SUPPRESSION OF PRETERM LABOR : COMPARISON BETWEEN NIFEDIPINE AND ISOXSUPRINE

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SUMMARY

Forty cases of preterm labor between 24-35 weeks were randomly divided into two groups. 20 were given nifedipine and the rest were given isoxsuprine. Both the groups were well matched regarding their demographic status. We compared the efficacy of both these drugs as tocolytics and also compared the maternal and fetal side effects and neonatal outcome. Delivery was prolonged for 23.2 ± 16.8 days by nifedipine as compared to 14.5 ± 18.4 days by isoxsuprine. Maternal side effects were more common and more serious in the group which received isoxsuprine as compared to those which received nifedipine. However fetal and neonatal outcomes appeared to be similar.

INTRODUCTION

Of all the major problems in medical care, none has experienced such dramatic progress during the past decade as has the management of preterm birth and its sequelae. Paradoxically the almost miraculous progress in survival of very preterm births has in turn bred a whole new set of problems as more and more infants survive after being born at lower and lower birth weights. Hence we at the Nowrosjee Wadia Maternity Hospital decided to tackle preterm labour by using a relatively new drug, Nifedipine, a dihydropyridone calcium entry blocker and comparing its tocolytic effectiveness and also maternal, fetal, neonatal effects with a well known tocolytic, isoxsuprine, which is widely used in India.

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MATERIALS AND METHODS

This study was conduced at the Nowrosjee Wadia Maternity Hospital during the year August 1992 to January 1993. Forty cases of preterm labour with a gestational age between 24-35 weeks were randomly

allotted to two groups.

Patients with the following maternal factors were excluded : Diabetes, hyperthyroidism, Cardiac disease, severe PIH or Eclampsia, abruptio placentae, chorioamnionitis, multiple pregnancy, hydramnios, cervical dilatation more than 4 cms. The fetal factors considered for exclusion were fetal distress, severe IUGR, dead fetus and fetal anomaly incompatible with life. The patients detailed history was taken, followed by a through examination including General examination and Obstetric examination. A vaginal examination was carried out taking all aseptic precautions. Patients were then observed for 30 minutes during which time frequency, and duration of uterine contractions and fetal heart rates were monitored.

To patients receiving Nifedipine, an intravenous infusion of Ringer Lactate solution at the rate of 100 ml/hr was infused after a bolus of 200 ml. Intravenous infusion was continued only till sublingual Nifedipine was administered. Nifedipine was given 5 mg sublingual. If uterine contractions persisted after 15 minutes, 5 mg S. L. Nifedipine was repeated upto a maximum of 8 doses (40 mg) during the first two hours of treatment. If uterine activity did not cease after two hours, the patient was deemed as a failure and treatment stopped. If sub-lingual Nifedipine stopped uterine activity, then oral therapy of 10 mg 8 hrly was initiated 3 hrs after the last sublingual dose. This was continued for 3 days. Before each sublingual or oral dose, maternal vital signs and fetal heart rate was also monitored along with the uterine activity. If the maternal pulse, B.P. were not within the normal range, the next dose was withheld and symptomatic treatment started. Patient was examined every 5 minutes until she was settled. If the fetal heart rate was not within 110-150 beats/min, therapy was with-held and patient was subjected to a NST and treated accordingly.

Those patients to be treated with Isoxsuprine were given a loading dose of 0.2 mg/min over 10 minutes and the dose was later adjusted according to maternal pulse and B.P. The maintainence dose was 75 ug/min over 24 hours. Subsequently patients received injectable 10 mg 8 hrly for 2 days followed by oral for 2-3 weeks.

Patients in both groups were given head low position and Injection dexamethasone 12 mg IM 12 hrly for 4 doses and Injection phenergan 25 mg IM as a sedative so as to ensure complete rest. Prospective controlled clinical trials have all shown a reduction in the incidence of RDS when glucocorticoids are given to the mother more than 24 hours and less than 7 days before birth (Liggins et al 1972) Patients who had recurrent preterm labor in both groups were treated with the same drug used initially as per the schedule followed earlier.

In both groups, our goal for tocolysis was to delay delivery till 36 completed weeks of gestation or atleast 48 hrs till dexamethasone given would help to decrease HMD. Treatment failure was said to exist if, despite maximal dose mentioned of both, uterine relaxation was not achieved or patient/fetus developed some significant side-effects that necessitated discontinuation of therapy. Side-effects were noted. Further date regarding type, mode of delivery, gestational age, baby's sex, weight, Apgar scores, general examination of neonates was recorded. Neonates were followed till they were discharged.

OBSERVATIONS

The patients in both groups were well matched regarding age, antenatal care, gravidity, previous obstetric history and socio-economic status. (Table I)

Mean gestational age at time of study was 31.3 ± 3.4 weeks in Nifedipine group

Table I

Clinical Parameters

	Nifedipine	Isoxsuprine
Age (Years)	23.1 ± 3.8	22.8 ± 4.2
Parity		
Primidravida	7	8
Multigravida	13	12
Gestation at treatment (weeks)	31.3 ± 3.4	31.4 ± 2.2
Mean prolongation of delivery (Days)	23.2 ± 16.8	14.5 ± 18.4

and 31.4 ± 2.2 weeks in Isoxsuprine group. The maximum prolongation in Nifedipine group was 40 days as compared to 56 days in Isoxsuprine group. The man prolongation in Nifedipine was 23.2 ± 16.8 days as compared to 14.5 ± 18.4 days in Isoxsuprine group. Hence Nifedipine gave a success rate of 85% as compared to Isoxsuprine which successful in 75% of cases (Table II).

As regards side-effects of both tocolytics, Nifedipine patients experienced much fewer side-effects as compared to Isoxsuprine group. Although both group patients experienced hypotension, it was very significant (average fall 10-15 mm diastolic) in Isoxsuprine group. Nifedipine caused mild to moderate headache in 5 patients. The most common side-effects of Isoxsuprine was chest pain, nausea and vomiting. It was experienced by more than 50% of patients in varying grades. Only two patients required stopping the infusion to alleviate the symptoms. Rest were relieved by reducing the infusion rate. (Table III)

The mean birth weight was 2.0 ± 0.55 Kg in Nifedipine group as compared to 2.1 ± 0.40 Kg in Isoxsuprine group.

Table II

Pregnancy Outcome in Treatment Groups

	Nifedipine (n = 28)	Isoxsuprine (n = 20)
Success	17 (85%)	15 (75%)
Failure	3 (15%)	5 (25%)

Table III

Side Effects

	Nifedipine	Isoxsuprine
Tachycardia	1 (5%)	10 (50%)
Headache	5 (25%)	7 (35%)
Hypotension	3 (15%)	10 (50%)
Nausea	3 (15%)	4 (20%)
Vomiting	1 (5%)	5 (25%)
Hot Flushes	2 (10%)	4 920%)
Host Flushes	2 (10%)	4 (20%)
Chest Pain	0 (0%)	3 (15%)

Table IV

Perinatal Complications

	Nifedipine	Isoxsuprine
Fetal Tachycardia	4 (20%)	5 (25%)
R. D. S.	2 (10%)	4 (20%)
Hyperbilirubinemia	2 (10%)	2 (10%)
Septicaemia	0 (0%)	1 (5%)

There were 2 cases of RDS in Nifedipine group as compared to 4 cases in Isoxsuprine group. There were 2 cases of hyperbilirubinemia in each group. There was only one case of septicaemia in Isoxsuprine group (Table IV). There was no significant difference in Apgar scores of babies in both groups. There was only one neonatal death in Nifedipine group as compared to 3 deaths in Isoxsuprine group.

DISCUSSION

Preterm labor is defined as regular uterine contractions at a frequency of eight or more per hour with a documented change in cervical dilatation or effacement before 36 completed weeks of gestation.

Over the past 15 years a number of drugs have been used to suppress uterine activity, either alone or in combination. Intravenous ethanol has fallen into disuse because it caused troublesome nausea, vomiting, hangovers and it was less effective than Beta sympathomimetic drugs (Lauerson et al 1977). Beta sympathomimetic drugs although proved useful have been proved not to have any therapeutic value in light of high incidence of side-effects also they were not suitable for women with significant cardiovascular disease or diabetes. (Hemminki et al 1978; Spellacy et al 1979).

Activity in uterine muscle, in vitro, is dependant upon extracellular calcium (Bolton 1979) so that it would be anticipated that contraction would be inhibited by calcium antagonists. Nifedipine, a dihydropyridone calcium entry blocker, may represent an attractive therapeutic alternative to the Beta adrenergic agents. It has a well known relaxing effects on the myometrium and it exhibits greater selectivity for inhibition of uterine activity relative to its cardiovascular effects. (Granger et al 1985)

Brazy et al 1979 reported that high concentration of Isoxsuprine increases the neonatal risk of ileus, hypotension and neonatal death. In our study with Nifedipine we found transient fetal tacchycardia which was first reported by Read MD 1986. Further, theoretically there is a possibility of negative influence on fetal myocardial performance during labor. (Nayler WG 1983)

For Beta sympathomimetics and Calcium antagonist the dose limiting factor is the drug induced impairment of the atrio-ventricular conduction. Nifedipine has fewer-effects on atrio ventricular conduction and has more specific effects on myometrial contractility. Significant inhibition of uterine activity is seen both in pregnant and non-pregnant women. It also reduces the amplitude of uterine contraction. (Andersson K. E. 1977) Hence our study shows that Nifedipine is not only more effective in preventing Preterm labor but also safer for both mother and the fetus as compared to Isoxsuprine. Because of the small number of patients involved, we believed a further study is warranted, preferably as a co-ordinated multi-centre trial.

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