

DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20205228>

Original Research Article

Assessment of the efficacy of glyceryl trinitrate patch as a tocolytic

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Received: 31 August 2020

Accepted: 17 October 2020

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ABSTRACT

Background: Preterm labor is defined as onset of delivery after the age of gestational viability (20-28 weeks) and prior to 37 weeks. Preterm birth complicated 5-10% of all births and accounts for 75% of perinatal deaths. Several drugs are now available to delay delivery in spontaneous preterm labour. Delaying the delivery for at least 24-48 hr for lung maturity of fetus is the primary goal. Glyceryl trinitrate has less maternal side effects.

Methods: The study included 100 women who were admitted in view of preterm labour with gestational age between 28-36 weeks and were given trans dermal nitroglycerin therapy for arrest of preterm labour.

Results: The efficacy of nitroglycerine patch to arrest preterm labour was studied. 88 patients were successfully progressed for more than 48 hours with minimum prolongation of 3 days and maximum prolongation of 65 days and average prolongation of 26 days of pregnancy.

Conclusions: Glyceryl trinitrate patch as a tocolytic is very effective. This drug has a good patient acceptability and compliance due to its minimal side effects, low cost and simple dosage schedule.

Keywords: Glyceryl trinitrate, Preterm labor, Tocolytics.

INTRODUCTION

Preterm labor is defined as onset of delivery after the age of gestational viability (20-28 weeks) and prior to 37 weeks or 259 days of pregnancy. It is diagnosed by observable uterine contractions (at least once in 10 min), rupture of the membranes, cervical dilatation 2cm or more and cervix length less than 1 cm. Preterm labor is considered as main confounding factor in the neonatal morbidity and mortality.¹ Preterm birth complicated 5-10% of all births and accounts for 75% of perinatal deaths.^{2,3} Nearly three million preterm infants are born in South East Asia each year, directly contributing to 75% of neonatal mortality and 50% of long term neurological impairment in children.⁴ In developed countries the incidence of preterm birth varies between 5-10% In India the true incidence is not well known because of lack of documentation but it is estimated to be more than 10%.

Although there has been a significant increase in the neonatal survival rate of preterm babies, morbidity is still

high and late neurological handicap remains a big burden on society. Many survivors needed special education facilities, had subnormal (IQ less than 70%) and many had visual hearing disability and chronic lung disease. Prolonged hospitalization and long-term intensive care accounts for 35% of health care costs and makes preterm birth an expensive issue. Moreover, during the past forty years the rate of preterm birth has not drastically declined.⁵

It has been widely recognized that its prevention or effective management will improve neonatal outcome and will have a profound impact on social and long-term public health care costs. Therefore, prevention of preterm labour is one of the primary objectives of prenatal care.⁶

The rationale attempting to keep the healthy fetus in utero is based on the knowledge of that for every additional 2 weeks of intrauterine life between 25-37 weeks of gestation, perinatal morbidity is halved. Several drugs are now available to delay delivery in spontaneous preterm

labour. Optimization of obstetric management besides tocolysis includes the stimulation of fetal lung maturation by giving corticosteroid as means of preventing respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis in infant. Delaying the delivery for at least 24-48 hr is the primary goal.⁷ This not only facilitate in utero transfer of the fetus to a tertiary care center but also enabled sufficient time to enhance fetal lung maturity by the concomitant corticosteroid therapy.

Now a days several drugs are used as tocolysis including beta adrenergic, calcium channel blocker, prostaglandin synthetase inhibitor like-indomethacin and magnesium sulphate, nitrous oxide donor and oxytocin antagonist (atosiban).⁸

Glyceryl trinitrate (nitrous oxide donor) receiving a lot of attention and very effective in treating preterm labor.⁹ Nitrous oxide act by reducing intracellular cellular calcium which causes smooth muscles (including vascular, gastrointestinal, urogenital) relaxation.

Advantages of transdermal nitroglycerine patch 1) ease of administration without inconvenience to the patients 2) cheaper 3) low risk of maternal, fetal and neonatal side effects is steadily gaining acceptance as a tocolytic agent.

METHODS

The study was carried out in the Department of Obstetrics and Gynecology at Geetanjali Medical College and Hospital, Udaipur for a period of one year from 1st September 2018 to 30 th August 2019. It was a hospital based prospective observational study. The study included 100 women who were admitted in view of preterm labour with gestational age between 28-36 weeks and were given trans dermal nitroglycerin therapy for arrest of preterm labour after written consent. Both primigravida and multigravida were selected. A detailed history was recorded including age, occupation, menstrual history and last menstrual date wherever possible. Past obstetric history was taken in detail including past history of abortion, preterm labour, preterm rupture of membranes etc. General examination including maternal vital parameters and obstetrics examination including fetal presentation, fetal heart rate, liquor quantity. Frequency and intensity of uterine contractions were noted. Per speculum and per vaginal examination was done to note the presence of white discharge, draining of liquor, bleeding, dilatation and effacement of cervix, presence of membranes and station of head was noted. In all patients' basic investigations like haemoglobin estimation, blood grouping and RH typing, complete urine examination, blood sugar and vaginal swab for culture & sensitivity were done. USG examination was done to know the correct gestational age, amount of liquor and to rule out fetal malformation and intrauterine growth restriction.

Inclusion criteria

Inclusion criteria were, gestational age 28 to 36 weeks, uterine contractions 2-3 per 10 minutes, cervical dilatation<3.

Exclusion criteria

Exclusion criteria were, ruptured membranes, cervical dilatation>3cm, antepartum haemorrhage, pre-eclampsia, intrauterine growth restriction, intrauterine fetal death, abnormal presentation, severe oligohydramnios, fetal distress previously enrolled in the study, significant medical disorder in the mother, fetal malformation incompatible with life, uterine malformations.

Protocol for trans dermal nitroglycerine therapy

1) Nitroglycerine patch (nitroderm TTS 5 novartis, dose 25 mg) release 5 mg in 24 hours with drug releasing area of 20 sq.cm 2 patches were kept simultaneously of same doses each of 5 mg, 2) site of application: Anterior abdominal wall over the region of fundus, 3) prior to application patients were given two doses of injection betamethasone 12 mg in 24 hours apart to achieve lung maturity and hydrated with 1000 ml of ringer lactate to counter act the hypotensive effect of nitroglycerine 4) the flat multilayer system is designed to deliver nitroglycerine continuously through a release membrane following application to the skin. Active substance penetrates the skin and this becomes directly bio available to the systemic circulation at relatively constant concentration. 5) If uterine contraction persisted even after two hours of application of the patches another 2 patches of same dosage applied, leaving the first patch undisturbed. Not more than 4 patches(20mg) applied per 24 hours for the same patient. 6) During this study, the patches were removed every 24 hours and fresh patches applied till uterine contractions had completely subsided for 24 hours.

Monitoring

Pulse rate, blood pressure, uterine contraction, fetal heart rate, bleeding or leaking PV, side effect.

The monitoring was done

Every 15 minute in first 2 hours, every 30 minutes for next 4 hours, every 2 hours for next 6 hours, every 4th hourly thereafter.

Treatment was suspended in the event of the following

Progressive cervical dilatation>3 cm, persistent uterine contractions, rupture of membranes/fever/bleeding pv, maternal tachycardia>120 min not subsiding even after foot end elevation and iv fluids, persistent hypotension <90/60 mmhg not corrected with I.V. fluids, intractable

headache, not responding to tablet paracetamol 500 mg orally, severe allergy to patch.

Clinical efficacy was assessed based on

Prolongation of pregnancy for 48 hours or more, perinatal outcome criteria for failure included are, persistent uterine contraction and progressive cervical dilatation despite therapy, intolerable side effects.

Statistical analysis

To describe nominal data simple percentages were used. Software used for analyzing data SPSS 21.

RESULTS

A total of 100 pregnant women admitted with preterm labour were included in this study. Efficacy of nitroglycerine patch to arrest preterm labour was studied.

Women were in the age group of 18-32 years (Table 1). 32 patients were primi gravida and 68 patients were multigravida. Gestational age at the time of entry was 28 weeks to 36 weeks. Fetal presentation was cephalic in 97 patients whereas breech presentation was seen in 3 patients. Maternal height was around 145-167 cm.

Drug outcome: 88% patients had successful tocolysis with NTG patch (Table 2). Pregnancy was prolonged for more than 48 hours (Table 3).

Table 1: Distribution of patients according to gestational age.

Gestation age of patients	No. of patients
28-30 weeks	16
31-33 weeks	22
34-36 weeks	62

Table 2: Efficacy of drug according to gestational age.

Gestational age	success
28-30 weeks	87.5%
31-33 weeks	90.9%
34-36 weeks	87.0%
Overall success rate	88%

Table 3: Duration of prolongation of preterm labor.

	No. of patients	%
Total	88	88
48 hours-7 days	16	18
>7 days	72	81.1

Prolongation of pregnancy

Total 88 patients were successfully progressed for more than 48 hours with minimum prolongation of 3 days and

maximum prolongation of 65 days and average prolongation of 26 days of pregnancy (Table 4).

Table 4: Days of prolongation distributed with week of gestation.

Group	Week of gestation	Days of prolongation
Group 1	28-30 week	40 days
Group 2	31-33 week	23 days
Group 3	34-36 week	17 days

Pregnancy was prolonged for more than 37 weeks in 51.4% babies without using any other tocolytic.

Duration of therapy observed for successful tocolysis

The mean time taken to stop the contraction was 3-4 hours. Duration of tocolytic therapy maintained was 12 hours in 18 patients and 24 hours in 70 patients.

Table 5: Maternal adverse effect during therapy.

Adverse effect	No.	%
Headache	20	20
Tachycardia	24	24
Nervousness	2	2
Palpitation	4	4
Hypotension	10	10
Nausea and vomiting	4	4
Allergy to patch	2	2

Headache and tachycardia were the most common adverse effect seen during study but managed with tablet paracetamol and IV fluids.

Perinatal outcomes

The parameters taken for study the perinatal outcome was mean gestational age at delivery, mean birth weight, APGAR score at birth and duration of stay in NICU. Perinatal outcome data was not available for patient (18) who were lost for follow up. Mean gestational age at delivery was 34.5 weeks. Mean birth weight was 2520 gms. The APGAR score at birth was 8.

Table 6: Number of perinatal morbidity and mortality with GTN therapy.

Birth asphyxia	5
Respiratory distress syndrome	7
Septicemia	1
Total mortality	2

Perinatal morbidity & mortality

Total 7 babies developed respiratory distress syndrome born at around 30-42 weeks. One baby developed septicemia. 5 babies developed mild to moderate birth

asphyxia which recovered later on. 2 babies died 1 is due to septicemia and another one is due to respiratory distress syndrome.

DISCUSSION

Preterm labour and the attendant complications of preterm delivery assume its position as the most common, costly and catastrophic complication of pregnancy.

It is difficult to assess the efficacy of various treatment modalities for preterm labour. There can be a margin of error in the accurate diagnosis of preterm labour as the assessment of tension of membrane in the fore-water or study of uterine contractions with tocometers are not usually carried out. Success of arresting preterm labour is more when treatment is initiated early and therefore there is a possibility of over diagnosis and over treatment. If the clinician waits for the cervical effacement and dilatation in doubtful cases it may be too late for effective inhibition of uterine contraction in some of the cases. Bedside it is not possible to withhold other therapies such as bed rest, progesterone, mild sedation and in some cases ant prostaglandin drugs for short period.

In a trial by Rowlands et al used a 50 mg patch whereas lees et al and Shah et al also used a 10 mg patch as in my study Anne D. Walling did a randomized trial to compare glyceryl trinitrate and ritodrine in tocolysis.¹²⁻¹⁵ He also used 10 mg patch and they used second patch after one hour if there was no reduction in contraction. This study also supported by Aruna kumar et al and Praveen et al. Similar results were quoted in study by Michael and lee.^{16,17}

Past history of early spontaneous abortion increases the incidence of preterm labour 1.5 -2-fold. In this study 12% patient had past history of early spontaneous abortion. 10% patients had history of 1 and 2 trimester bleeding. lee et al in their study showed association of bleeding in 15.7% patient with preterm labor.

In this observational study successful tocolysis was achieved in 88% of patients with failure rate or 12%.

This observational study has suggested that glyceryl trinitrate as NO donor, may be effective in prolonging gestation. The only reported maternal side effect was head ache. No adverse fetal effects were noted . This study concluded that glyceryl trinitrate may provide an effective and safe method of tocolysis well suited for long term use. Purpose of reporting this study is to highlight the monitoring accumulation of data on glyceryl trinitrate and reinforce the need to evaluate its use in randomized controlled trial.

Over all complication rate was less and prognosis was good.

CONCLUSION

Glyceryl trinitrate patch as a tocolytic is very effective. This drug has a good patient acceptability and compliance due to its minimal side effects, low cost (compared to other tocolytics) and simple dosage schedule. We concluded that transdermal nitroglycerine patch is safe with ease of administration, advantage of ambulation, without inconvenience to the patients, few tolerable side effects to mother and low risk for baby therefore well suited for long term use.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mogri S, Choudhary L, Verma A. Assessment of the efficacy of glyceryl trinitrate patch as a tocolytic. *Int J Reprod Contracept Obstet Gynecol* 2020;9:4953-7.