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COMPARATIVE STUDY OF THE EFFICACY OF NIFEDIPINE AND ISOXSUPRINE AS TOCOLYTICS FOR PRETERM LABOUR

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ABSTRACT

Background: A retrospective study was conducted to compare the efficacy of nifedipine against isoxsuprine in preventing preterm labour and also to evaluate maternal side effects and neonatal outcome. Methods: This was a retrospective comparative study done at BRIMS Teaching Hospital Bidar by scrutinizing the in patients case sheets from Medical Record Department, from June 2015 to Aug 2015. 100 antenatal women with gestational age between 28 to 36 weeks fulfilling the inclusion criteria and who received Nifedipine and Isoxsuprine were compared. Results: Groups were compared with mean prolongation of delivery, side effects, neonatal outcome, parity, cervical effacements. It was found that Nifedipine was twice more effective than isoxsuprine hydrochloride as a uterine tocolytic agent while side effects were comparable with fewer side effects in nifedipine group in comparison to Isoxsuprine. Neonatal outcome was also better with nifedipine in comparison to isoxsuprine. Conclusions: The present study found that nifedipine was better tocolytic agent with lesser side effects and better tolerability as compared to isoxsuprine.

Keywords: Preterm labor, Tocolytics, Nifedipine, Isoxsuprine hydrochloride, Ritodrine.

INTRODUCTION

Preterm birth the major cause of neonatal morbidity and mortality complicating about 10% of all pregnancies. Mortality rate after 32 weeks of gestation are same as those at term [1]. Therefore it is the preterm deliveries at greatest risk of neonatal morbidity and mortality, accounting to 1-2 percent of obstetric population [2]. There are no accurate recent worldwide data but estimates of preterm birth range from a relative stable 5-10% in developed countries to as high as 25% in some of the worst hit developing countries [3].

Tocolytic therapy to delay preterm delivery is an important intervention in obstetric. Although tocolytics help us to delay the preterm delivery, but have not shown to improve neonatal outcomes [4]. Use of antenatal corticosteroids reduce the morbidity and mortality [5].

Determination of efficacy and safety of tocolytic agents has been difficult task. Ritodrine, beta sympathomimetic is one such agent which was commonly used as tocolytic. It has serious maternal and fetal side effects, limiting its use [6]. Beta adrenergic receptor blocking agent isoxsuprine and nifedipine, a calcium channel blocking agent is the most widely used tocolytic agent in India [7]. Several trials suggest that nifedipine is effective in suppressing preterm labor with minimal side effects on the mother and fetus [6,8-10]. Nifedipine is an effective smooth muscle relaxant with low toxicity and low teratogenicity [11]. This retrospective study was designed to find out the safety, efficacy and perinatal outcome of Isoxsuprine and Nifedipine in women with preterm labour.

METHODS

This was a retrospective study of 100 antenatal women conducted at BRIMS teaching hospital, Bidar in the department of OBG. The **Inclusion criteria** in the study were between 28-36 weeks of gestational age and four uterine contractions in 20min with or without cervical dilatation more than 1cm or effacement 80% or greater were recruited in the study as per the ACOG criteria. **Exclusion criteria** were patients with more than 36 completed weeks, those in active labour (>4cm dilatation), those with severe pregnancy induced hypertension, eclampsia, gestational Diabetes mellitus, cardiac disease, Abruptio placenta, chorio-amnionitis, fetal distress, fetal anomaly, hyperthyroidism, multifetal.

TREATMENT PROTOCOL

For group1: Pregnant women were given 20mg oral nifedipine initially followed by 10mg at four hour interval for 48 hour. If contractions persisted at 90min, the first 10mg dose was started at the same time.

For group 2: Patient were started on infusion of injection isoxsuprine 40mg in 500ml ringer lactate at 0.08mg/min, increasing the infusion rate up to 0.24mg/min depending on the status of uterine contractions and occurrence of side effects. After discontinuation of intravenous infusion, patient's were maintained on oral isoxsuprine 10mg eight hourly for upto 7 days. Either of the treatment was discontinued if no uterine contraction occurred within 48 hours.

During this period vital signs, uterine contractions and fetal heart sound were monitored half hourly and side effects were noted until the patient was

discharged and started on maintenance doses. All patients received injection Betamethasone 12mg intramuscularly for two doses 24hours apart, to enhance fetal lung maturation. Patients were followed up weekly for cervical dilatation till 37 weeks. Goal of tocolysis was to delay delivery for 24hours, in patient with ruptured membranes. Tocolysis was considered failed if uterine relaxation was not achieved despite maximum dose and delivery occurred within 48hours. Data regarding mean prolongation of pregnancy (at 48hour, 1 week, 37 weeks), side effects, failure of treatment, gestational age at delivery and neonatal death were recorded.

RESULTS:

During the retrospective study, 50 women who received oral Nifedipine and 50 women who received oral Isoxsuprine, following results were found.

In group I, 90% of patient was primigravida with mean age of 23.2 ± 5.5 Yrs and with mean gestation at treatment was 30.4 ± 3.5 weeks and mean prolongation of delivery was 23.2 ± 15.7 days where as with the isoxsuprine in group II patient mean prolongation of delivery was 17.2 ± 15.4 days.

From Table 2, we conclude that 90% success rate was seen in group I while the success rate in group II was only 76%.

Nausea, vomiting and headache were main side effects in both the group. Incidences of 40%, transient hot flushes was seen in group A than in group B. Pulmonary edema was reported in one case with isoxsuprine, following which therapy was discontinued. Hypotension and tachycardia were commonest maternal side effects.

Table 1: Mean prolongation of delivery

	Nifedipine	Isoxsuprine
Age (Years)	23.2 ± 5.5	24.4 ± 4.6
Parity		
i. Primigravida	45 (90%)	42 (80%)
ii. Multigravida	5 (10%)	8 (20%)
Gestational Age in weeks	30.4 ± 3.5	31.3 ± 2.8
Mean Prolongation of delivery	23.2 ± 15.7	17.2 ± 15.4

Table 2: Pregnancy outcome

	Nifedipinen (%)	Isoxsuprinen (%)
Success	45 (90%)	38 (76%)
Failure	5 (10%)	12 (24%)
Total	50 (100%)	50 (100%)

n= number of patients.

Table 3: Side effects

	Nifedipinen (%)	Isoxsuprinen (%)
Hypotension	10 (20%)	18(36%)
Tachycardia	38 (76%)	25 (50%)
Headache	15 (30%)	6 (12%)
Hot flushes (transient)	20 (40%)	19 (39%)

Nausea/Vomiting	5 (10%)	17 (34%)
Chest pain	2 (4%)	5 (10%)
Pulmonary edema	0 (00%)	1 (2%)

DISCUSSION

Incidence of preterm labor is quite high in India compared to developed countries (11% in USA). Obstetricians face the challenge of managing an established preterm labor with pharmacological agents, which differ in uterine specificity, efficacy and side effects both maternal and fetal. These tocolytic drugs inhibit uterine contractions and relax the uterine myometrium by different mechanisms leading to arrest of preterm labor. 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 blockers are safer and more effective than betamimetics. The measures taken to prolong pregnancy have shown to reduce neonatal morbidity and mortality. This retrospective study was designed to find out the safety, efficacy and perinatal outcome of Isoxsuprine and Nifedipine in women with preterm labour.

Cochrane review 2004¹² on preterm labor concludes that tocolysis is definitely indicated before 34 weeks gestational age. This is because of the reduction in number of women delivering within next 7 days and resultant decrease in neonatal morbidity from RDS, necrotizing enterocolitis, intra-ventricular hemorrhage and neonatal jaundice.

Most of the studies so far conducted have compared the efficacy and safety between Nifedipine and Ritodrine. Only few studies have been done between Nifedipine and Isoxsuprine. Kedar MG et al, Kalita D et al, Rayamajhi R et al, Singh N, Seema BN et al, Prerana Jain et al have conducted studies about comparison between the efficacy and safety of Nifedipine and Isoxsuprine in the suppression of preterm labour [6,13-18].

The mean prolongation of pregnancy in the present study was 23.2 days with nifedipine and 17.2 days

with isoxsuprine. Kalita et al reported mean prolongation of pregnancy as 31.16 days with nifedipine and 23.06 days with isoxsuprine [14].

In this study, there was no significant difference in maternal and neonatal side effects but lesser side effects was seen with nifedipine. Ferguson, Meyer, Kupfermine and Papatsonis all found nifedipine to have lesser maternal side effects as compared to isoxsuprine. Similar results were seen with Kalita et al who reported lesser maternal side effects with nifedipine then with isoxsuprine [8,9,14,19].

Incidence of tachycardia were seen in both the groups which was similar to that of Tewari et al [20]. In the present study, transient hypotension, nausea, vomiting, tachycardia, chest pain, headache in 20%, 10%, 46%, 4%, 30% in nifedipine group. Headache was more in nifedipine group as seen in present study similar to Rayamajhi et al.¹⁵ In this study, cardiovascular side effects were more seen in isoxsuprine group which was comparable to the study of Read and Wellby [21].

The RCOG recommends that if a tocolytic drug is to be used, ritodrine is no longer the first choice [22]. Atosiban and nifedipine appear to be preferable as they have lesser adverse effects and seem to have comparable effectiveness. The experience with nifedipine as a tocolytic has been found to be encouraging in view of the increasing evidence of its efficacy and safety combined with its ease of administration.

CONCLUSION

Nifedipine was found to be more effective than isoxsuprine in this study. Significant difference can be seen in success rates among the two tocolytics agents, indicating thereby that early initiation of tocolysis with nifedipine is definitely beneficial in cases of preterm labor.

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