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Glyceryl Trinitrate Versus Magnesium Sulfate in the Suppression of Preterm Labor.

Mirteimoori M*, Sakhavar N **, Teimoori B*.

*Assistant Professor, ** Associate Professor, Department of Obstetrics and Gynecology, Zahedan University of Medical Science, Zahedan, Iran.

Correspondence: Dr. M. Mirteimoori, Department of Obstetrics and Gynecology, Ali Ebne Abitaleb Hospital, Zahedan, Iran, Telephone: +98(915)3106875, Email: nsakhavar@yahoo.co.uk .

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Abstract:

Introduction: Preterm births (before 37 completed week gestation) account for approximately 5-10% of births and are the major cause of perinatal mortality in North America and Europe. This is largely because of a lack of standard treatments for this problem, therefore, the aim of this study was to compare glyceryl trinitrate with magnesium sulfate for their ability to suppress preterm labor.

Material and Methods: A clinical trial was performed at the Ali Ebne Abitaleb Hospital, in the Zahedan University of Medical Science. In total, 42 women with preterm labor and intact membranes with a gestational age between 27 and 37 weeks were divided into two groups at random. Patients in the experimental group received glyceryl trinitrate (5mgr transdermal patches /24 hours) and in the control group, magnesium sulfate (at first 4 gr infusion: 1gr/min and then 2gr/hour) was used until the suppression of preterm uterine contractions was observed. Results were obtained through observation and interview forms, and the resulting data was analyzed using chi square and T tests available in the SPSS statistical software (P <0.05).

Results: Mean duration of pregnancy prolongation was 14.87 days in the case group (min: 11 max: 59.38 SD: 14.28) and 13.44 days in the control group (min: 26 max: 36.63 SD: 14.77). There was no significant difference in the prolongation of pregnancy between glyceryl trinitrate and magnesium sulfate (P<0.05).

Conclusion: Glyceryl trinitrate is a suitable substitute for magnesium sulfate in the suppression of preterm labor.

Keywords: Glyceryl Trinitrate, Magnesium Sulfate, Preterm Labor.

Introduction:

Birth is the period of time from the onset of regular uterine contraction to expulsion of the placenta, and typically takes place in a process called labor. Preterm birth, which is defined as delivery before 37 completed weeks of gestation, has been implicated in approximately two thirds of infant mortality cases (reference?). Neonatal morbidity and mortality are primarily influenced by gestational age and, to a lesser extent, by birth weight.⁽¹⁾

The etiology of preterm labor is unknown, and a wide spectrum of causes and demographic factors have been implicated, such as chorioamnionitis, genetics, ante partum hemorrhage, lifestyle factors and preterm membrane rupture. The first step in the prevention of preterm births is early identification. As such, the American College of Obstetricians and Gynecologists (ACOG) proposed the following risk factors for preterm labor: 1) four uterine contractions in 20 minutes; 2) eight uterine contractions in 60 minutes; 3) cervical dilatation greater than 1cm, and 4) cervical effacement of 80 percent or greater.⁽¹⁾ In the past 30 years, treatments used for preterm labour have included β_2 sympathomimetics, magnesium sulfate and nonsteroidal anti-inflammatory agents. These treatments have been less than ideal, as the first two agents have limited efficacies, and the nonsteroidal anti-inflammatory agents have unacceptable fetal side effects. Therefore, further research in this area is greatly needed.

One drug that has received a lot of attention recently is glyceryl trinitrate (GTN).⁽²⁾ In a clinical trial, researchers reported that transdermal GTN (5mg/day) was very effective in treating preterm labor.⁽³⁾ In an observational trial evaluating the efficacy of GTN, Zhonghua et al reported that 30 women with preterm uterine contraction recorded a mean prolongation of pregnancy of 25 days.^(4, 5) In a similar study, prolongation of pregnancy with GTN in 13 women admitted with preterm labor was 34 days.⁽⁶⁾ Several other authors have reported similar results in randomized double blind clinical trials using transdermal nitroglycerin, which reduced the rate of neonatal morbidity and mortality before the 28th week of pregnancy.^(7, 8, 9) In many treatment centers, magnesium sulfate is the first line of treatment for preterm labor; however, the lack of side effects observed in patients who used GTN to suppress preterm births highlights the importance of continuing to examine this drug for its use as an alternative to magnesium sulfate.

In this study, we compared the success of nitroglycerin trinitrate in treating preterm births with the effects of treatment with magnesium sulfate. In doing so, we used the following guiding principles:

- 1) Patients who have received magnesium sulfate must be monitored closely for evidence of hypermagnesemia by examining respiratory rate, patellar reflex and urinary volume during treatment.
- 2) The maternal side effects (such as nausea, vomiting, hyperthermia and hypotension) and neonatal side effects (hy-

potony, restlessness, etc) of magnesium sulfate are very common and cause significant discomfort.

3) The mean prolongation of pregnancy by magnesium sulfate is only 48 hours in many reports.

4) In some randomized clinical trial studies, the effectiveness of magnesium sulfate has been similar to results seen in patients treated with a placebo.

Materials and Methods:

This study was a prospective, randomized clinical trial that examined 42 pregnant women in preterm labor with an intact membrane, less than 4cm dilatation of the cervix and a gestational age between 27 and 37 weeks. After Ethics committee approval, patients were divided randomly in two equal groups using of a table of random numbers and the last two numbers on a patient's file to determine each patient's group assignment. Patients in the control group received magnesium sulfate manufactured by the Pastour Institute of Iran (4gr bolus, infusion: 1gr/min and then: 2gr/hour) and the experimental group received GTN manufactured by Cadila Dholka Pharmaceuticals of India (5mg/24 hour transdermal patches on their Abdomen skins).

In order to be eligible for participation in the study, the patient needed to be experiencing regular uterine contractions at a rate of at least 4 contractions in a 20 minute period, with or without cervical changes, as well as cervical dilatation less than 4cm and a cervical effacement

of 80 percent or more. Exclusion criteria included placental abruption, placenta previa, hypertension, fetal growth restriction, chorioamnionitis (pyrexia greater than 37/5 with maternal tachycardia and uterine tenderness with or without vaginal discharge), and a history of recurrent vaginal bleeding, urinary tract infection, sensitivity or contraindication to nitrates or magnesium sulfate, rupture of the membrane, renal insufficiency and fetal abnormality. Maternal blood pressure (BP) and pulse were recorded before, during and after the start of treatments and fetal heart rate (FHR) was recorded continuously. Uterine contractions were measured after one hour of treatment with magnesium sulfate, and patients were checked regularly for magnesium sulfate toxicity.

Data was obtained through interviews and observation forms. The instrument used to conduct the interview included questions about age, parity, education, social class and occupation, while observation forms were used to collect information from the examination of patients during treatment. Recorded parameters included BP, FHR, contraction duration, as well as contraction interval. Non-parametric data were analyzed using a chi-square test and parametric data were analyzed with a T test using the SPSS statistical software ($P < 0.05$).

Results:

Both groups shared many of the same outcomes and characteristics, such as mean BP (blood pressure), mean FHR (fetal heart rate), BMI (body mass index), parity, age, education, social class

and occupation. In addition, both groups had a similar frequency of pregnancy and urinary infections, and shared a similar mean interval period between previous and present deliveries. Finally, both groups shared a similar history of pre-term labor and abortions, as well as similar contraction durations and intervals. The results were analyzed with SPSS software using a chi square and T test (P value<0.05).

According to the results of this study, there was no significant difference in the prolongation of pregnancy in patients using GTN vs. magnesium sulfate (Table 1), nor was there any significant change in maternal blood pressure or fetal heart rate.

Table (1): comparison of the variables in GTN group and Magnesium Sulfate group

Variable	Group	Average	SD	Min	Max	Pvalue
Age(year)	1	25.52	4.33	19	36	0.92 (NS)
	2	24.90	6.21	15	36	
Gestational Age(week)	1	32.25	2.58	28	35.5	0.66 (NS)
	2	32.37	2.80	26	35.71	
BMI	1	26.2	4.80	21.5	30	0.32 (NS)
	2	25.1	2.80	22.4	28.8	
Pregnancy Frequency(number)	1	3.4	2.20	1	5	0.21 (NS)
	2	3.1	1.60	1	6	
Prolongation of pregnancy(day)	1	14.87	14.77	0.26	36.63	0.81 (NS)
	2	13.44	14.28	0.11	59.38	

SD=Standard Deviation Min=Minimum Max=Maximum

NS=Non Significant (P>0.05)

1=GTN Group 2=Magnesium Sulfate Group

Discussion:

The present research indicates that using glyceryl trinitrate for the suppression of preterm labor was just as effective as magnesium sulfate, but produced fewer side effects. This is consistent with a similar study that compared GTN with Ritoderine, and found that the tocolytic effects of the two drugs were similar but the side effects of GTN on maternal and fetal cardiovascular characteristics were minimal.⁽¹⁰⁾ In another study, no difference was found between glyceryl trinitrate and Ritodrine in acute tocolysis of preterm labor, however a possible advantage of glyceryl trinitrate over Ritodrine

was found in its ability to reduce preterm delivery rates.⁽¹¹⁾ Research has shown a neonatal survival increase from approximately 20 percent at 24 weeks to 50 percent at 25 weeks of pregnancy (an increase of almost 4 percent each day). Although a number of drugs and other interventions have been used to prevent or inhibit preterm labor, none of these have been shown to be completely effective. Because of these uncertainties, the ACOG has recommended that tocolysis be considered when there are regular uterine contractions in addition to documented cervical change or appreciable dilatation and effacement. This may

prove to be challenging, however, because there is currently a lack of standard treatments for the suppression of preterm labor once it has been identified. In addition, treatments that have been employed to suppress preterm labor have not been able to delay delivery for more than 48 hours. Nonetheless, this additional time has afforded clinicians an opportunity to administer glucocorticoids in order to accelerate lung maturation. This greatly reduces the risk of neonatal intraventricular hemorrhage and necrotizing enterocolitis, ultimately causing a reduction in neonatal mortality. Another advantage to delivery delay is that it gives clinicians time to refer the patient to an advanced neonatal intensive care unit (NICU), if such facilities are not available in their place of practice.

Leduc et al (2004) announced that GTN, magnesium sulfate and calcium channel blockers have similar efficacy in the treatment of preterm labor.⁽¹²⁾ Nitroglycerin, a nitric oxide donor and potent smooth muscle relaxant, acts on smooth muscle by elevating cyclic guanosine monophosphate, giving it a rapid onset and a short duration (half life of 2 minutes).^(13,14) It has been used for a wide range of obstetric emergencies including: removal of retained placenta, facilitating fetal extraction during cesarean delivery^(15,16), correction of uterine inversion and intrapartum external version of the second twin.^(17,18) Bootsaylor et al⁽¹⁹⁾ investigated maternal and fetal hemodynamic change in sheep during GTN infusion at 1.5, 2.5, 5.0 and 10µgr/kg/min.⁽¹⁹⁾ In a study by Lees et al⁽²⁰⁾, 10mgr of GTN was used over 24 hours. Reported side effects included headaches, occasional

redness at the patch site and temporary hypotension.⁽²⁰⁾ In our study, the dose of GTN was only 5mgr/24 hours, so these side effects didn't appear and GTN suppressed preterm labor successfully.

Nitroglycerin relaxes the uterus during cesarean delivery to draw out the low birth weight fetus.⁽²¹⁾ Nitric oxide and its metabolites increased fetoplacental blood flow and reduced the possibility of fetal hypoxia.^(22, 23)

In conclusion, glyceryl trinitrate (GTN) and magnesium sulfate have the same efficacy in the suppression of preterm labor but since GTN has no maternal or neonatal side effects, it may be a good alternative for the suppression of preterm labor.

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