Efficacy of Transdermal Nitroglycerine in idiopathic pre-term labour
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Abstract

Objective: To determine the efficacy of transdermal Nitroglycerine patch in idiopathic pre-term labour and foeto-maternal outcome.

Methods: This quasi-experimental study was conducted at the Obstetrics Unit-II of Shaikh Zayed Hospital for Women, Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, from Jan 1 to June 30, 2010. Sixtyfive pregnant women at 28-34 weeks of gestation were recruited after they met the selection criteria based on non-probability consecutive sampling. Initially, 73 patients were selected, but 65 of them completed the treatment, while 8 patients refused to continue. Patients diagnosed with pre-term labour were given glyceryl trinitrate (GTN) 5 mg/12 hours transdermal patch which was applied on the anterior abdominal wall. The second patch of same dose was given after 12 hours. Arrest of labour, prolongation of pregnancy in days or weeks along with side effects of the agent were monitored. Patients were followed till delivery to know the foeto-maternal outcome.

Results: Dramatic effects were seen in around 60 (92.3%), of the total patients who had felt relief from premature labour pains within the first hour and only 5 (7.6%) patients could not go beyond 24 hours, as among them 3 (4.61%) had previous uterine scar and 2 (3.07%) developed ruptured membranes after 12 hours of admission and their babies also could not survive. Mean pregnancy prolongation was 15.35±9.45 days (min: 4 max: 35), so delivery was deferred up to 48 hours, 3 to 7 days and more than 7 days in 4 (6.15%), 6 (9.23%) and 50 (76.92%) respectively.

Conclusion: Glyceryl trinitrate, trans dermal patch is effective and safe tocolytic in idiopathic preterm labour. By prolonging pregnancy it improves neonatal outcome.

Keywords: Pre-term labour, Glycerinal nitrate, Prolongation of pregnancy (JPMA 62: 47; 2012).

Introduction

Pre-term labour is defined as the onset of labour after the age of viability (20-24) and before 37 completed weeks of pregnancy and its incidence is 6-10% of all births in developed countries.1 It is common in patients with low body weight, low stature, unsupported mothers, smokers and lower social classes.2 Risk factors that have been linked to pre-term delivery include cervical incompetence, haemorrhage like abruptio placenta, genital tract infection like bacterial vaginosis, hormonal changes due to maternal or foetal stress, multifetal pregnancy and previous history of pre-term labour.3 In Pakistan perinatal mortality is 96 per one thousand births.1 Neonatal mortality gradually rises between 28-34 weeks from 2-8% and then more dramatically and exponentially to 80% at 23 weeks.3 Pre-term labour is a leading cause of long-term morbidity in babies, including neurodevelopmental handicap, cerebral palsy, seizure disorders, blindness, deafness and non-neurological disorders like bronchopulmonary dysplasia and retinopathy of prematurity. Hence the aim of the treatment for pre-term delivery is to suppress the uterine contractions so as to delay the pre-term birth to allow administration of complete course of corticosteroids in order to reduce incidence of respiratory distress syndrome and to subsequently arrange in utero transfer to a centre with neonatal intensive care unit facility to reduce perinatal morbidity and mortality associated with severe prematurity.1 For this purpose a wide variety of agents have been advocated like beta agonists, calcium channel blockers, prostaglandin synthetase inhibitors, magnesium sulphate and also oxytocin receptor antagonists.4 Most of these drugs require strict monitoring of both mother and foetus due to their adverse effects.1

Nitroglycerine (nitric oxide donors) may be an effective choice as a tocolytic agent due to its safety profile with infrequent maternal and foetal side effects.5 It is a vasodilator that is essential for maintenance of normal smooth muscle tone of uterus. There is now considerable evidence that nitric oxide is involved in the regulation of myometrial contractility during pregnancy, where nitric oxide donors have been applied on myometrium in vitro, inhibition of spontaneous and oxytocin-induced activity was found when amplitude or force of contraction was measured.6 Pregnancy is prolonged by its direct effect on the uterine blood flow.7 In a randomised controlled study
tocolysis with nitric oxide donor, it was found that transdermal glyceryl trinitrate was effective in delaying the pregnancy beyond 48 hours and prolonging gestation to 37 weeks.\(^8\) In that study, out of 153 women 74 who received a nitroglycerine patch had reduced neonatal complications compared to the 79 who had received a placebo.\(^8\)

As about 5-10\(^\%\) of the patients, at our tertiary care hospital report with idiopathic pre-term labour and because of increased turnover of patients having multiple risk factors, our study was an attempt to determine the efficacy of nitroglycerine patch in pre-term labour to help in the prolongation of pregnancy and subsequent neonatal outcome by improving their APGAR score. Also the use of nitroglycerine for women in pre-term may result in major cost cuts and long-term benefits.

**Subjects and Methods**

The study was conducted from January to June 2010. It was carried out at the Obstetrics and Gynaecology Unit-II of Shaikh Zayed Hospital for Women, Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, after taking formal Institutional Review Board's approval. A total of 73 women with pre-term labour pains who were admitted to labour room via OPD or Emergency and those who fulfilled the inclusion/exclusion criteria, were recruited in the study after informed written consent. The sample size was calculated according to prevalence of condition (5\%)\(^7\) with non-probability convenience sampling technique with the following formula:

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Z_{a/2} \times 95\% \text{ Confidence Level} = 1.96
\]

Prevalence 5\%; \(p = 0.05 \& 1-p = 0.95\) \(n = 73\)

Eight women refused to continue with the trial once the treatment was started. This reduced the study size to 65 patients.

The inclusion criteria were: gestational age between 28-34 weeks, women in the age group of 20-35 years, women with parity up to four, singleton pregnancy, and patients with pre-term labour pains but intact membranes.

The exclusion criteria were: history of hypertensive disorders and major cardiac disease, diabetese, poly hydramnios, cases of antepartum haemorrhage, foetal anomaly, foetal distress and intrauterine death, and uterine anomalies like bicornuate uterus or uterine fibroids.

Pre-term labour was diagnosed on history and findings on examination on the basis of 3 or more uterine contractions per 30 minutes and cervical dilatation <4cm. The procedure was explained to all women. Nitroglycerine patch of 5mg was applied over the anterior abdominal wall. Uterine contractions were noted on the pre-designed proforma. The second patch of same strength (5mg) was applied after 12 hours. To avoid expected hypotensive effect of glyceral trinitrate patch, prophylactic infusion of 500 ml of normal saline was given to all women and blood pressure was monitored every 30 minutes for 3 hours and six hourly afterwards. Side effects were observed and recorded; they included maternal hypotension, headache, flushing, local irritation and foetal heart rate changes. Blood samples for complete blood picture, blood sugar, urine for detailed report, and high vaginal swab were taken at admission to rule out any infection. Ultrasound was done for foetal well-being and to exclude uterine anomalies.

The outcome of treatment was the prolongation of pregnancy or delivery in hours or days after the start of tocolytic therapy and was deemed successful if delivery was deferred for at least 48 hours. The women, therefore, stayed in the ward for at least 48 to 72 hours to complete corticosteroid doses and were then discharged and counselled for follow-up until delivery. At delivery APGAR score and the weight of the newborn were recorded on the pre-designed proforma.

Data analysis was done with the help of SPSS software (version 10.0). Frequency and percentage were computed for categorical variables like doses of nitroglycerine patch, uterine contractions, maternal side effects, neonatal APGAR score/weight and gestational age prolongation period. Mean and standard deviation were computed for quantitative variables and analysed by applying Pearson test and \(p\)-value <0.05 was taken as level of significance.

**Results**

The study initially recruited 73 patients with pre-term labour once they fulfilled the exclusion and inclusion criteria from January 1 to June 30, 2010. Eight patients did not continue with the trial. Hence, the results were based on 65 patients who were given 5mg GTN patch immediately and 5mg after 12 hours. We found pre-term labour more in multiparous women (parity taken up to four) i.e. 45 (70\%) as compared to primiparous which numbered 20 (30\%). The mean age was 25 ± 3.5 years (range 20 to 35). Of the total, 30 patients (46\%) were admitted through OPD, while 35(54\%) reported in the Emergency Ward. Only 27 (41\%) patients were booked. Of the patients, 57 (87.6\%) had gestation between 28-30 weeks, while 8 (12.3\%) patients came between 31 to 34 weeks. A total of 60 (92\%) women benefited from the GTN patch and the labour pains stopped within the first few hours (\(p\)- <0.05). Only 5 (7.6\%) patients could not go beyond 24 hours, as among them 3 (4.61\%) patients had previous uterine scar and 2 (3.07\%)
women developed ruptured membranes after 12 hours. Delivery was deferred for 48 hours, 3 to 7 days and more than 7 days in 4 (6.15%), 6 (9.23%) and 50 (76.92%) respectively (Table).

Mean pregnancy prolongation was 15.35±9.45 days (min: 4 max: 35). All the (100%) babies were born alive. Birth weight of more than 2.4 kg was noted in 18 (27.6%), while 32 (49.2%) were born with birth weight between 2.2 to 2.4kg. Eight (12.3%) babies had weight of 1.9kg to 2.1kg and only 7 (10.7%) had weight of less than 1.8kg. In the last group 5 babies were born within 24 hours of the start of tocolytic, and died in their first week of life due to the refusal of the parents to stay in the neonatology ward for long enough and left against medical advice. The most common side effect noticed among the mothers was headache (10.7%) followed by hypotension (4.6%), vomiting (4.6%) and irritation (3.07%) at patch site. No mother had positive vaginal swab culture. All patients had normal blood and urinary reports. No one reported changed foetal behaviour once they were explained how to maintain the kick chart (count-to-ten).

**Discussion**

Delaying the delivery has two-fold benefits: one is to get enough time to complete the course of antepartum glucocorticosteroids 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.

Tocolytic drugs have been tried for long and even glyceryl trinitrate (GTN) is not a new drug as more than 100 years ago nitric oxide donor was used in pregnancy and was first reported in the British Medical Journal. Glyceryl trinitrate is convenient in its application and patients themselves can have control on symptoms as the patch can be applied and removed as required and due to shorter half-life of GTN, patches have been found to be safe and effective even at higher doses while treating serious patients of angina as well.

In our study 60 of the 65 (92%) patients benefited from the GTN patch which is significantly higher than reported by Parveen S, in whose study about 64% women had arrest of labour for a short term. All the treatments are used mainly to prolong the pregnancy as it has reflective effect on neonatal mortality and short- and long-term morbidity. Therefore, the chance of survival improves by 2% per day from 23 to 26 weeks' gestation and by 28 weeks it reaches approximately 80%. Beyond 30 weeks, more than 90% of newborns survive.

Out studies found that the maximum prolongation of pregnancy was 35 days, and the mean latency period seen was 15.35 days which is comparable with other national and international trials that also supported GTN as effective in delaying the delivery.

The patients who dominated the group treated with the GTN patch had gestation between 28-30 weeks which constituted about 87% of the total patients getting maximum benefit. Not only GTN helps in normo-tensive pregnancies, but also superadded effects are proven especially in pre-eclamptic women in controlling blood pressure, lengthening pregnancy and subsequently improving foeto-placental circulation, halting the process of growth restriction.

Although we have not done double blind controlled trials, but many comparative studies have found GTN as a superior drug in tocolysis.

During the current study, no mother had any change...
in foetal movements as per the kick chart that was given to them, and 50 (77%) babies were born with good APGAR score and the weight ranged from 2.2kg upwards; 32 (49%) babies had weight more than 2.2kg and another 18 neonates (27.6%) weighed 2.5kg. Only 5 (8%) of the patients delivered babies who died in their first week of life due to low birth weight (<1.8 kg) and parental refusal to stay long enough in the neonatal ward. Perinatal outcome is directly related to pregnancy prolongation, which is comparable to many studies utilising GTN in premature labour in their comparative trials using either placebo or other drugs. One international trial found that the risk of developing neonatal morbidity was reduced by 79% and more when mothers were treated with GTN. Another study suggested improved foetal outcome after GTN-induced pregnancy prolongation by confirming decrease in total vascular resistance in maternal and foetal vasculature.

All kinds of tocolytics are associated with one or the other side effect. The commonest side effect seen with GTN is headache, as found by our study where 10.7% of the patients had it. Hypotension was seen in 4.6%, and vomiting in 4.6%. There were treated with stat dose of simple analgesic (tablet paracetamol), oral fluids (I/V fluids were already being given to all patients) and antiemetic respectively. Irritation at patch site was reported by 3.6% of the subjects (being given to all patients) and antiemetic respectively. While irritation at patch site was reported by 3.6% of the subjects (being given to all patients) and antiemetic respectively. While this did not result in the removal of the patch. While headache has been reported upto 30% of patients, but comparatively other tocolytics like ritodrine is associated with maternal tachycardia, palpitation and sometimes even pulmonary oedema. Foetal effects are seen upto the extent of constriction of ductus arteriosus and intraventricular haemorrhage with indomethacin. Fortunately we did not find any serious foetal effect with GTN.

Valuable and desirable results achieved with the GTN, its straightforward administration and safety suggests there shall be multicentre comparative trials of GTN with established therapy or placebo involving larger number of recruited populations. This study obviously showed that GTN has a positive effect on maternal and foetal cardiovascular systems than drugs used previously. Its secure use on record shall make it an alternative to other tocolytic agents, like salbutamol, ritodrine or calcium channel blockers for pre-term labour and could make a major involvement in the management of pre-term labour. Preventive strategy is important, especially when causes of pre-term labour are not known.

**Conclusion**

There is no better incubator than a mother's womb. The GTN patch appears to be a safe, non-invasive method of suppressing uterine contractions in pre-term labour and also simple, quicker and cost-effective tocolytic agent. Current trials with nitric oxide donors may lead to a major breakthrough in the treatment of pre-term labour to decrease perinatal mortality.

**References**