Vol. 16, No. 1
ORIGINAL PAPER

SUPPLEMENT
OBSTETRICS & GYNAECOLOGY

MEDICAL CHANNEL
JANUARY - MARCH 2010

SHORT TERM TOCOLYTIC EFFICACY OF TRANSDERMAL NITROGLYCERINE.

1. **SHAKIRA PERVEEN**
MBBS, FCPS.
2. **JEHAN ARA AINUDDIN**
MBBS, MCPS, FCPS.
3. **SHAISTA NAZ**
MBBS, FCPS.

1. ***Assistant Professor.***
DOW UNIVERSITY OF HEALTH SCOENCES KARACHI
2. ***Associate Professor.***
DOW UNIVERSITY OF HEALTH SCOENCES KARACHI
3. *R.M.O*
SIND GOVT. LYARI GENERAL HOSPITAL KARACHI

Correspondence:
DR SHAKIRA PERVEEN
Address:
B-7 RUKNUDDIN FLATS, F.B AREA, BLOCK-1, KARACHI, PAKISTAN
Cell No: 0300-2483551

ABSTRACT:

OBJECTIVE: *To assess tocolytic efficacy & safety profile of Glyceryle trinitrate (GTN) in threatened preterm labour.*
STUDY DESIGN, SETTING & METHODS: *Quasi-experimental study carried out at a tertiary care private hospital from Jan 2008 – Dec 2008. Fifty pregnant women at 28-34 weeks of gestation underwent GTN (a nitric oxide donor) short-term tocolysis for threatened preterm delivery. A 10 mg/ 24 hr Nitroderm transdermal patch was placed on anterior abdominal wall & replaced by second patch of same dose after 24 hours. Cessation of contraction, prolongation of gestation & side effects of agent was observed.*
RESULTS: *Out of 50 experimental subjects 66% were more than 25 years, 78% were para 2-3, 88% were between 28- 30 weeks of gestation. Around 46% had complete cessation of contraction within 2 hours & 64 % had successful tocolysis of 48 & more than 48 hours. Out of them 12% were with previous uterine scar. Commenest side effect (40%) was maternal headache. None of them had fetal side effects.*

KEY WORDS: Preterm labor, tocolysis, side effects, transdermal Nitroglycerine.

INTRODUCTION :

Preterm delivery caused by spontaneous preterm labor accounts for approximately one-third of preterm births [1]. Preterm births remains an important public health problem & leading cause of neonatal morbidity & mortality, is a major contributor to loss of life, long term disability & health care costs. For children born before 37-32 weeks, 25 % & 45% respectively, require special educationn[2]. World data on the incidence of preterm birth are unreliable, but incidence ranges between 5% in developed countries & 25% in developing countries[3]. Wide scale national data is lacking in this respect to show the incidence in our country[4]. According to Pakistan Demographic & Health Survey (PDHS) 2006-2007 perinatal mortality rate is 159/1000 pregnancies & prematurity is major contributor. One study in civil hospital Karachi found 77% perintal deaths are in preterm & 23 % in term pregnancies [5].

The goal of tocolytic therapy is to reduce neonatal mortality & morbidity by delaying birth, allowing for corticosteroid administration & maternal transfer to a tertiary care centre [6]. An effective tocolytic agent has to work rapidly to ensure that labor does not progress beyond the point of no return especially in settings where in utero transfer is necessary. The choice tocolytic agent which could improve neonatal outcome with no maternal or neonatal side effects, has not yet surfaced [1]. Available tocolytic like betamimetics have proven efficacy, but potential serious side effects like cardiac arrhythmia's & hypokalemia , effect on fetal heart rate as it crosses placenta [1,7], prostaglandin synthesis inhibitor (indomethacin) is also effective tocolytic but with fetal side effects like premature closure of ductus arteriosus after 32 weeks of pregnancy [8] , Ca channel blockers like nifedipine is safe & effective but dangerous in women with evidence of cardiovascular disease or unstable hemodynamically [9] , magnesium sulphate is ineffective tocolytic agent with adverse outcome [10] , oxytocin receptor antagonist atosiban is effective but expensive agent, complicated intravenous route of administration & not universally available [11].

GTN skin patches have the attraction of convenience, potential effectiveness, low cost & few side effects. Several studies have reported varying degree of success with this approach of tocolysis [12,13,14]. In preterm labor prior to 34 weeks of gestation, there appears to be a place for short term tocolysis to gain time so that corticosteroids can

Table I :
MATERNAL CHARECTERISTICS

Age (years)	No	%	Parity	No	%	Previous CS	No	%	Gest Age	No	%
20-25	17	34	0-1	8	16	0	44	88	28-30	44	88
26-30	30	60	2-3	39	78	1	4	8	31-32	1	2
>30	3	6	>3	3	6	2	2	4	33-34	2	4

be administered to enhance fetal lung maturation & if necessary, to transfer the women to a facility with a neonatal ICU. As many recent studies also favors high safety & efficacy for GTN transdermal patches in treatment of preterm labor [15,16] highlight the importance of continuing to examine this drug.

AIM OF STUDY:

To evaluate tocolytic efficacy & safety profile of GTN patches in threatened preterm delivery between 28- 34 weeks of pregnancy.

RATIONALE:

High societal & health costs associated with significant neonatal morbidity, the use of transdermal GTN for women in preterm labor may result in major cost saving & longer-term benefits.

MATERIAL & METHODS:

Fifty pregnant women with clinical diagnosis of preterm labor (between 28- 34 weeks) were included for study. Clinical criteria of labor was 6-8 uterine contractions / hour & cervical dilatation of < 4 cm. Women excluded were with multiple gestation, maternal or fetal condition necessitating delivery, ruptured membranes, intrauterine fetal demise or suspected lethal fetal anomalies, treatment with tocolyics within 24 hours, known sensitivity to GTN or failure to consent. Selected subjects received 500ml intravenous normal saline over 30 min as prophylaxis against potential GTN induced hypotention. Maternal blood pressure was monitored at every 15 min for 1 hour, & every 4 hours thereafter. A GTN 10 mg / 24 hr Nitroderm transdermal patch was placed on anterior abdominal wall & replaced by second patch of same dose after 24 hours.

Maternal outcome measure includes tocolytic efficacy of GTN at 24 hour, 48 hour & after 48 hour. Data was obtained through interviews & observation. Observation forms include information from examination of subjects during treatment. Parameters noted were BP, fetal heart rate, uterine contraction. Non parametric data were analyzed using a chi-square test & parametric data were analyzed with t test using SPSS-10 statistical software.

Table II :
STRENGTH OF CONTRACTIONS AFTER 2 HOURS OF PATCH APPLICATION

Strength	No	%
None	*23*	*46*
Mild	11	22
Moderate	9	18
Strong	3	6

Table III:
DURATION OF TOCOLYSIS

Duration (hrs)	No	%	p-value
<24	*12*	*24*	*0.00*
24 – 48	*16*	*32*	*0.01*
>48	*19*	*38*	*0.09*

Table IV:
SIDE EFFECTS RELATED TO TREATMENT

Side Effects	No	%
Headache	*20*	*40*
Local irritation	12	24
Hyporension	4	8
Flushing	2	4
Dizziness	0	0
Fetal bradycardia	0	0

RESULTS:

Fifty pregnant women fulfilling inclusion criteria were taken for study between Jan 2008-Dec 2008. These selected subjects underwent GTN tocolysis. Demographic characteristics of them are presented in (Table I). Majority (66%) of them was more than 25 years of age, 78% were para 2-3, 88% were between 28-30 weeks of gestation, 12% had previous uterine scar of cesarean section. At 2 hours of commencement of tocolysis intensity & frequency of uterine contractions were observed (Table II). Around 46% had complete cessation of contractions followed by mild contraction in 22%. Main outcome measures were prolongation of pregnancy for 24 hrs, 48 hrs & > 48 hrs (Table III). About 64% underwent successful tocolysis of 48 hours with administration of full course of corticosteroids, 12 % of them also had previous one or more cesarean scar. There was significant decrease in the time of delivery within 24 hrs (P value 0.00). Adverse side effects (Table IV) were observed. Commonest side effect was maternal headache (40%) & 4% of them required removal of GTN patch. None of subject had fetal adverse effect. Non of subject received other tocolytic agent from period of selection till full course of corticosteroid therapy.

DISCUSSION :

Improved neonatal mortality & morbidity

is the primary reason for tocolysis. We observed short-term tocolytic efficacy of the agent, though benefit of tocolytic agent in prolongation of gestation for 48 hrs is unlikely to improve neonatal outcome in terms of physical maturation but , these golden hours used to optimized by in utero transfer of the mother to a tertiary care center with neonatal facilities & administration of antenatal corticosterids to mother. Approximately 25% cases of preterm birth occurring at a gestational age < 34 weeks which accounts for about 1% of births [11]. In the largest randomized tocolytic trial done by Canadian preterm labor Investigators Group only 34.6% of women completed glucorticoid treatment [16]. This is despite the fact that antenatal administration of corticosteroid reduced the overall incidence of respiratory distress syndrome in preterm infants by approximately 50% & intraventricular hemorrhage by 52% [17].

Major finding in our study regarding short-term tocolytic efficacy of GTN is termination of contraction in 46% within 2 hrs & successful tocolysis in 64% with completion of corticosteroid therapy. Many comparative studies of GTN with magnesium sulphate , ritodrine & salbutamol conclude that GTN is safe & at least equivalent tocolytic [14,15,18,19]. This is specially true for those cases with previous uterine scar where extra precaution is necessary, as other tocolytics like ritodrine produce fetal & maternal side effects which mimics with scar dehiscence [1,7]. Commonest maternal side effect was headache as seen in other studies also [13,14]. In our study 4% cases required removal of patch for headache, but infrequently resulted in removal in other studies [13,15]. One study did not found this effect at a dose of 5mg / 24 hr with successful tocolysis [15]. Maternal hypotension occurred in only 8% subjects. Maternal hypotension is usually associated with intravenous GTN & not with transdermal patch. Administration of intravenous fluid bolus before initiation of treatment further decreases risk of hypotension [13]. Non of our subject had bradycardia similar to one study comparing GTN with ritodrin [14]. It has been shown that GTN has beneficial effect on fetus by improving uteroplacental resistence [20].

Several Canadian tertiary centers & many referral centers have already adopted the use of transdermal GTN as the standard agent for tocolysis. However further adequatly powered research focusing on preterm labor using more specific indication of true preterm labor (e.g fetal fibronectin) would be useful to confirm.

CONCLUSION:

The management of threatened preterm delivery with first line tocolytic therapy can prolong gestation. There is no clear first line tocolytic agent, should individualized & based on maternal condition, potential side effects & gestational age.

REFERENCES:

1. Tan TC, Devendra K, Tan LK, Tan HK. Tocolytic treatment for the management of preterm labor: a systematic review. Singapore Med J 2006; 47(5):361-66.
2. Bouyer J, Isernman D, Long term development of preterms; the state of health at age 6 years in: Papiernik E, Keith L, Bouyer J, Dreytus J, Lazar P, eds. Effective prevention of preterm births.The French experience measured at Haguenau , 25(1) ed, New York: White Plains: 1989: 195 - 203.
3. Anumba DOC. Managment of women with a previous preterm birth. Obstetrics, gynaecology & reproductive medicine 2007; 188-191.
4. Tufail A, A Hashmi H, Naheed F. Risk factors for preterm labor in a rural cohort. Medical Channel April-June 2009;15(2): 55-57.
5. Ainuddin JA,Memon U G, Ramejo B B. Factors contributing to high perinatal mortality in a tertiary referral center Civil hospital Karachi. Medical Channel July- September 2007; 13(30): 27-29.
6. Moutquin J-M. Classification & heterogeneity of preterm birth. BJOG 2003; 110(suppl 20): 30-3.
7. Roel de Heus, Eduard J.H. Mulder, Jan B. Derks, Piet H.J. Kurver, Leo Van Wlfswinkel, Gerard H.A. Visser. A prospective randomized trial of acute tocolysis in term labor with atosiban or ritodrine. European Journal of Obstetrics & Gynaecology & Reproductive Biology2008; 139: 139-145.
8. Mois KJ. The effect of advancing gestational age on the frequency of ductal constriction secondary to maternal indomthacin use. Am J Obstet Gynecol 1993; 168: 1350-1354.
9. King JF, Flenady VJ, Papatsonis DNM, et al. Calcium Channel blockers for inhibiting preterm labour; a systematic review of the evidence & a protocol for administration of nifedipine. ANZJOG 2003; 43: 192-198.
10. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour (cochrane review). The Cochrane Library 2004; Issue 3, Chichester, UK; John Wiley & Sons, Ltd.
11. James Forrester King. Tocolysis & preterm labour. Curr Opin Obstet Gy ecol 2004; 16: 459-463.
12. Morgan PJ, Kung R, Tarshis J, Nitroglycerine as a uterine relaxant: a systematic review. Journal Obstet & Gynecology 2004; 191: 612-15.
13. Graeme N. Smith, Mark C. Walker, Arne Ohlsson, Karel O' Brien, Roy Windrim. Randomized double- blind placebo-controlled trial of transdermal nitroglycerine for preterm labour. Am J Obstet Gynecol Jan 2007; 196: 37.e1-37.e8.
14. M.P. Wani , N. Barakzai , I. Graham. Glyceryl trinitrate vs. ritodrine for the treatment of preterm labor. International Journal of Gynecology & Obstetrics 2004; 85: 165-167
15. Mirteimoori M, Sakhavar N, Teimoori B. Glyceryl trinitrate versus Magnesium sulphate in the suppression of preterm labor. Shiraz E- Medical Journal April 2009 ; 10 (2):48-97.
16. CPIG. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. N Engl J Med 1992; 327: 349-51.
17. Management of preterm labor. ACOG practice Bulletin No.43, May 2003.
18. Bists A, Madsen G, Knox M, et al. The randomized nitric oxide tocolysis trial (RNOTT) for the treatment of preterm labor, Am J Obstet Gynecol 2004; 191 : 683-90.
19. de Spirtet M, Treluyer JM, Chevret S, et al . tocolytic effect of intravenous nitroglycerine, Fundam Cin Pharmacol 2004; 18 : 207-13.
20. Kehler CS, Chleussner EA, Seewald HJ. Nitric oxide donors: effects on fetoplacental blood flow. Eur J Obstet Gynecol Reprod Biol 2004; 115 (1) :4-10.