

Transdermal Nitroglycerine as a Tocolytic in Preterm Labor

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Abstract-

Objective: To determine the effect of transdermal nitroglycerine for acute tocolysis in preterm labor with regard to its efficacy in delaying delivery for 48 hours to allow the maximum benefit of glucocorticoids to take effect on the foetal lungs, and analysis of side effects.

Methods: The present study was conducted in the Department of Obstetrics and Gynaecology, Government Lalla Ded Hospital, Srinagar from February 2007 to December 2008. After fulfilling the inclusion criteria seventy five pregnant women presenting at 24-36 weeks of gestation in preterm labor were included in the study to receive 2 doses of transdermal nitroglycerine applied 24 hours apart as patches for tocolysis. Patients, in whom delivery was delayed for at least 48 hours to obtain benefit from two doses of corticosteroids, were taken as cases of primary success.

Results: Excellent results were seen in 66(88%), of the total patients receiving therapy in whom progression of labor could be postponed successfully. In the remaining 9 patients, progress` of labor could not be stopped in 6(8%) despite giving tocolysis while as therapy had to be discontinued in 3(4%) patients due to development of severe headache or other side effects.

Conclusion: Glyceryl trinitrate, transdermal patch is an acceptable, cost effective, complication free and a fairly reliable management in preterm labor and assists in delaying delivery for 48 hours to allow the maximum benefit of glucocorticoids to take effect on foetal lung and thus improves neonatal outcome.

Index Terms- Transdermal nitroglycerine, Preterm labor, Corticosteroids, Tocolysis.

I. INTRODUCTION

Preterm labor refers to the onset of uterine contractions of sufficient strength and frequency to effect the progressive dilatation and effacement of cervix between 20 and 37 weeks of gestation. It is a leading cause of neonatal morbidity and mortality worldwide and complicates 5-10% of all pregnancies. ⁽¹⁾ It accounts for more than 85% of all perinatal complications & deaths. About 50% cases of preterm labor occur spontaneously whereas iatrogenic induction to avoid maternal or fetal compromise and preterm rupture of membranes (PROM) account for 25% each. ^(1, 7, 8)

In many instances preterm labor represents the desperate needs of the growing fetus to escape from the unfavorable intrauterine environment. Many modalities of treatment are presently being recommended to halt preterm labor. Bed rest and hydration are most commonly recommended in managing preterm labor but without any proven benefit, therefore making drug therapy the mainstay of modern management. ⁽²⁾ Although many drugs are now routinely available and although no single drug has a clear therapeutic advantage, it is usually the side effects of the drugs which will determine which ones to use in a particular woman. The literature clearly supports the use of parenteral tocolysis over oral therapy in delaying delivery for at least 24 to 48 hours so as to allow time for administration and effect t of corticosteroids to enhance pulmonary maturity and reduce the severity of fetal respiratory distress syndrome and prevent intraventricular hemorrhage.

Nitroglycerine, a nitric oxide donor is an effective choice as a tocolytic agent due to its high efficacy, lesser side effects and better patient compliance. ⁽⁵⁾ It is a vasodilator that is essential for maintenance of normal smooth muscle tone of uterus. The principal pharmacological action of nitroglycerine is relaxation of vascular smooth muscle, and consequent dilatation of peripheral arteries and veins, especially the latter. Pregnancy is prolonged by its direct effect on the uterine blood flow. ⁽⁷⁾ In our study conducted on 75 pregnant women in preterm labor it was found that transdermal nitroglycerine was effective in delaying delivery upto 48 hours and beyond and prolonging gestation to variable periods.

II. MATERIALS AND METHODS

Our study was conducted in the labor ward of L.D Hospital for a term of two years from February 2007 to December 2008. All the patients presenting with preterm labor were scrutinized to select the patients for tocolysis. A total of 75 pregnant women presenting with preterm labor and fulfilling the inclusion criteria were enrolled into study after explaining the procedure offered and obtaining written consent. The inclusion criteria were: painful, regular uterine contractions palpated, at least 3 contractions every ten minutes for more than an hour with or without cervical changes at the gestational age of 24-36 weeks. Tocolysis was given in only those patients

where maternal or fetal benefits outweighed the risks/side effects of tocolytic drugs and there were no medical or obstetrical contraindications to use of tocolysis.

The exclusion criteria were: multiple gestations, obstetric hemorrhage, fetal anomaly, gestation <24 or >36 weeks, chorioamnionitis, fetal distress and intrauterine death, and uterine anomalies like bicornuate uterus or uterine fibroids, hypersensitivity reactions, hypertension or diabetes.

Successful tocolysis was described as continuation of pregnancy for at least 48 hours after the tocolytic therapy allowing time for corticosteroid administration to accelerate fetal lung maturity whereas failed tocolysis was described as delivery occurring within 48 hours or discontinuation of therapy due to development of intolerable side effects.

Patients in the study were admitted with strict bed rest to the labor ward. At the outset of treatment maternal and fetal measurements were recorded every 15 minutes during first two hours followed by hourly recording while patient remained in the ward. After the pelvic examination was completed, the patient was placed in the lateral recumbent position and externally monitored for fetal heart tones and contractions. Intravenous boluses of 500 ml of normal saline was infused as a protective measure against the hypotensive effect of nitroglycerine and diminishes the contractions of an irritable uterus and help to differentiate this condition from preterm labor. Once the diagnosis was confirmed and basic investigations obtained, tocolytic therapy was initiated as 10 mg nitroglycerine (Nitroderm TTS) patch was applied directly to the skin of the abdomen. If after one hour there was no reduction in contraction frequency or strength, an additional patch was applied. Not more than two patches (2mg) were to be worn simultaneously. Mild headache was treated with paracetamol. Patches were kept in place for full 24 hours, at the end of which they were removed and women reassessed.

The primary outcome measure of this study was delay in delivery for at least 48 hours to buy time for administration of two of corticosteroids (betamethasone 12mg intramuscularly, repeated in 24 hours) to improve foetal lung maturity.

III OBSERVATIONS

Our study included 75 patients with preterm labor once they fulfilled the inclusion and exclusion criteria. In the study group n, the gestational age ranged from 26 to 36 weeks with a mean gestational age of 31.96 ± 3.02 weeks. The age of participating subjects ranged from 18 to 37 years, with a greater majority of patients in study group in the age group of 21 to 25 years (40%). Primigravidas formed the major segment comprising of 47(62.66%) out of a total of 75 patients. In the study group the mean cervical dilatation was seen to be 1.28 ± 0.67 . (Table 1)

Baseline Maternal Variables (Table 1)

Maternal Age(years)	21-25
Gestational Age (weeks)	31.96 ± 3.02
0	47(63%)
>1	28(37%)
Cervical Dilatation	1.28 ± 0.67
PROM	27(36%)

Outcome of tocolytic therapy with Transdermal Nitroglycerine Patch (Table 2)

	Number of subjects (n)	Percentage (%)
Pregnancy Prolongation beyond 48 hours	66	88
Failure of therapy	6	8
Discontinuation of therapy (intolerable side effects)	3	4

Preterm rupture of membranes was the most common cause for initiation of preterm labor which was present in 21(28%) subjects. More than 59 (78%) subjects did not have any previous history of abortions while only 7(9%) had 2 or more abortions in the past. A review of other associated conditions is provided in table 2.

The progression of labor could be postponed successfully for more than 48 hours in 66(88%) out of 75 patients in the study group. The delay in delivery time was desirable for administration of two doses of betamethasone given 24 hours apart to improve neonatal outcome. In 6 patients the progression of labor could not be stopped and they progressed towards delivery or needed alternate tocolysis. Table 3 shows an overview of side effects or nitroglycerine therapy. The major side effects of nitroglycerine therapy were headache in 33(44%) and hypotension in 21(28%) subjects. In 2 patients therapy had to be discontinued due to development of severe headache or hypotension (table3).

Side effects associated with tocolytic therapy. (Table 3)

	Number of subjects (n)	Percentage (%)
Headache	33	44
Hypotension	21	28
Light headedness	6	8
Nausea/vomiting	6	8
Rash	9	12
Chest discomfort	0	
Fetal heart rate changes		

IV CONCLUSION

Incidence of preterm labor is quite high in our country ⁽²⁾ compared to developed countries (11% in USA) ⁽¹⁾It has been found to be 22% in our study. Obstetricians who face such patients on everyday basis also face the dilemma of managing an established preterm labor with very few drugs with proven or equivocal efficacy which differ in uterine specificity and both maternal and foetal side effects. These tocolytic drugs inhibit uterine contractions and relax the myometrium by different mechanisms leading to arrest of preterm labor.

The aim of delaying delivery has double benefits: one is to buy enough time to administer two doses of glucocorticoids in order to reduce the incidence and severity of respiratory distress syndrome while arranging for in utero transfer to a centre with services for dealing with even extreme prematurity; and the second benefit is to reduce the perinatal mortality and morbidity associated with severe prematurity.

Nitroglycerine, a nitric oxide donor and potent smooth muscle relaxant, acts on smooth muscle by elevating cyclic guanosine monophosphate. ⁽⁹⁾ It has a rapid onset and a short duration (half-life of 2 minutes) and has been used increasingly for various obstetric emergencies including removal of a retained placenta ⁽¹¹⁾, facilitating foetal extraction during caesarean delivery; correction of uterine inversion ⁽¹²⁾ and intrapartum external version of the second twin.

III. CONCLUSION

The nitroglycerine patch appears to be a safe, cost effective and a relatively safer method of halting the progress of uterine contractions in pre-term labour especially in low resource settings of our developing countries where advanced healthcare facility is not available to the vast majority of population. A delay in delivery for even a short period can drastically improve the neonatal outcome in these patients due to corticosteroid benefit and time gained in referral to a higher centre with better neonatal care available and thus decreases perinatal mortality.

V. REFERENCES

1. Elliot JP. Magnesium sulfate as a tocolytic agent. Am J ObstetGynecol 1983;147:277– 84.
2. Spisso KR, Harbert GM, Thiagarajah S. The use of magnesiumsulfate as the primary tocolytic agent to prevent premature delivery. Am J Obstet Gynecol 1982;142:840 –5.
3. Abouleish AE, Corn SB. Intravenous nitroglycerin for intrapartumexternal version of the second twin. Anesth Analg 1994;78:808 – 9.
4. Altabef KM, Spencer JT, Zinberg ST. Intravenous nitroglycerin foruterine relaxation of an inverted uterus. Am J Obstet Gynecol1992;166:1237– 8.

5. Riley ET, Flanagan B, Cohen SE, Chitkara U. Intravenous nitroglycerin: A potent uterine relaxant for emergency obstetric procedures. Review of the literature and report of three cases. *Int J Obstet Anesth* 1996;5:264–8.
6. Lees C, Campbell S, Jauniaux E, Brown R, Ramsay B, Gibb D, et al. Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. *Lancet* 1994;343:1325–6.
7. Rowlands S, Trudinger B, Visva-Lingam S. Treatment of preterm cervical dilatation with glyceryl trinitrate, a nitric oxide donor. *Aust N Z J Obstet Gynaecol* 1996;36:377–81.
8. Harrison MR. Fetal surgery. *Am J Obstet Gynecol* 1996;174:1255–64.
9. Chuprin JR, Rappoport RM. Nitroglycerin-induced desensitization of vascular smooth muscle may be mediated through cyclic GMP-disinhibition of phosphatidylinositol hydrolysis. *Experientia* 1986;43:316–8.
10. Physicians' Desk Reference. 50th ed. Montvale, New Jersey: Medical Economics Data, 1996:1523–4.
11. Riley ET, Flanagan B, Cohen SE, Chitkara U. Intravenous nitroglycerin: A potent uterine relaxant for emergency obstetric procedures. Review of the literature and report of three cases. *Int J Obstet Anesth* 1996; 5:264–8.
12. Altabef KM, Spencer JT, Zinberg ST. Intravenous nitroglycerin for uterine relaxation of an inverted uterus. *Am J Obstet Gynecol* 1992; 166:1237–8.

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