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Effect of Maintenance Therapy with Isoxsuprine in the Prevention of Preterm Labor: Randomized controlled trial

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Abstract

Background: Isoxsuprine (Vasodilan) is a beta-adrenergic that directly affects the vascular smooth muscle and results in peripheral vascular dilation. Isoxsuprine relaxes the uterine smooth muscles and is used for treatment of pre-term labor and dysmenorrhea. Isoxsuprine is used extensively in hospitals and private clinics in Iran; however, few studies have reported its safety and efficacy in the prevention of pre-term labor.

Objective: The aim of this study was to assess the effect of maintenance therapy with oral isoxsuprine for the prevention of pre-term labor.

Methods: We undertook a blinded prospective randomized trial of 70 women with singleton pregnancies who presented in pre-term labor between 26 to 34 weeks of gestation. After arresting the contractions with intravenous magnesium sulfate, the patients were randomized into two groups, with the treatment group receiving oral isoxsuprine until 34 weeks of gestation. Response to treatment was assessed by the progression of the pregnancies in both groups. The data were analyzed using SPSS software.

Results: Our results showed that 14 (40%) of the patients in the case group and 12 (34.29%) of patients in the control group had pre-term births, and there was no significant difference between the two groups (P=0.621). Also four women (11.43%) in the case group and five women (14.29%) in the control group delivered before 34 weeks (P=0.721).

Conclusion: Oral isoxsuprine was not effective as a maintenance treatment in preventing pre-term births or in delaying delivery until after 34 weeks. Larger studies are needed to identify the best treatment for pre-term labor.

Clinical Trial Registration: The study is registered in the Iranian Clinical Trial Registry Center (IRCT201101115591N1).

Funding: This study was conducted with financial support provided by the Hormozgan University of Medical Sciences.

Keywords: pre-term birth, tocolytic, isoxsuprine

1. Introduction

1.1. Background

Pre-term labor is defined as delivery before 37 full weeks of gestation (1). In the United States, the incidence is one in every ten births accounting for about 75% of neonatal mortality unrelated to congenital malformations. Unfortunately, the incidence hasn't decreased during the past 40 years. Neonatal morbidity in pre-term labor is expected to decrease with early definite diagnosis and interventions in order to postpone the delivery, including corticosteroid administration and suitable perinatal care (2). Neonatal morbidity and mortality are affected significantly by gestational age and fetal maturity. Death and severe morbidity are associated with births before 26

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weeks of gestation, and they occur almost universally in births before 24 weeks. Another important issue after survival is overcoming the physical and mental disabilities in extremely low birth-weight neonates (3).

1.2. Statement of problem

Many medications are used for preventing pre-term labor, but their effectiveness is not clearly known, and recent studies do not support some of the medications being used for this purpose (4, 5). Beta-agonists, such as ritodrin, terbulin, isoxsuprine, salbutamol, and phenotrol, have long been used in the prevention of pre-term labor with better neonatal outcomes, but further studies are needed for evaluating their efficacy and side effects (5, 6).

Beta-agonists act via beta 2-adrenergic receptors, and they increase intra-cellular cAMP in the myometrium and decrease myometrial contraction (4). Isoxsuprine (Vasodilan) is a beta-adrenergic that directly affects vascular smooth muscle and results in peripheral vascular dilation. Isoxsuprine relaxes the uterine smooth muscles and is used for treatment of pre-term labor and dysmenorrhea. It is absorbed in the gastrointestinal system and is excreted in urine. Its effect is seen within 10 minutes after intravascular use and one hour after oral administration. It is contraindicated in patients who have cardiovascular disease (especially arrhythmias), hyperthyroidism, chorioamnionitis, bleeding, and eclampsia or severe pre-eclampsia (7). Few studies have reported its efficacy and safety in pre-term labor (8), but it is used extensively in hospitals and private clinics in Iran. This may be due to the easier accessibility of this agent in Iran and because the physicians are more familiar with its effects and side effects.

1.3. Objectives

The general objective of this study was to evaluate the safety and effectiveness of isoxsuprine as a maintenance therapy in preventing pre-term labor. The specific objectives were:

1) To compare the proportions of delivery before 37 weeks of gestation in the isoxsuprine group and the no-treatment group
2) To compare the proportions of delivery before 34 weeks of gestation in the isoxsuprine group and the no-treatment group
3) To compare dilatation and effacement 48 hours after treatment in the isoxsuprine group and the no-treatment group
4) To compare dilatation and effacement one week after treatment in the isoxsuprine group and the no-treatment group
5) To compare dilatation and effacement at 34 weeks of gestation in the isoxsuprine group and the no-treatment group

2. Materials and Methods

2.1. Research design and setting

Eighty-one pregnant women (singleton pregnancies) between 26 to 34 weeks of gestation with definite diagnosis of pre-term labor and intact membranes were included in this single-blinded, randomized, controlled trial.

2.2. Ethical consideration

A written informed-consent form was obtained from each of the patients. The study was approved by the Hormozgan Fertility and Infertility Research Center at Hormozgan University of Medical Sciences, and it was registered in the Iranian Clinical Trial Registry Center (IRCT201101115591N1). Also, the study was performed in accordance with the Helsinki Declaration and Consort statements.

2.3. Selection criteria

Patients were assigned randomly into two groups (40 patients in the treatment group and 41 patients in the placebo group). The inclusion criteria were:

1) Pregnant women
2) Single pregnancy
3) Gestational age between 26 and 34 weeks
4) Intact membranes

The exclusion criteria were:

1) Gestational age of more than 34 weeks
2) Pre-term rupture of membranes
3) Chorioamnionitis
4) Placenta previa or abruption

5) Multi-gestational pregnancy
6) Associated systemic disease (pre-eclampsia, diabetes, cardiovascular disease, renal disease, asthma, and hypothyroidism)
7) Congenital malformations
8) Evidence of urinary infection
9) Previous pre-term labor

2.4. Initial proceedings

After admission, all of the patients underwent examination using a sterile speculum. A fern test was done in order to ensure that the membranes were intact. A routine urine analysis (UA) was done to rule out urinary infection. All patients with positive UA received suitable antibiotics after performing a urine culture (UC), and they were excluded from the study. Patients with a negative fern test and uterine contractions present at a frequency of four contractions every 20 minutes or eight contractions in 60 minutes, or dilatation of the cervix exceeding 1 cm or effacement equal to or more than 80% with the diagnosis of pre-term labor and intact membranes were included in the study (1). Contractions were confirmed by a contraction monitor. It wasn't possible for us to measure fetal fibronectin.

All patients received 500 ml of Ringer's solution and 75 mg of intramuscular pethidine for pain relief. Patients who didn't respond to the initial Ringer's solution and pethidine administration received 4 g of magnesium sulfate as a loading dose, which was continued at the rate of 1g/min and then intravenous infusion of 2 g/hr of magnesium sulfate for 12 hr after discontinuation of the contractions. Patients were excluded from the study if the contractions did not stop 2 hr after the administration of magnesium sulfate. Patients were observed for 48 hours if their contractions stopped, and they received two doses of 12 mg of betamethasone upon enrollment in the study and 24 hours later for fetal lung maturation.

2.5. Randomization

The patients were assigned randomly into two groups, and each patient received a unique code. All information about age, weight, gravidity, parity, occupation, educational level, previous pre-term labor, gestational age based on last menstrual period (LMP) or first trimester sonography, vital signs, and the results of the initial examination were recorded.

2.6. Interventions

The treatment group received 10 mg of oral isoxsuprine every 8 hr during hospitalization and until 34 weeks of gestation at home. The control group did not receive isoxsuprine or a placebo. The duration of the follow-up was the same for both groups.

2.7. Post-intervention assessments

After 48 hours of observation (before discharge), the patients were examined, and their blood pressure, heart rate, and respiratory problems were assessed. The patients were discharged if they had not had contractions or changes in dilatation and effacement. It was recommended that the patients return for a visit after one week and at 34 weeks of gestation. At each visit, all participants were evaluated for contractions, dilatation, effacement, blood pressure, heart rate, and the presence or absence of any respiratory problems. During the study, five patients in the treatment group and six patients in the control group did not return for visits. We assessed 35 patients in each group.

2.8. Study outcomes

The primary outcome was occurrence of pre-term birth which was defined as delivery before 37 weeks of gestation. The secondary outcomes were delivery before 34 weeks of gestation and dilatation and effacement 48 hours after treatment, one week after treatment, and at 34 weeks of gestation.

2.9. Statistical analysis

The data were analyzed using SPSS 13.0 software and descriptive statistics, chi-squared, and independent samples T-test. P value less than 0.05 was assumed to be significant.

3. Results

Baseline characteristics were almost similar between the two groups, but the weight was higher in the isoxuparine group, and the parity was higher in the control group (Table 1). Also, we didn't find any statistically significant

differences between the two groups in primary and secondary outcomes (Table 2). No adverse effects were reported 48 hours or one week after contractions had stopped.

Table 1. Baseline characteristics in two groups

		Isoxsuprine	Control	P Value
Age		25.43±5.7	26.03±7.01	0.7
Weight		63.17±6.84	59.6±10.1	0.09
Gravida		2.11±1.28	2.20±1.55	0.8
Parity		0.34±0.72	0.94±1.52	0.042
Gestational age	26-28w	1 (2.86%)	1 (2.86%)	0.609
	28-30w	5 (14.29%)	6 (17.14%)	
	30-32w	12 (34.29%)	7 (20%)	
	32-34w	17 (48.57%)	21 (60%)	

Table 2. Comparison of study outcomes between two groups.

			Isoxsuprine	Control	P Value
Preterm birth (Primary outcome)			14 (40%)	12 (34.29%)	0.621
Delivery before 34 weeks of gestation			4 (11.42%)	5 (14.29%)	0.721
48 hours after contraction discontinuation	Dilatation	Closed	22 (62.86%)	17 (48.57%)	0.323
		1cm	11 (31.43%)	17 (48.57%)	
		2-3 cm	2 (5.71%)	1 (2.86%)	
	Effacement	Yes	15 (42.86%)	19 (54.29%)	0.339
		No	20 (57.14%)	16 (45.71%)	
1 week after contraction discontinuation	Dilatation	Closed	22 (64.71%)	17 (50%)	0.466
		1cm	10 (29.41%)	16 (47.06%)	
		2-3 cm	2 (5.88%)	1 (2.94%)	
	Effacement	Yes	15 (44.12%)	18 (52.94%)	0.307
		No	19 (55.88%)	16 (47.06%)	
34 weeks of gestation	Dilatation	Closed	19 (61.29%)	17 (54.84%)	0.87
		1cm	11 (35.48%)	13 (41.94%)	
		2-3 cm	1 (3.23%)	1 (3.23%)	
	Effacement	Yes	14 (45.16%)	15 (48.39%)	0.799
		No	18 (54.84%)	16 (51.61%)	

One patient in the treatment group and one patient in the control group delivered between the first and second visits. Also, three patients in the treatment group and three in the control group delivered between the second and third visits. At week 34, one patient developed mild tachycardia, and another patient developed mild dyspnea, but there were significant differences in side effects of the drug between the two groups (P=0.63).

4. Discussion

Pre-term labor is responsible for about one-third of pre-term births and is an important cause of prenatal mortality and morbidity. This study was designed to assess the efficacy of oral isoxsuprine as a maintenance therapy after acute pre-term labor was control by magnesium sulfate for the prevention of pre-term birth. This study showed that isoxsuprine is not effective in reducing pre-term births or increasing the delivery rate after 34 weeks of gestation. Although many studies have compared beta-agonists with no treatment or with other tocolytics, few studies have assessed isoxsuprine as a maintenance therapy for preventing pre-term labor. This agent is still widely used in Iran for maintenance therapy of pre-term labor.

Our findings provided evidence to physicians in Iran of the ineffectiveness of isoxsuprine as maintenance therapy for pre-term labor. Often, studies on the efficacy of beta-agonists in preventing pre-term births have focused on the acute phase of pre-term labor; however, in this study, we used this oral beta-agonist for maintenance therapy after

acute pre-term labor was controlled. Previous studies on the efficacy of terbutalin for treatment of pre-term labor haven't found any significant difference in pregnancy outcomes between the terbutalin and placebo groups (9, 10). Our study had a smaller sample size than these studies, but we also did not find any significant difference in pregnancy outcomes between the two groups with or without the administration of beta-agonists. Raymajhi et al. showed that nifedipine was more effective in the treatment of pre-term labor than isoxsuprine (11). Researchers in this study reported that isoxsuprine was safe for treating acute pre-term labor and also as a maintenance therapy. Also, it was shown that prophylactic oral isoxsuprine does not lower the risk of pre-term labor in high-risk, single pregnancies (12). As in our study, other studies have reported the safety of isoxsuprine in pregnant women (13), but our results do not show that this beta-agonist is an effective treatment for pre-term labor. Studies on the treatment of acute-phase pre-term labor have shown that these drugs can postpone the delivery for 24 to 48 hr, but the difficulty in distinguishing between true and false labor may have biased their results.

5. Conclusions

Based on the results of our study, despite the safety, availability, and low price of isoxsuprine, we do not recommend its use as a maintenance therapy after stopping the acute phase of acute labor with magnesium sulfate. Larger studies are still needed to identify the best treatment for pre-term labor.

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Clinical Trial Registration: The study is registered in the Iranian Clinical Trial Registry Center (IRCT201101115591N1).

Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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