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Original Article

Suppression of Pre-term Labour: A Comparative Study Between Isoxsuprine And Nifedipine"

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ABSTRACT

BACKGROUND: Preterm labour and delivery remains a major cause of perinatal morbidity and mortality. Tocolysis, the pharmacologic inhibition of uterine contractions, is currently the principal preterm birth preventive measure and will remain so until the aetiology of preterm labour is better understood. OBJECTIVES: To compare the tocolytic efficacy of parenteral and oral Isoxsuprine with oral Nifedipine in the suppression of preterm labour. Maternal side effects and neonatal outcome were also evaluated. METHODS: This is a prospective randomised study. 60 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) 30 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. Mean prolongation of pregnancy was 31.68 days in Nifedipine and 27.54 days in Isoxsuprine group which was statistically significant. 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.

CONCLUSIONS: Nifedipine is a better tolerated, more effective and safe tocolytic agent than Isoxsuprine with few maternal complications.

1. Introduction

Despite improvements in obstetric care over the past three decades, the incidence of preterm birth remains unchanged. There are no accurate recent worldwide data but estimates of preterm birth range from a relative stable 5-10%[1] in developed countries to as high as 25% in some of the worst hit developing countries. Preterm labour and delivery is one of the biggest challenges for obstetricians and so are the preterm babies for the paediatricians[2]. Increasing rates of preterm labour could be due to artificial reproductive techniques, psycosocial stress or medically induced prematurity[2].

Preterm delivery affects 11%in US[3] or even greater in developing countries(23.3%) in india[4].These birth represent more than 70% of all perinatal morbidity and mortality. The mainstay of hospital therapy has been the use of tocolytic agents.Tocolytic use is justified in woman with preterm labour because they will stop contractions and preterm delivery in 75-80% of patients for 48-72hrs for steroid action which decreases respiratory distress in the neonate ultimately improving the neonatal outcome.

This study was done to compare the efficacy and side effects of two widely used tocolytic agents nifedipine and isoxsuprine in a tertiary centre of south india.

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2. Material and method

Source of data:

This is a prospective cohort study, carried out in the department of Obstetrics and Gynaecology of Sree Siddhartha Medical College and Research centre, Tumkur over a period of 18 months- from January 2009 to June 2010. Written informed consent was taken from the subjects recruited in the study. 60 antenatal cases with 28-36 weeks of gestation with painful intermittent uterine contractions are considered for the study. The following inclusion criteria were satisfied, after which they were randomly allotted into two groups- Group A (Isoxsuprine) and Group B (Nifedipine).

Antenatal woman with gestational age between 28-36 weeks, having 1-2 regular uterine contractions occurring in 10 min, each lasting for 30 seconds, Cervical effacement of more than 80% and with dilatation of less than 3cms with intact membranes and with no previous administration of tocolytics were included in the study.

Female patients with systemic diseases like diabetes mellitus, cardiac diseases, liver or renal diseases, obstetric complications like severe pregnancy induced hypertension, eclampsia, antepartum haemorrhage, hydramnios, hyperthyroidism, foetal complications like chorioamnionitis, IUGR, congential anomaly, foetal distress, oligoamnios,multifoetal gestation were excluded from the study.

A detailed history, complete physical and obstetric examination and routine investigations were done for all the patients. Patients randomly allotted into two groups- Group A (Isoxsuprine) and Group B (Nifedipine). Those patients assigned to Isoxsuprine group, started on Isoxsuprine infusion of 30- 60 mg in 500 ml of 5% dextrose at 0.02 mg/min, increasing the infusion rate up to 0.08 mg/min, dose administration did not exceed 0.5 mg/min, depending on the status of uterine contractions and occurrence of side effects. After discontinuation of i.v infusion, patients maintained on oral Isoxsuprine 10 mg 8 hourly for up to 7 days.

Those assigned to Nifedipine group, received prehydration with intravenous infusion of ringer lactate at the rate of 100 ml/hr, continued only till oral Nifedipine was administered. Nifedipine 10 mg was given oral, and the same dose was repeated every 20 mins for up to 4 doses. 4-6 hrs after the last dose, tablet Nifedipine 10-20 mg was given orally every 6-8 hrs, for not more than 7 days as a maintenance dose.

Patients in both groups were given antibiotics and injection betamethasone 24 mg in 2 divided doses, 24 hrs apart. Uterine contractions, foetal heart rate and vital signs were monitored in both the study groups. Side effects are noted from the time of administration of drug till the patient was discharged from the labour ward.

Treatment was considered successful, if there was abolition of uterine contractions, no progression of cervical dilatation, and also if contractions did not recur with in 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.

3. Results

Out of the 60 women with singleton pregnancies who enrolled for the study, 30 were assigned to Isoxsuprine group and 30 to Nifedipine group after randomization. In the present study, primigravidae were more in Isoxsuprine group (56.67%) as compared to Nifedipine group (46.67%).

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 [Table-1]. There is no statistically significant difference in both study groups with respect to gestational age.

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 -2].

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[Table -3].

In the present study, mean birth weight of infants delivered is 2.06 kgs in Nifedipine group with apgar scores of >7 at 1' and 5' are 84% and 100% respectively. In Isoxsuprine group, infants delivered had mean birth weight of 1.94 kgs with apgar scores of >7 at 1' and 5' are 41.66% and 83.33% respectively.

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. No other serious side effects noted in both groups[Table -4].

In present study, there is higher incidence of RDS in Isoxsuprine group about 20% (6 infants) as compared to Nifedipine group (0%), while foetal tachycardia was observed in 9 infants delivered in Nifedipine group as compared to Isoxsuprine group (6 infants). All 6 babies in Isoxsuprine group had mild RDS and were in NICU for nearly 5-6 days and were discharged with the mother.

In our study Nifedipine group has highest success rate of 96% and failure rate of 4%. In this study group one patient delivered within 48 hours of cessation of therapy. Where as in Isoxsuprine group, success rate was noted in 75% and failure in 25% of patients. Out of 6 failure patients noted in this group, 5 patients had significant fall in blood pressure that necessitated discontinuation of the therapy (out of 5, 4 patients developed hypotension and 1 had significant fall in blood pressure); and in 1 patient the drug failed to arrest uterine contractions at the end of loading dose[Table 5].

Table No.1: Distribution of the patients according to gestational age at admission (n=60)

Gestational age (weeks)	Isoxsuprine group No. of patients	Percentage	Nifedipine group No. of patients	Percentage
28-30	08	26.66	09	30.00
31-32	13	43.34	10	33.33
33-36	09	30.00	11	36.67
Total	30	100	30	100
Mean	31.62		31.9	
Minimum	28		28	
Maximum	35		36	
SD	1.91		1.93	

Table. 2 Total duration of prolongation of pregnancy in days

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 No.3: Gestational age at delivery in weeks

Gestational age at delivery (weeks)	Isoxsuprine group No	Percentage	Nifedipine group No	Percentage
<37	10	33.33	05	16.66
≥37	14	46.67	20	66.68
Lost to follow up	06	20	05	16.66
Total	30	100	30	100

Table No.4: Maternal side effects

Side effects	Isoxsuprine group No	Percentage	Nifedipine group No	Percentage
Tachycardia≥110bpm	02	6.67	01	3.33
Headache	00	0	00	0
Hypotension <90/60	04	13.33	00	0
Nausea	00	0	00	0
Vomiting	00	0	00	0
Facial flushing	00	0	05	16.66

Table No.5: Results of treatment in the study groups:

	Isoxsuprine group No. of patients	Percentage	Nifedipine group No. of patients	Percentage
Success	18	7	24	96
Failure	06	25	01	4
Total	24	100	25	100

Table 6:- Comparison of prolongation of pregnancy in days

Study	Mean prolongation of pregnancy in days Nifedipine group	Isoxsuprine group
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 7: - Comparative analysis of outcome of tocolysis

Parameters	Rayamajhi et al N	I	Kedar et al N	I	Present study 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 8:- Comparative analysis of maternal side effects

Side effects	Rayamajhi et al N(%)	I(%)	Kedar et al N(%)	I(%)	Present study 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	-	-

4. Discussion

Determination of efficacy and safety of tocolytic agents has been a difficult task because the cause of preterm labour is generally unknown. Therefore 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. Patients were included into the study group in which uterine contractions continued even after complete bed rest. This could reduce the number of patients in false

labour being included in the study.Since the late 1970's Nifedipine has been known to relax the pregnant and non pregnant uterus (Ulmsten, Anderson KE)[5].

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)[6] Kalita D et al (1998),[7] Rayamajhi R et al (2003)[8], singh nisha(2009)[2].

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 Isoxsuprine. Kedar M G et al[6], Kalita D et al[7] , Rayamajhi R et al[8] and singh nisha et al[2] have conducted studies about comparison between the efficacy and safety of Nifedipine and Isoxsuprine in the suppression of preterm labour.

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[Table 6]. These results were similar to those reported by Kalita D et al[7] 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[6] reported mean prolongation of pregnancy as 22.4 ± 15.6 days with Nifedipine and 16.5 ± 14.5 days with Isoxsuprine. Rayamajhi et al [8]reported mean prolongation of pregnancy as 25.71 days with Nifedipine and 19.18 days with Isoxsuprine. Tewari et al[9] reported mean prolongation of pregnancy as 39.26 ± 25.5 days with Nifedipine and 25.5 ± 15.75 days with Isoxsuprine.

Indian study conducted by Singh S and Gupta K[10] 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 96% with Nifedipine group and 75% with Isoxsuprine group[Table 7]. 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 and Rayamajhi et al study[Table 8]. 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 of prehydration in the nifedine regime.

5. Conclusion

Prematurity continues to be the major contributor to the perinatal morbidity and mortality. The approaches which prevent and treat preterm labour will have great impact on society and long term public health care costs. None of the currently available tocolytic agents are ideal. Calcium channel blocker (Nefidipine) are safer and more effective than betamimetics. The measures taken to prolong pregnancy have shown to reduce neonatal morbidity and mortality. Our study found a favourable outcome with Nifedipine in this aspect (96% vs 75%). 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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