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A RANDOMIZED CONTROLLED TRIAL OF ORAL NIFEDIPINE AND PARAENTRAL ISOXSUPRINE IN ARRESTING PRETERM LABOUR

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AUTHORS' CONTRIBUTIONS
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In our study the success rate of Isoxsuprine was slightly more as compared to Nifedipine group but the maternal and foetal side effects were more in Isoxsuprine group. Nifedipine is better tolerated drug as compared to Isoxsuprine. Study involved 80 patients with the diagnosis of preterm labour with the gestational age of 28-36 weeks. 40 were assigned to Nifedipine and 40 to Isoxsuprine group. Drugs were administrated according to protocol. Patients were followed up till delivery and outcome parameters measured. Preterm labour was found to be more common in women from rural area and with low socioeconomic status.

Keywords: Nifedipine; isoxsuprine; tocolysis; preterm labour; tocolytic.

1. INTRODUCTION

Over the last 50 years, extensive research has been conducted with the objective of preventing, predicting and optimizing the outcome of patients with preterm labour. The therapeutic Foundation for treating preterm labour involves the use of tocolysis [1]. Beta-agonists, like isoxsuprine, ritodrin, phenotrol, salbutamol, and terbulin, are utilized in the suppression of preterm labor showing effective neonatal outcomes [2]. It is pertinent to point out that these drugs are used for arresting preterm labour regardless of the specific aetiology contributing to the event. Recent advance in neonatal intensive care technology have led to increase in number of infants surviving preterm delivery even at the margins of viability [3]. Economic assessment revealed an inverse relationship between costs during the neonatal period and gestational age at birth.

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2. AIM AND OBJECTIVES

2.1 Aim

To compare the efficacy of oral Nifedipine and parentral Isoxsuprine in arresting preterm labour.

2.2 Objectives

To study the efficacy of oral Nifedipine and parentral Isoxsuprine in arresting preterm labour. To study maternal side effects after treatment. Foetal outcome after treatment. To study causes of preterm labour.

3. REVIEW OF LITERATURE

Despite improvements in obstetrics care over the past three decades, the incidence of preterm birth remains unchanged even in the industrialized world. The theoretic principle which guides the prescriptions of tocolytic is that, if contractions are stopped, preterm delivery can be stopped. An alternative approach to preterm labour is to identify and treat the aetiology for preterm contractions. After years of controversies in tocolytic therapy, it should be emphasized that the purpose of tocolytic use is not the prevention of preterm delivery, but a temporizing therapy to improve neonatal outcome. The nature of tocolysis is to palliate symptoms; it is neither a treatment nor prevention. Tocolytics stop contractions. Contractions are not the cause of preterm labour, they are one of the last steps in a complex series of biochemical and hormonal alterations. To prevent preterm delivery, a physician must treat the initiating aetiology. Tocolytic use is justified in women with preterm labour because they will stop contractions and prevent delivery in 70% patients for 48-72 hours. Temporarily allows for the interventions which can improve the perinatal outcome.

Abarmson and Reid [4] in 1955 reported on the use of relaxin in the treatment of threatened preterm labour. Among 5 cases treated at 29 to 31 weeks gestation all delivered within the range of 36-40 weeks of pregnancy, a 100 percent success rate. In 1955 Majewski and Jennings [5] reported on the use of a uterine relaxing agent presumably relaxin, administered for the suppression of established preterm labour. In their initial report they found that drug would suppress labour in 16 out of 20 cases (80% success). Two years later they reported an extended series in which success rate dropped to 68.4%. [6] In 1961, the first non-selective betamimetic tocolytic agent, isoxsuprine was proposed for the treatment of preterm contractions [7,8]. The need to develop safe and effective alternatives to beta mimetic agents led to a re-evaluation of tocolytic effects of magnesium sulphate during the early 1980s.Obstetrician in the United states had a long standing familiarity and presumed margin of safety with magnesium therapy and were aware of the drug‟s potential tocolytic effects from the treatment of eclamptic patients. The terms, foetal growth restriction, or intrauterine growth restriction, are also used to explain the same. SGA infants may be preterm or post term. Infants with somatic growth or birth weight above 90th percentile for his or her gestational age are termed Large for Gestational Age (LGA).

A predominant source of confusion, particularly in evaluating the effectiveness of tocolytic drugs is the definition of preterm labour. The different criteria used by different clinicians to diagnose preterm labour create difficulty in comparing different clinical trials. In an attempt to overcome this problem, a set of criteria have been proposed that are becoming increasingly accepted [9]. The incidence of threatened preterm, because of problems of definition is not available but is likely to be higher than that of spontaneous preterm delivery. In one study 1/3rd of women with preterm uterine activity went home undelivered within 48 hrs [10]. In most trails of tocolysis, where preterm uterine activity is the only entry criterion, more than 50% of pregnancies deliver after 37 weeks. In a study by Lams et al [11] the length of the cervix was found to be closely correlated with the risk of preterm delivery throughout the range of lengths. A woman‟s risk was particularly high if the length of the cervix was below the 10th centile for the entire group. Using a cut off of 25 mm or less between 20-24 weeks of gestation, It was found to be an accurate test in predicting spontaneous preterm birth before 37 weeks gestation in asymptomatic pregnant women with an positive likelihood ratio of 25.61 & negative likelihood hood ratio 0.47 [12]. It seems that ultrasonographic cervical measurement can increase the ability to predict spontaneous birth prior to 35 weeks in high risk women [13]. In asymptomatic singleton pregnancies an estriol level of 2.3 ng/ml was found to be optimal cut-off for predicting women at risk for preterm labour with a sensitivity of 71%, specificity of 77% & positive predictive value of 23%. The post test probability of a pre term birth less than 35 weeks of gestation was 58.8% if both tests were positive and it is clear that this is more likely to influence clinical decision making [14]. Leitich et al [15] demonstrated in their meta analysis a powerful association between second trimester bacterial vaginosis and pre term birth. Early treatment (< 20 weeks) may be the key to prevention of pre term birth before the abnormal bacterial invade the upper genital tract and initiate the cascade of the events preceding pre term birth. Goodwin (2004) has

reviewed the history of atosiban both in United states & in Europe where this drug is approved for use & is widely used as a tocolytic [16].

Use of corticosteroids in circumstances where preterm delivery is expected or imminent is of proven value and is strongly recommended in all such circumstances unless there are specific contraindications. Administration of maternal steroids causes many effects in the foetus leading to increased maturation. These are major effects on the foetal lung, (surfactant production and structural), gastrointestinal and central nervous systems.

4. MATERIALS AND METHODS

This is a prospective study, carried out in the Department of Obstetrics and Gynaecology of Krishna Institute of Medical Sciences Deemed University (KIMSDU), Karad over a period of 24 months- from June 2014 to may 2016. Consequently, 80 antenatal cases with 28-35 weeks of gestation with painful intermittent uterine contractions were considered for the study. Sample size was based on the hospital statistics, exclusion criteria and noncooperation of the patients. The subject were enrolled for the study after taking informed consent and the following inclusion criterias were satisfied, after which they were randomly allotted into two groups by odd and even OPD numbers- Group A (Isoxsuprine) and Group B (Nifedipine).

4.1 Inclusion Criteria

Pregnant women with singleton pregnancies, having gestational age between 26 to 34 weeks, with no prior tocolytics administration and with intact membranes. Pregnant women satisfying the said criteria and admitted to KIMSDU.

4.2 Exclusion Criteria

Female patients with systemic diseases such as cardiovascular diseases, diabetes mellitus, urinary infection, etc. Additionally, undergone previous preterm labor, or having obstetric complications such as pregnancy induced hypertension, hydramnios, preterm rupture of membranes, hyperthyroidism, eclampsia, haemorrhage, ante-partum foetal distress, foetal complications like IUGR, congential malformations, chorioamnionitis, multi-foetal gestation, oligoamnios, etc.

3. OBSERVATIONS AND RESULTS

As seen in Table 1, in nifedipine group 47.5% patients and 50% in isoxsuprine group were nulliparous. 52.5% patients were multiparous in nifedipine group and 50% in isoxsuprine group. Were multiparous. There is no significant difference in both study groups with respect to maternal age, gestational age and parity.

As seen in Table 2, 100% patients in both the groups came with complaints of abdominal pain. In Isoxsuprine group 3 patients came with complaints of burning micturation, 2 patients with gastroenteritis and 1 with URTI and 2 with white PV discharge. In Nifedipine group 2 patients came with burning micturation,1 with URTI and 2 with gastroenteritis and 4 patients with white PV discharge.

Table 1. Distribution of patients according to parity

Parity	Isoxsuprine group		Nifedipine group	
	No. of patients	Percentage	No. of patients	Percentage
Nulliparous	19	47.5%	20	50%
Multiparous	21	52.5%	20	50%
total	**40**	**100%**	**40**	**100%**

Table 2. Distribution of patients according to symptoms

Symptoms	Isoxsuprine group		Nifedipine group	
	No of patients	Percentage	No of patients	Percentage
Abdominal pain	40	100%	40	100%
Associated complaints	10	25%	9	22.5%

Table 3. Distribution of patients according to Risk factors for preterm delivery

Risk factors	Isoxsuprine group		Nifedipine group	
	No. of patients	Percentage	No. of patients	Percentage
Previous preterm	4	10%	2	5%
Infections	12	30%	13	32.5%
Abortion	5	12.5%	5	12.5%
Multiple Pregnancy	3	7.5%	2	5%
Cervical Incompetance	4	10%	2	5%
Anemia(<8 gm%)	7	17.5%	3	7.5%
Uterine malformation	2	5%	1	2.5%
Previous S&E	2	5%	3	7.5%
Polyhydraminos	1	2.5%	2	5%
No risk factors found	14	35%	15	37.5%

As seen in Table 3, by applying Z test of difference between two proportions the proportion of risk factors infections, anaemia previous preterm are significantly commonest in both the groups ($p<0.05$). 65% of our study population in both groups had one or the other known risk factor for preterm delivery. Infection was found to be most common risk factor for preterm labour in both groups followed by anaemia, previous preterm delivary and cervical incompetence. In 35% cases no risk factors was found.

As seen in Table 4, by applying Z test of difference between two proportions the proportion of side effects tachycardia and facial flushing is significantly higher in Isoxsuprine group as compared to Nifedipine. ($p<0.05$). Maternal side effects like facial flushing (37.5%), tachycardia (37.5%), palpitations (17.5%), flushing (37.5) hypotension (10%) were common in Isoxsuprine group, while facial flushing was seen in 25% patients and tachycardia in 17.5% in Nifedipine group.

As seen in Table 5, 14 babies were shifted to NICU out of which 9 were having low birth weight and 5 were having RDS in Isoxsuprine group, out of which there were two twins. In Nifedipine group 4 babies were shifted to NICU for low birth weight and 3 for RDS.

Table 4. Maternal side effects

Side effects	Isoxsuprine group		Nifedipine group	
	No. of patients	Percentage	No. of patients	Percentage
Tachycardia (>120bpm)	15	37.5%	7	17.5%
Headache	3	7.5%	2	5%
Hypotension (<90/60 mmhg)	4	10%	0	0%
Nausea	2	5%	0	0%
Vomiting	1	2.5%	0	0%
Facial flushing	15	37.5%	10	25%
Palpitations	7	17.5%	4	10%

Table 5. No. of neonates shifted to NICU

No. of neonates	Isoxsuprine group	Nifedipine group
Low birth weight (< 2 Kg)	9	4
RDS	5	3
Total	14	7

4. DISCUSSION

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. Patients with pain in abdomen but with pv leaking and patients with anomalies and iatrogenic causes of preterm deliveries were excluded from this study which is an important contributor in preterm deliveries [17]. A large no of patients need to be studied for the drug efficacy on a large scale. Poojary et al. [18] has studied comparison between ritodrine, isoxsuprine, nifedipine, glyceryl trinitrate and MgSO4 in suppression of preterm labour its efficacy and safety.

In present study, Nifedipine dose administered was orally well correlated with Singh et al. [18] and Nandaagopal & Shivalingappab [19] as compared to sublingually in Kundu, Saha & Das [20]. While maintenance dose was continued for 3 days in our study and 7 days in [19]. Isoxsuprine loading dosage used in [19] and [20] was higher than used in our study. Nifedipine was administered orally in in our study for loading, due to its ease of administration and also to have a control over administration, if any maternal side effects manifest. Lag time by oral administration can be reduced by taking sub-lingual route. Whereas Isoxsuprine administration over 24 infusions is cumbersome for the patient, as the patient has to lie down in supine position for 24 hours and also for the clinician as administration requires continuous monitoring [21]. Acute stage preterm labour intervention trials have demonstrated that these medications can delay deliveries from 24 to 48 hours, but problems in making the distinction between real and phony research could have had misrepresented the outcomes. Researchers have confirmed that isoxsuprine is suitable for the prevention and management of severe preterm labour. In context of high risk individual births, prophylactic oral isoxsuprine was also foude associated with reduced risks of preterm labour [22].

5. CONCLUSION

Prematurity appears to be the major contributor to perinatal morbidity and mortality. Preventing and treating premature labor is essential to reduce adverse neonatal and infant outcomes and to improve survival and quality of life. Such strategies would have a huge effect on culture and on the long-term expense of universal health services. Tocolysis is the prevailing approach for the management of preterm labor. Neither of the commercially usable tocolytic agents is optimal. Calcium channel blocker (Nifedipine) is better and more efficient than beta-mimetic.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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