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PRETERM LABOUR
EFFECTIVENESS OF TRANSDERMAL GLYCERYL TRINITRATE PATCH

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ABSTRACT... Objective: To determine the effectiveness of transdermal patch of glyceryl trinitrate as tocolytic agent. **Study design:** Interventional- Quasi experimental study. **Setting:** Department of Obstetrics and Gynecology Unit- 1, Services hospital, Lahore. **Duration with dates:** One year (February 10, 2006 – February 10, 2007). **Sample size:** Fifty pregnant women with preterm labour were included in the study. **Results:** 54% of pregnant women were between G2 – G4. Majority (48%) of the women presented between 31 – 34 weeks of gestation. 46% of pregnant women had bishop score of 4 or more. 64% of patients found to have no risk factor for preterm labour. Majority (86%) responded after application of second patch (10 mg glyceryl trinitrate patch). 84% had no side effects. Local skin reaction (10%) and headache (4%) observed in few patients. 58% of pregnant women delivered after 48 hours and 78% of them delivered vaginally which was statically significant and majority of babies delivered weight more than 1.5 kg and with good Apgar score. **Conclusions:** It is concluded from the study that glyceryl trinitrate is a safer tocolytic, which has simple method of application; rapid onset of action with low cost, low risk from side effects and it does not require intensive monitoring.

Key words: Preterm labour, labour, tocolysis, transdemal glyceryl trinitrate.

INTRODUCTION

Preterm labour is defined as labour, which occurs from viability of the fetus (that is 28 weeks of gestation in under developing countries) until completed 37 weeks of gestation. Preterm births complicate 10% of pregnancies and are the single largest cause of perinatal morbidity and mortality. To make the diagnosis of labour is sometimes difficult. Frequently used criteria for labour are uterine contractions with a frequency of two or more every 10 minutes with duration of 30 seconds or more and progressive change in effacement and dilatation of cervix.

Commonly used drugs in tocolysis are beta sympathomimetic (ritodrine, salbutamol and terbutaline), cyclo-oxygenase inhibitors (indomethacin), calcium channel blockers (nifidipine), nitric oxide donors and oxytocin antagonist (atosiban)[1]. Nitric oxide donors such as glyceryl trinitrate are undergoing tria after encouraging preliminary reports. Recent recommendations are to use these agents in combination[2].

Tocolysis is rarely successful in prevention of preterm labour but can delay delivery for 48 hours and this may allow sufficient time for the maternal steroid treatment or in utero transfer to specialized neonatal care facility,[3] this can considerably reduce complications related to prematurity[4]. American college of Obstetrics and Gynecologists stated in a 2003 guideline that no optimal first line agent for tocolysis has been identified. Both the potential benefits and harms of tocolytic agents need to be considered. Research is needed to develop a drug, which has a greater uterospecificity with no effect on other organs with a rapid onset and a short duration of action[5].

Glyceryl trinitrate 10 mg patch applied transdermally was reported to be effective and safe for treatment of preterm labour. The pharmacological active principle of glyceryl trinitrate is nitrous oxide, which is an important mediator of relaxation of various smooth muscles including vascular, gastrointestinal and urogenital. Nitric oxide activates soluble guanylate cyclase, which results in increased cyclic guanine monophosphate (cGMP) level that acts as a second messenger of muscle relaxation.

Glyceryl trinitrate produces concentration-dependant inhibition of uterine activity. Low concentration of glyceryl trinitrate produces transient inhibition, while higher concentration has been reported to abolish the uterine contractions completely. The long-term transdermal treatment affords possibilities for pregnancy prolongation and improves the foetal development conditions. The side effects of treatment are transient and affected only mothers.

This study is aimed to use glyceryl trinitrate as tocolytic agent. It is free of many side effects and can also be used in patients when preterm labour is associated with diabetes, hypertension, pulmonary oedema or arrhythmia in mother. Glyceryl trinitrate has simple method of application; rapid onset of action, low cost, low risk from side effects and it does not require intensive monitoring.

MATERIAL AND METHODS

The study was carried out on fifty patients in the department of Obstetrics and Gynecology, Services hospital, Lahore from February, 2006 to February, 2007.

All pregnant women who were diagnosed to be in preterm labour were included in the study. On the other hand women with cervical dilatation beyond 4 cm, fetal malformations, fetal death, fetal distress, severe pre – eclampsis or eclampsia, vaginal bleeding, chorioamnionitis and hypersensitivity to glyceryl trinitrate were excluded from the study.

The effects, route of administration and side effects of transdermal glyceryl trinitrate patch will be explained to the patient. After informed consent 10 mg transdermal glyceryl trinitrate patch will be applied which can be repeated after 12 hours if required. Data collection will be done on proforma attached. Effectiveness of transdermal glyceryl trinitrate patch will be determined. Record will be kept and all the patients will be requested to return for regular antenatal check up as per department routine and will be followed till she delivers.

The data will be computer based; SPSS 10 will be used for analysis. Frequency of arresting preterm labour, tocolysis-delivery interval (mean ± standard deviation), frequency of side effects in mothers, Apgar score of babies and frequency of admission in neonatal unit will be calculated. For comparison with other studies T-test of proportion will be used.

RESULTS

Glyceryl trinitrate patch was applied on fifty pregnant women fulfilling the inclusion criteria.

54% of pregnant women were between G2-G4, 28% were PG and 18% were G5 or above as shown in Table I.

Table-I. Distribution of study according to parity

Parity	No. of cases	%age
PG	14	28
G2-G4	27	54
≥G5	9	18
Total	50	100

Distribution according to duration of pregnancy is shown in Table II. Majority of the pregnant women presented between 31-34 weeks of gestation i.e. 48%. 44% presented between 34-36 weeks only 8% presented between 28-30weeks.

Table-II. Distribution according to duration of pregnancy

Gestational age	No. of cases	%age
28-30 weeks	4	8
31-34 weeks	24	48
34-36 weeks	22	44
Total	50	100

46% of pregnant women had bishop score of 4 or more, 30% with bishop of 3 and 20% with bishop score of 2 as shown in Table III.

Table-III. Distribution according to Bishop score

Bishop score	No. of cases	%age
1	2	4
2	10	20
3	15	30
≥4	23	46
Total	50	100

Number of patches required for arresting preterm labour is shown in Table IV. In 14% of pregnant women only single patch of 10mg was used but majority i.e. 86% responded after the application of second patch. 84% of pregnant women had no side effects of drug.

Table-IV. Number of patches required

No. of patches required	No. of cases	%age
One	7	14
Two	43	86
Total	50	100

Table-V. Maternal side effects

Maternal side effects	No. of cases	%age
Allergic skin reaction (Local skin reatcion)	5	10
Headache	2	4
None	43	85
Total	50	100

Chi-Square = 62.28 Degree of freedom = 2
P-value = 0.000 (Significant)

Frequency of maternal side effects is shown in Table V. Only 10% had local skin reaction in the form of redness and 4% had headache. 86% had no side effects (p value 0.000).

Majority i.e. 58% of the pregnant women delivered after 48hours, 26% between 24-48 hours and 16% delivered before 24hours (p value 0.001) as shown in Table VI.
Table VII shows mode of delivery. 78% of pregnant women delivered vaginally and 22% had cesarean section (p value 0.048).

Fetal weight is shown in Table VIII. 48% of babies had weight between 1.5 – 2 kg at birth, 34% had weight of >2 kg and only 24% were < 1.5 kg at birth.

Most of newborn delivered to mothers receiving glyceryl trinitrate for tocolysis had 1 min A/S of 4 to 6 and 5 min A/S of 8-10 as shown in Table IX.

Frequency of admission in neonatal unit is shown in Table X. The perinatal outcome was excellent and there was only 1 early neonatal death. 36% of babies required admission in neonatal unit and all of them were discharged in satisfactory condition. Mostly discharged within 7 days of admission.

Table-VI. Tocolysis delivery interval

Time	No. of cases	%age
<24 hours	8	16
24-48 hours	13	26
>48 hours	29	52
Total	50	100

Chi-Square = 14.40 Degree of freedom = 2
P-value = 0.001 (Significant)

Table-VII. Mode of delivery

Mode of delivery	No. of cases	%age
SVD	39	78
C-Section	11	22
Total	50	100

Chi-Square = 3.920 Degree of freedom = 1
P-value = 0.048 (Significant)

Table-VIII. Outcome

Weight	No. of cases	%age
<1.5Kg	12	24
1.5-2 Kg	21	42
> 2Kg	17	34
Total	50	100

Chi-Square = 2.440 Degree of freedom = 2
P-value = 0.295 (Insignificant)

DISCUSSION

Improved neonatal morbidity and mortality is the primary reason of tocolysis[6] Use of any tocolytic is a balance of the risks of the drug to the mother or fetus against the potential benefits of the tocolysis[7]. It remains plausible that for selected women, such as those who require transfer for neonatal care time to complete a course of corticosteroids, there may be benefit associated with tocolysis[8,9].

Table-IX. Apgar Score

Apgar score	No. of cases	%age
1-3	1	1
4-6	48	11
8-10	1	38
Total	50	100

Chi-Square = 88.360 Degree of freedom = 2
P-value = 0.000 (Significant)

Table-X. Admission in neonatal Unit

	No. of cases	%age
Admission in neonatal unit	18	36
No. admission in neonatal unit	32	64
Total	50	100

The risk for neonatal respiratory distress is higher at 34 weeks compared to 35 and 36 weeks. Most studies have evaluated the effectiveness of tocolytic treatment during 48 hours. The ultimate goal of treating preterm labour is to prolong the pregnancy long enough to decrease the incidence of neonatal morbidity and mortality associated with prematurity, while minimizing maternal and fetal risks[10].

Transdermal patches releasing glyceryl trinitrate afford possibilities for pregnancy prolongation until the term of delivery and improve the fetal development conditions[11]. The side effects of treatment are transient and affected only mothers[12]. Reduction of CRH secretion may be the mechanism of nitroglycerine patch on preterm labour therapy. It may act as an effective, safe, well-tolerated, non invasive method of treatment of pretrm labour[13].

In my study it was noted that mostly multigravidas had preterm labour. This was also supported by trail of Malik M et al[14] who treated seventy women with preterm labour with glyceryl trinitrate and majority of them were multigravidas and only 30% were primigravida.

In this study majority of pregnant women presented between 31 – 34 weeks of gestation, which was also concluded by Aruna-Kumar et al[15] that maximum number of patients with preterm labour were enrolled between gestational ages of 31 – 32 weeks.

In this study 10 mg patch was used with maximum of 2 patches 12 hours apart. In a trial by Rowlands et al[16], he used a 50 mg patch whereas Lees et al[17] and Krishna et al[18] also used a 10mg patch as in my study. Anne D. Walling[19] did a randomized trial to compare glyceryl trinitrate and ritodrine in tocolysis. He also used a 10 mg patch but they unlike my study used a second patch after one hour if there was no reduction in contraction.

Nitroglycerine proves to be an effective tocolytic agent because the main aim was to delay delivery by 48 hours so that steroids can have their desired effect and if required in utero transfer can be arranged. Most of the pregnant women in this study delivered after 48 hours of tocolysis which was statistically significant and was also supported by Aruna Kumar et al[15] who did a prospective study on 100 patients of preterm labour to assess the efficacy of glyceryl trinitrate as tocolytic and concluded a delay of delivery for 48 hours was observed in 95% patients. Similar results were also noted in study conducted by Parveen S et al[20] who concluded that 64% had successful tocolysis of 48 and more than 48 hours.

The safety of the drug was judged on the basis of its side effects. In this study maternal side effects were fewer which was also statistically significant. Majority of the patients had no side effects to the drug. Equivalency trials done by Less C et al[21], Wani MP et al[22] and Black RS et al[23] using transdermal glyceryl trinitrate have not reported problems with hypotension.

10% 0f women had local skin reaction with glyceryl trinitrate in this study that also consistent to the trial by Aruna Kumar et al[14] who observed that 7% of the patients in his study had skin rash and itching at the site of patch. This was also noted in a study conducted by Santoro A et al[24] on assessment of skin safety of a new glyceryl trinitrate trasdermal patch. On the application site a light and transient erythema was often found demonstrating the transcutaneous absorption of the vasodilating glyceryl trinitrate from the patch.

It was seen in this study that negligible number of pregnant women had headache, which did not necessitate the removal of patch. This also supported by the randomized double blind placebo controlled trial of transdermal nitroglycerine for preterm labour by Graeme N et al. In this study they randomized 153 women with preterm labour to receive either transdermal nitroglycerine or placebo patches and there was no statistically significant difference in adverse events.

Bustard MA et al[25], Bootstaylor BS et al[26] in their animal studies and Bistis A et al[27], Schleussner E et al[28] and Bustard MA et al[29] in their human studies suggested that glyceryl trinitrate is safe when used in tocolytic doses. While small amounts of glyceryl trinitrate does cross the placenta, which was studied by Bustard MA et al[30] in his study of pharmacokinetics of glyceryl trinitrate with the use of glyceryl trinitrate in vitro term human placental perfusion setup. Human Doppler studies suggest that glyceryl trinitrate does not alter normal fetal or uteroplacental blood flow this is supported by the studies conducted by Leszczynska-Gorazelak B et al[31] in studying the influence of transdermal nitroglycerine patches on fetal blood flow parameters.

In this study it was seen that majority of the pregnant women delivered vaginally. An antegrade study conducted at Lady Wallington Hospital, Lahore by Ahmed K et al on perinatal morbidity and mortality in case of preterm labour suggested that complications related to prematurity can be avoided by delivery by cesarean section in low birth weight babies[32]. The use of glyceryl trinitrate prolongs pregnancy to that gestation at which vaginal delivery can be safely attempted with good fetal outcome.

It was concluded from the study that perinatal outcome was better with advancing gestation and increasing weight of baby. This was also supported by Fatima F et al[33] in retrospective review; found overall perinatal mortality in preterm group was 368/1000. The perinatal mortality fell with advancing gestation being 66% at 28 – 31 weeks, 38% at 32 – 33 weeks to 20% at 34 – 36 weeks. The perinatal mortality rate also felt with birth weight from 826/1000 birth of 1 – 1.4 kg to 115/1000 at 1.5 – 2.5 kg.

Nitroglycerine is an effective tocolytic with minimal complications, rapid onset of action and brief half life[34]. Glyceryl trinitrate appear to be a safe, well-tolerated and non-invasive method of suppressing uterine contractions in preterm labour[35]. Pregnancy prolongation improves the fetal developmental conditions. The side effects are transient and affected only mothers[36].

CONCLUSION

It is concluded from the study that transdermal glyceryl trinitrate is a safe and effective tocolytic, which has simple method of application; rapid onset of action, low cost, low risk from side effects and it does not require intensive monitoring. Transdermal nitroglycerine appears to be a safe therapy for the mother and fetus and is a promising new option for the treatment of preterm labour.

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