 mins, up to a maximum of 4 doses (40 mg). **Maintenance Dose**: 4-6 hrs after last S/L dose, Tab. Nifedipine 10-20 mg orally, 6-8 hrly, for not more than 7 days.	40 mg of inj. Isoxsuprine was added in 500 ml. of RL, infusion was started at rate of 0.08 mg/min increasing up to 0.24 mg/min depending on the status of uterine contractions and occurrence of side effects. Later patients were maintained on oral Isoxsuprine 10 mg 8 hrly for up to 7 days.
Present study	**Loading Dose**: Nifedipine 30 mg **Maintenance Dose**: Tab. Nifedipine 20 mg orally, 6-8 hrly, for not more than 7 days.	Isoxsuprine 10 mg 8 hrly for 7 days

Table 11. Comparison of Tocolytic Dosage Administrated

The mean prolongation of pregnancy in the present study was 31.68±8.37 days with Nifedipine and 27.54±7.38 days with Isoxsuprine. These results were similar to those reported by Kalita D et al study. Kalita et al reported mean prolongation of pregnancy as 31.16±10.2 days with Nifedipine and 23.06 days with Isoxsuprine.

Kedar et al reported mean prolongation of pregnancy as 22.4±15.6 days with Nifedipine and 16.5±14.5 days with Isoxsuprine. Rayamajhi et al reported mean prolongation of pregnancy as 25.71 days with Nifedipine and 19.18 days with Isoxsuprine. Tewari et al reported mean prolongation of pregnancy as 39.26±25.5 days with Nifedipine and 25.5±15.75 days with Isoxsuprine (Table 12). Indian study conducted by Singh S and Gupta K 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. This infers 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.

Study	Mean Prolongation of Pregnancy in Days	
	Nifedipine Group	**Isoxsuprine**
Kedar et al	22.4±15.6	16.5±14.5
Rayamajhi et al	25.71	19.18
Kalita D et al	31.16±10.2	23.06
Tewari et al	39.26±25.5	25.5±15.75
Present Study	31.68±8.37	27.54±7.38

Table 12. Comparison of Prolongation of Pregnancy in Days

In the present study, successful tocolysis was achieved in 96% with Nifedipine group and 75% 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. (Table 13).
The mean birth weight was slightly more in Nifedipine group (2060 grams vs 1940 grams) as compared to Isoxsuprine group in our study. These results were similar to those reported by Rayamajhi et al study, 2383 grams in Nifedipine and 1940 gms. in Isoxsuprine group. While perinatal mortality was reported in Rayamajhi et al study, none of the babies have died in our study.

Parameters	Rayamajhi et al		Kedar et al		Present Study	
	N	**I**	**N**	**I**	**N**	**I**
Successful tocolysis	81.25%	70%	88%	76%	96%	75%
Mean Birth Weight (Grams)	2383	1940	-	-	2060	1940
Perinatal Mortality	1 (3.33%)	2 (6.66%)	-	-	-	-

Table 13. Comparative Analysis of Outcome of Tocolysis

The maternal side effects observed in our study were less as compared to Kedar et al and Rayamajhi et al study (Table 14).

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. Clinical trials with Nifedipine have reported either an insignificant decrease in blood pressure or no change in maternal heart rate or transient hypotension, which resolves spontaneously in most patients without evidence of prolonged maternal and foetal symptoms.

Side Effects	Rayamajhi et al		Kedar et al		Present Study	
	N (%)	I (%)	N (%)	I (%)	N (%)	I (%)
Tachycardia	18.75	26.66	23	28	3.33	6.67
Hypotension	18.75	13.33	20	36	-	13.33
Pulmonary Oedema	-	3.33	-	2	-	-
Headache	6.67	3.33	30	12	-	-
Flushing	3.33	-	40	34	16.66	-
Nausea & vomiting	3.33	3.33	10	34	-	-

Table 14. Comparative Analysis of Maternal Side Effects

CONCLUSION

Prematurity continues to be the major contributor to the prenatal morbidity and mortality. Prevention and treatment of preterm labour is essential to reduce adverse neonatal and infant outcome and to improve survival and quality of life. These approaches will have great impact on society and long term public health care costs. Tocolysis remains the predominant modality for the treatment of preterm labour. None of the currently available tocolytic agents are ideal. Calcium channel blocker (Nifedipine) are safer and more effective than betamimetics. The present situation, more achievable goal of tocolytic therapy is to delay delivery for at least 48 hours, an important interval during which the mother may be transferred to a tertiary centre for delivery, administer corticosteroids to the mother as well as to treat maternal infection when present. These measures have shown to reduce neonatal morbidity and mortality and aggressive pursuit of these achievable goals may be expected to lead to further improvements in neonatal outcome. Our study found a favourable outcome with Nifedipine in this aspect. In the view of increasing evidence of efficacy and safety, combined with its ease of administration, it appears likely that Nifedipine will play an expanded role in the suppression of preterm labour. Nifedipine is a better tolerated, more effective and safe tocolytic agent than Isoxsuprine with few maternal complications.

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