

PRETERM LABOUR;

COMPARISON OF EFFICACY OF GLYCERYL TRINITRATE PATCH WITH SALBUTAMOL FOR PROLONGING GESTATION FOR MORE THAN 48 HOURS, 7 DAYS AND UPTO 37 WEEKS OF GESTATION.

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ABSTRACT... Objective: To compare the efficacy of Glyceryl trinitrate patch for prolonging gestation for more than 48 hours, 7 days or up to 37 weeks of gestation with Salbutamol in preterm labour. **Study Design:** Comparative descriptive study. **Setting:** Fatima Memorial Hospital Lahore. **Period:** Dec 2003 to Jan 2005. **Patients & Methods:** The study was carried out on 60 pregnant patients admitted in hospital with the symptoms and signs of preterm labour. The results were statistically analyzed using SPSS version 8.0. **Results:** Two groups (Transdermal Glyceryl Trinitrate group and Salbutamol) comprising 30 patients each were made. In Glyceryl Trinitrate group, transdermal patch was applied and in Salbutamol group,. Intravenous infusion titrated according to frequency, duration and intensity of uterine contractions. All the patients in each group were evaluated for prolongation of gestation for 48 hours till 37th week of gestation. The mean prolongation of pregnancy was 26 days in GTN group and 32 days in Salbutamol group. The decrease in frequency of uterine contractions by $67.51 \pm 7.74\%$ in first 48 hours of applying transdermal Glyceryl Trinitrate patch and by $80.14 \pm 8.43\%$ in Salbutamol group which was statistically significant. **Conclusion:** Trinitrate appears to be a safe, well tolerated and non-invasive but less effective method of suppressing uterine contraction in preterm labour as compared to Salbutamol.

Key words: Preterm, Glyceryl Trinitrate, Salbutamol, Pregnancy.

INTRODUCTION

Preterm labour is defined as "labour, which occurs from viability of the fetus (currently defined in UK as 24 completed weeks of gestational age from the date of last menstrual period assuming a 28 days menstrual cycle or 22 completed weeks from the date of conception, if that is accurately known) until the completion of the 37th week of gestation (i.e. 36 weeks and 6 days is preterm, 37 weeks and 1 day is not.

Preterm birth resulting from preterm labour (PTL) is the most common cause of perinatal morbidity and mortality. Its presentation and treatment are major concerns in obstetric care¹.

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The consequences of PTL and preterm birth occur with increasing severity and frequency with earlier the gestation age of the newborn².

Besides perinatal death in a very young fetus, common complications of PTL includes:

- ▶ Respiratory distress syndrome
- ▶ Necrotizing enterocolitis
- ▶ Sepsis
- ▶ Seizures
- ▶ Hypothermia
- ▶ Feeding Problems
- ▶ Metabolic disturbances
- ▶ Intraventricular hemorrhage

Long term morbidity associated with PTL and delivery includes bronchopulmonary dysplasia and developmental abnormalities. The significant impact of preterm birth is best summarized by the fact: that 10% of babies born prematurely³.

Any attempt to reduce the perinatal wastage of fetal life calls for a successful obstetrical misfortune is more extravagant in this respect, and half of neonatal deaths occurs in premature infants. There are three facts to consider, namely, the prevention^{4,5} of premature labour^{6,7} its management when it becomes inevitable and the rearing of the infants so born.

The responsibility for the first two sides of problem lies with the obstetrician, but the there is now increasingly the pediatrician's concern in any sizeable and up to date maternity unit, and good team work between the two services is essential.

For obstetrics point of view, a lots of drugs have been tried to prevent and treat preterm labour but current drug therapies have not shown in randomized controlled trials to significantly affect perinatal morbidity and mortality. Furthermore, most are associated with significant maternal and fetal side effects. Traditionally used tocolytic agents like Salbutamol and Ritodrine have profound effects on maternal cardiovascular and

metabolic systems and even cause arrhythmias, symptomatic myocardial ischaemia and pulmonary oedema. Use of these tocolytic agents require preliminary investigation. Beta adrenergic agents should not be first choice in women with cardiac diseases, diabetes mellitus, or hyperthyroidism.

Nitric oxide is a potent smooth muscle relaxant produced when nitric oxide synthetase acts on amino acid L-arginine. Its presence has been documented in human myometrium. Human myometrium⁸ is known to synthesize and respond to nitric oxide. Glyceryl- trinitrate⁹ (nitric oxide donor) reduces amplitude and frequencies of uterine contractions in a dose dependant manner, so a potent uterine relaxant and tocolytic effect of Glyceryl trinitrate can be reversed with ease by oxytocics¹⁰.

The safety of Glyceryl trinitrate during tocolysis appears high with no adverse maternal and neonatal outcome. No fetal side effects noted. Only maternal side effects are headache and hypotension¹¹. The use of nitrovasodilators for achieving rapid uterine relaxation in obstetrical emergencies has been documented for nearly 120 years¹². It may provide an effective, safe, non-invasive, and cheap method of tocolysis well suited for long term use.

MATERIAL AND METHODS

It is comparative clinical drug trial, conducted in Gynaecology and Obstetric department of Fatima Memorial Hospital, Shadman, Lahore for one year period.

The study was carried out on 60 pregnant patients admitted on hospital with the symptoms and signs of preterm labour between 28th an 36th week of gestation.

Patients were randomly assigned to receive transdermal Glyceryl trinitrate or intravenous Salbutamol as tocolytics using a random number table.

On admission, patients in both groups were evaluated through detailed history including presenting complaints, history of presenting symptoms, past medical, surgical and obstetrical, gynecological, drug and family history.

Various risk factors like urinary tract infection, vaginal discharge etc. were identified.

Examination including general physical examination, (pulse and BP etc), systemic, abdominal, per speculum and per vaginal examination was carried out.

Investigations like complete blood count, blood group, uterine and high vaginal swabs were carried before the administration of the drug.

Obstetrical ultrasonography was done in all patients assigned to each group to assess gestational age, liquor volume, placental localization, approximate fetal weight, number of fetuses, lie and presentation, to rule out fetal anomalies and for fetal well being (biophysical profile).

Baseline cardiography of every patient was done.

The study includes obstetric patients with preserved amniotic sac, no vaginal bleeding, and no cardiovascular diseases.

Criteria for excluding patients from our study was as follows: abnormal cardiotocographic results, Symptoms of intra uterine infections, preterm premature rupture of membrane, intrauterine fetal demise, severe intrauterine growth retardation, antepartum hemorrhage with hemodynamic instability and cervical dilatation more than 4cm.

Technique

On 30 random patients, 10mg Glyceryl trinitrate patch was applied to the skin of the abdomen. After one hour, if there was no reduction in contraction frequency or intensity, an additional patch of 10mg was applied; no more than two patches were applied simultaneously. The patches were left in place for 24 hours, after which these patches were removed and patient reassessed.

On other 30 random patients, Salbutamol was used. To 500ml of 5% dextrose solution, 5mg of Salbutamol was added. The infusion was started at rate of 10 drops per minute and then increased by 10 drops every 5-10

minutes until contraction ceased. Then tapered off slowly in next 12 hours.

The patients remained in the left lateral recumbent position for few hours. After administering each drug, contractility and muscular tension of uterus, frequency and intensity of pain during uterine contractions were monitored.

During the first 3 hours after administration of each drug, pulse rate and arterial blood pressure of obstetric patients were observed every 15 minutes then 2 hourly onwards.

Following treatment discontinued if serious side effects developed in any group, or if pulse rate more than 130beats per minute in Salbutamol group.

Gestational period prolonged was noted for less than 48 hours, uptill 1 week or till 37th week of gestation.

Both treatments were discontinued if contractions ceased for 24 hours or delivery occurred.

The obtained results were statistically analyzed, using computer software SPSS version 8.0.

Statistical Analysis

Data collected was entered in computer software SPSS version 8.0 and following statistical tests were done.

Mean and standard deviation was calculated for gestation prolonged in Glyceryl trinitrate group and Salbutamol group.

Then gestation prolonged was compared between transdermal Glyceryl trinitrate and Salbutamol group using paired sample "T-Test and a P-value" was obtained. All these results were multiplied with 100 to get the percentage.

RESULTS

This comparative clinical drug trial was done at Department of Obstetrics and Gynecology, of Fatima

Memorial Hospital Shadman, Lahore. The study performed was of one- year period, purpose of study was to compare the transdermal Glyceryl Trinitrate and Salbutamol in preterm labour.

Two group (Transdermal Glyceryl Trinitrate group and Salbutamol) comprising 30 patients were made. In Glyceryl trinitrate group, transdermal patch was applied and in Salbutamol group. Intravenous infusion titrated according to frequency, duration and intensity of uterine contractions.

There were 12 (40%) patients from 18-25 years, 11 (33.67%) from 25-30 years and 7 (23.33%) patients were more than 35 years in both transdermal Glyceryl Trinitrate and Salbutamol group (Table I).

Age (years)	GTN Group	Salbutamol Group (n=30)
18-25	12 (40.00%)	12 (40.00%)
25-35	11 (33.67%)	11 (11.67%)
>35	7 (23.33%)	7 (23.33%)

In this study, 5 (16.67%) patients in each group presented with preterm labour are 28-32 weeks of gestation. 12 (40.00%) patients in transdermal GTN and 15 (50.00%) patients in Salbutamol group were presented at 32-35 weeks of gestation and 13 (43.33%) patients in transdermal GTN and 10 (33.33%) patients were presented at 35-36 weeks of gestation (Table II).

Gestational age (Wks)	GTN Group (n=30)	Salbutamol Group (n=30)	P-value
28-32 Wks	5 (16.67%)	5 (16.67%)	0.696
32-35 Wks	12 (40.00%)	15 (50.00%)	
35-36 Wks	13 (43.33%)	10 (33.33%)	

6 (20.00%) patients in transdermal (GTN group and 7 (23.33%) patients in Salbutamol group were having uterine contractions less than 2 per 10minutes at time

patients in Salbutamol group were having uterine contractions 2-3 per 10 minutes and 8(28.68%) patients in transdermal GTN and 9 (30.00%) patients in Salbutamol group were having uterine contractions 3-4 per 10 minutes (Table III).

No. of contractions per 10 min	GTN Group (n=30)	Salbutamol Group (n=30)	P-value
< 2	6 (20.00%)	7 (23.33%)	0.874
2-3	16 (53.33%)	14 (46.66%)	
3-4	8 (28.66%)	9 (30.00%)	

Pervaginal examination was done in all patients of tranadermal GTN group and Salbutamol group to assess to cervical findings at time of presentation. Nine (30.33%) patients in transdermal GTN group 7 (23.33%) patients in Salbutamol group were having cervical dilation < 1 cm a time of presentation. Fifteen (50.00%) patients in transdermal GTN group and 16 (53.33%) patients in Salbutamol group were having cervical dilation between 1-2 cm, and cervical dilation of 3-4 cm was present in 6 (20.00%) patients in transdermal GTN group and 7 (23.33%) patients in Salbutamol group (Table IV).

Cervical Dilatation in cm	GTN Group	Salbutamol Group	P-value
< 1cm	9 (30.00%)	7 (23.33%)	0.836
1-2cm	15 (50.00%)	16 (53.33%)	
3-4cm	6 (20.00%)	7 (23.22%)	

All the patients in each group were evaluated for prolongation of gestation for >48 hour till 37th week of gestation.

Five (16.68%) patients on transdermal GTN group and 3 (10.00%) patients of Salbutamol group prolonged gestation for more than 24 hours. Fifteen (60.00%)

patients in transdermal GTN group and 8 (26.66%) patients in Salbutamol group prolonged gestation between 24-48 hours. 3 (10.00%) patients in transdermal GTN group and 5 (16.66%) patients in Salbutamol group prolonged gestation for 48 patients in Salbutamol group prolonged pregnancy for more than 1 week. Two (6.68%) patients of transdermal GTN and 5 (16.66%) patients in Salbutamol group prolonged pregnancy upto 37th week of gestation (Table V).

Duration Dilatation in cm	GTN Group (n=30)	Salbutamol Group(n=30)	P-value
< 24 hour	5 (16.66%)	3 (23.33%)	0.071
24-48 hours	15 (60.00%)	8 (26.66%)	
48 hours -1 week	3 (10.00%)	5 (16.66%)	
1 - 36 week	2 (6.66%)	9 (30.00%)	
Till 37 weeks	2 (6.66%)	5 (16.66%)	

Each patient in both group was evaluated for any maternal complications. Adverse effects were common, but differed between groups.

The mean prolongation of pregnancy was 26 days in GTN group and 32 days in Salbutamol group (Table VI).

GTN Group	Salbutamol Group
26 Days	32 Days

Treatment with transdermal Glyceryl trinitrate in the form of patches is simple, cheap, non-invasive, but less effective than intravenous Salbutamol. It was accepted both by the patients and the medical personnel because less side effects and no serious side effects noted and in case of side effects, it is easy to stop administering the drug by removing the patch in transdermal GTN group as compared to Salbutamol group.

DISCUSSION

Preterm labour and delivery accounts for a major proportion of neonatal deaths. Its incidence is 5-10%¹³ of all births. In Europe, about 3,75,000 preterm births occur per year and worldwide it accounts 13 million births per year. The cause of preterm birth is usually not known, but in more instances, maintaining the fetus in utero appears to be preferred than to allow the preterm delivery. Any treatment to prevent it could have a profound effect on neonatal outcome both in human and economic terms.

The pathogenesis and cause of preterm labour remain poorly understood. Our ability to predict¹⁴ those at risk of preterm labour is also inaccurate, despite the existence of scoring system, uterine activity monitoring, cervical ultrasound and several biochemical markers.

Currently, the beta-adrenoreceptor¹⁵ stimulants such as Salbutamol, ritodrine, terbutaline, isoxsuprine and fenoterol provide the good efficacy¹⁶ and commonest form of tocolytic therapy to prevent preterm labour. However, because of their potential adverse effects, adequate maternal and fetal surveillance needs to be maintained throughout their administration. Magnesium sulphate, although probably not as effective as other labour inhibiting drugs, is an appropriate choice when the beta- adrenoreceptor stimulants are either contraindicated or poorly tolerated. Other drugs such as the prostaglandin synthetase inhibitor (indomethacine), diazoxide or the calcium channel blocker (nifedipine, nicardipine) are also potent labour inhibitors.

Glyceryl – trinitrate as transdermal releasing system is a nitric oxide (NO) donor¹⁷. Nitric oxide is a potent smooth muscle relaxant^{18,19}. Its presence in the myometrium⁸ has been demonstrated in human myometrium since 120 years. Its use in preterm labour as tocolytic agent has been recognized. Evidence suggested that GTN, a NO donor, should be a safe, well tolerated and effective new tocolytic agent and early observations are encouraging and this can be a breakthrough in the management of preterm labour in terms of safety, tolerability, cost effectiveness and efficacy.

Our study aimed to compare the efficacy of Glyceryl-trinitrate patch on prolonging gestation for more than 48 hours, 7 days or upto 37th week of gestation with Salbutamol in preterm labour.

Sixty patients admitted in preterm labour in obstetric and gynaecology department of Sir Ganga Ram Hospital Lahore were selected. These patients were randomized in two randomized in two groups of 30 each using a random number table. These patients were between gestational age of 24 -36 weeks and were selected in our study according to inclusion and exclusion criteria.

On 30 random patients, Glyceryl – trinitrate patch was applied and patients were monitored for its effectiveness and adverse effects on both mother and fetus.

Efficacy and side effects evaluated and then two modes of treatment compared to find out the better efficacy.

Our study has shows the only common maternal side effect was headache (30%) in transdermal Glyceryl trinitrate group. Rowland & Trudinger B, Visual- lingam & in their study have shown the similar.

Our study has shown, no fetal adverse effects were noted in GTN group. Similar results were in Rowland et al¹⁹.

In our study mean prolongation of pregnancy was 26 days in GTN group. Which is comparable to study of Lee S, et al. i.e., 34 days²⁰.

In our study mean prolongation of pregnancy was 32 days in Salbutamol group. It is comparable to study of Hutchings MJ, et al. in which prolongation of pregnancy was 40 days²¹.

In our study 2 (6.66%) patients had fetal tachycardia and only one (3.33%) patient had cardiocotographic abnormalities in Salbutamol group as compared to no fetal side effects in GTN group.

As compared to Salbutamol, GTN patch has advantage

of no serious maternal and fetal side effects. Treatment discontinuation rates were also fewer. Besides headache, no maternal side effect found out in GTN group.

CONCLUSION AND SUGGESTIONS

- ▶ On the basis of our study, transdermal Glyceryll – Trinitrate appears to be a safe, well tolerated and non-invasive but less effectives method of suppressing uterine contraction in preterm labour as compared to Salbutamol.
- ▶ It can be used in patients with diabetes mellitus, hyperthyroidism, and cardiac diseases without risk which are associated with Salbutamol.
- ▶ Less frequent maternal and fetal monitoring is required in patients having Glyceryl – Trinitrate tocolysis than in patients having Salbutamol.
- ▶ Because our sample size was small, so large randomized controlled trials should occur to determine the significance of this breakthrough in the management of preterm labour.

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**The ripest peach is
the highest on
tree.**

Shakeel Talat