

COMPARATIVE STUDY OF EFFECTIVENESS OF TRANSDERMAL NITROGLYCERINE PATCH AND ORAL NIFEDIPINE IN MANAGEMENT OF PRETERM LABOR.

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Type of Article: Original Article

Conflict of Interest: None

Funding:

Abstract:

Background: *Preterm labour is a pressing public health issue. Currently, nearly one tenth of all the pregnancies are preterm, contributing to ~ 80% of neonatal morbidity and mortality. Although, preterm labour is defined as labour < 37 completed weeks, practically birth after 34 weeks of gestation have better survival outcomes. Tocolytics are the mainstay of reducing preterm deliveries. They cause partial uterine relaxation and hence help in prolonging the pregnancy for at least for 48 - 72 hrs, thus providing sufficient time for corticosteroids to aid in maturation of lungs; thereby preventing respiratory distress syndrome. While there are quite a few tocolytics available, most of them require close fetomaternal monitoring due to their adverse effects. Currently, nifedipine is tocolytic of choice. Nitroglycerine, which is rapidly metabolized in liver has fewer side effects and its transdermal use is beneficial due to its convenience of usage. Since there are very few studies documenting the comparison of the two drugs, our study will be beneficial.*

Objectives: *To study and compare the effectiveness of transdermal Nitroglycerine patch and oral nifedipine.*

Methodology: *This study will include a total of 130 women in preterm labour fulfilling the inclusion and exclusion criteria. These study subjects will be divided into two groups A and B randomly using envelope method. One group will be given transdermal nitroglycerine patch and the other will be given oral nifedipine as a tocolytic agent to reduce the preterm contractions. Treatment will be considered successful if contractions stopped and no recurrence of contractions occurred within or after 48 hours.*

Expected results: Transdermal Nitroglycerine patch is more effective than oral nifedipine in management of preterm labour.

Conclusion: Transdermal nitroglycerine patch is more effective in prolonging the pregnancy as compared to oral nifedipine with less adverse effects.

Key words: preterm labour, transdermal nitroglycerine patch, oral nifedipine

INTRODUCTION:

According to WHO, onset of labour before 37 completed weeks [259 days] counting from the first day of last menstrual period, is termed as Preterm labour. While the exact mechanism of preterm labour remains unclear, it is most frequently associated with either a pathology causing uterine contractions or early/untimely initialization of normal physiological uterine contractions, leading to preterm deliveries (1).

Preterm represents a serious public health problem in 7-12% of the pregnancies and results in up to 70-80% of neonatal morbidity and mortality(2). Practically, survival outcomes are better in births after 34 weeks of gestation, because of rapid advancements in fetomaternal medicine during the last few years.(3)

Use of tocolytics is among the best methods to reduce morbidity and mortality associated with preterm. They cause partial uterine relaxation and hence help in prolonging the pregnancy for at least for 2-3 days and thus, providing adequate time for administration of 4 doses of corticosteroids which would help in lung maturity and prevent respiratory distress syndrome in newborns. Over the time, numerous tocolytics with varying mechanism of actions have been used to delay labour. Use of drugs like Isoxsuprine, Ritodrine, Nifedipine are reported to cause adverse effects like pulmonary oedema, arrhythmia and myocardial ischemia in mothers and neonatal hyperglycemia, hypokalemia, hypoglycemia & paralytic ileus in the fetus.(3)

Nifedipine which works by blocking the voltage dependent calcium channels in the plasma membrane, increasing calcium efflux from cell and decreasing intracellular free calcium, thus causing inhibition of calcium dependent MLCK (Myosin Light Chain Kinase) phosphorylation and myometrial relaxation, is the most commonly used tocolytic drug (4). Another emerging drug which is used as a tocolytic is Nitroglycerine, worldwide known as glyceryl trinitrate (GTN). It is a low molecular weight nitrate which is highly volatile in nature and also known as nitro vasodilator. Nitroglycerine is a drug with a high first pass inactivation in liver. The active substance is rapidly metabolized in the liver by a glutathione dependent organic nitrate reductase. To avoid it, transdermal use of the drug is beneficial so that sufficient level of drug reaches plasma level.(2) It delays the delivery by relaxing the smooth muscles of uterus and also improve blood flow to the uterus and placenta.

It has high first pass metabolism and is rapidly metabolized in liver. But its transdermal use helps in preventing this and ensures that sufficient amount of drug reaches the plasma (2). It also relaxes the smooth muscles of uterus and improves uteroplacental blood flow, thus delaying the delivery.

Nitroglycerin and Nifedipine are both effective tocolytic drugs and very few studies have been done in India comparing the two. Our study aims to study the safety and efficacy of oral nifedipine v/s transdermal nitroglycerin patches as tocolytic agents in the management of preterm labour (5).

RATIONALE:

Various tocolytic drugs are available that are used for uterine relaxation, most of them require a strict monitoring of mother and fetus both due to their adverse effects. As Nitroglycerine is rapidly metabolized in liver, its transdermal use is beneficial due to its convenience of usage and fewer side effects. As there is hardly any local study comparing transdermal Nitroglycerine patch with oral nifedipine, so this study will be done to find out better option amongst the two and recommend a more effective therapeutic intervention for management of preterm labour.

AIM AND OBJECTIVES

AIM

We aim to study the comparison of the effectiveness of transdermal Nitroglycerine patch and oral nifedipine in management of preterm labor.

OBJECTIVES

The objectives of this study are-

- 1) To study the effectiveness of transdermal Nitroglycerine patch in management of preterm labour.
- 2) To study the effectiveness of oral nifedipine in management of preterm labour.
- 3) To Compare the effectiveness of transdermal Nitroglycerine patch and oral nifedipine.
- 4) To study and compare adverse effects of transdermal Nitroglycerine patch and oral nifedipine.
- 5) To study and compare the fetal outcome of transdermal Nitroglycerine patch and oral nifedipine.

MATERIAL AND METHOD:

Study design: prospective comparative observational study

Place of study: Department of Obstetrics and Gynecology JNMC, AVBRH, DMIMS (Deemed university), Wardha

Duration of study: September 2020 -September 2022

Study Population: Pregnant woman who is in preterm labour seeking care at inpatient unit of Obstetrics &Gynecology, in the, AVBRH hospital, Sawangi, Meghe, fitting into inclusion and exclusion criteria of study.

Inclusion Criteria:

- Gestational age between 28-37 weeks
- Regular painful uterine contractions minimum of 4 in 20 minutes or 8 in 60 minutes.
- With intact membranes
- Effacement \geq 80%.
- Cervical dilatation between 1cm to 3 cm
- Singleton pregnancy with cephalic presentation

Exclusion Criteria:

- Antepartum hemorrhage.
- Eclampsia (or) severe pre-eclampsia
- Severe anemia
- Hypotension (Blood pressure less than 90/60 mmhg)
- Heart disease in pregnancy
- Congenital anomaly
- Intra uterine foetal death
- Foetal distress
- Chorioamnionitis
- Hydramnios
- Premature rupture of membranes.
- Sensitivity or contra indication to nifedipine/nitrates
- Treatment with other tocolytics within 24 hours.

Data sources/measurement:

A total of 130 subjects full-filling the inclusion criteria will be admitted and monitored in the pre-labour room. A detailed history will be taken to exclude any contraindications for the intervention. General examination, systemic examination and a thorough obstetric examination including a detailed per abdominal and per vaginal examination will be done.

Routine investigations and an obstetric ultrasound and doppler will be done to check for fetal well-being in addition to other parameters like gestational age, placental site grading and liquor volume. Patients will be started on dexamethasone 6mg every 6th hourly for total of four doses IM and 2 doses of injection cefotaxime 1gm IV, 12th hourly once they are admitted.

The patients will be categorized into 2 groups, group A & group B by sealed envelope system. In this system the participating patients will be given two sealed opaque envelopes with name of group A drug in one envelope and name of group B drug in other and will be asked to pick one envelope without opening it. Patient will be allotted whichever group she selects. This process will be continued till the desired sample size is met.

Group A: Transdermal Nitroglycerine patch will be given

Group B: Tablet Nifedipine will be given orally.

For subjects assigned to **group A**, 10mg of nitroglycerine in the form of transdermal Nitroglycerine patch (Nitroderm TTS 10) will be applied on the anterior abdominal wall. If after one hour there is no subsidence in contractions strength and frequency, another patch of 10mg will be applied. Maximum dosage given will be 20mg/24hours. Patches will be changed every 24 hours till contractions terminate or to a maximum of 7 days.

Nitroderm TTS 10 patches contain 50 mg nitroglycerin and have a contact surface of 20 square cm, that releases approximately 10 mg nitroglycerine in 24 hours. It will be applied to an area which is free from sores, rashes or cuts. A new site will be used whenever a new patch will be applied.

- 1 pint of 500ml ringer lactate will be given prophylactically to avoid hypotension caused by nitroglycerine.

- Uterine contractions, blood pressure, heart rate and fetal heart monitored every 15 minutes in 1st hour, every 2 hours till 6 hours and then every 12th hourly till 48 hours.
- Any side effects like nausea, flushing, headache, hypotension, fetal and maternal tachycardia etc. will be noted.

Treatment will be withdrawn in,

1. Patients with complains of headache,
2. Patients having hypotension (BP < 90/60mmhg),
3. Patients having tachycardia (Pulse rate >100bpm),
4. Patient with PROM (premature rupture of membranes).
5. Patients experiencing persistent uterine contractions even after 48 hours of treatment.
6. Patients showing evident signs of fetal distress.
7. Patients complaining of irritation or burning sensation in the area where patch is applied.

Treatment will be considered successful if contractions stopped and no recurrence of contractions occurred within 48 hours. Another tocolytic will be considered after 48 hours of Nitroglycerine patch if there is no subsidence of uterine contractions. For subjects assigned to **group B**, oral nifedipine 30mg once and then 20mg after 90 minutes will be given if there is no subsidence in contractions and then 20mg every 8th hourly till a maximum of 7 days. A maximum dose of 130mg/day will be given to avoid any adverse effects.

- 1 pint of 500ml ringer lactate will be given prophylactically to avoid hypotension caused by nitroglycerine.
- Uterine contractions, blood pressure, heart rate and fetal heart monitored every 15 minutes in 1st hour, every 2 hours till 6 hours and then every 12th hourly till 48 hours.
- Any side effects like nausea, flushing, headache, hypotension, fetal and maternal tachycardia etc. will be noted.

Since 48hrs is considered adequate time for the corticosteroids to reduce respiratory complications in premature neonates hence, it is chosen as the minimum time interval for treatment to be considered successful that is if the contractions stopped and no recurrence of contractions occurred within or after 48 hours. If contractions stopped, patient will be reviewed till 37 weeks of gestation once weekly (or) follow up will be done, otherwise till delivery if it occurs less than 37 weeks. Transdermal Nitroglycerine patch (Nitroderm TTS 10) and oral Nifedipine 10mg tablets will be purchased with the help of intramural institutional grant and the study subject will not have to bear the expenses of this test. Consent will be obtained and ethical approval will be sought from institutional ethical board.

Sample size:

Sample size: 130

Formula for sample size:

Sample size for difference between two proportions:

$$n = \frac{(Z\alpha + Z\beta)^2 [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

Where,

$Z\alpha$ = level of significance at 5%

$Z\beta$ = power of test = 80% = 0.84

P_1 = proportion of efficacy of treatment in transdermal Nitroglycerine patch group = 85% = 0.85

P_2 = proportion of efficacy of treatment in oral nifedipine group = 65% = 0.65

$$n = \frac{(1.96 + 0.84)^2 [0.85 (1 - 0.85) + 0.65 (1 - 0.65)]}{(0.85 - 0.65)^2}$$

= 62.89

= 65 patients in each group.

Level of Significance: 5% (95% CI)

Power of the test: 80%

Side of the test: Two Sided

Statistical methods:

Statistical analysis will be done by using descriptive and inferential statistics using chi-square test, student's paired and unpaired t test

Expected outcomes:

Analysis: Data will be entered into excel sheet and SPSS software version 18 will be used for analysis. Mean \pm Standard deviation will be used to express results. For comparison of continuous variables, independent sample t-test and Mann Whitney U test will be used, while categorical variables will be compared using Chi-square test. Association between variables will be calculated using Pearson's correlation test. Subgroup analysis will be done by two - way Anova test. A p value < 0.05 will be taken as statistically significant.

Primary outcome

- Number of hours the labor got delayed.

Secondary outcome

- Side effects of transdermal Nitroglycerine patch
- Side effects of oral nifedipine
- Neonatal outcome, meconium staining of amniotic fluid, 1 minute and 5 minutes Apgar scores, neonatal ICU admission, early neonatal death mode of delivery

DISCUSSION:

Transdermal Nitroglycerine patch is more effective than oral nifedipine in management of preterm labour. Prematurity is the single greatest problem in perinatal medicine. Despite the availability of tocolytic agents the rate of prematurity has not declined over the past few years for several reasons. (6) Management of preterm births may cause a financial and emotional burden on the families thus leaving a huge psychosocial impact on them.(7)

The cause of preterm labour is unknown in about 45-50% of the cases, which is why it is important to make efforts in finding better alternatives to arrest preterm labour rather than to make attempts at preventing them. (7)

A tocolytic drug is considered successful if it reduces the number of deliveries within seven days of commencing the drug in patients with preterm labour. More the postponement of delivery, better are the perinatal and neonatal outcomes. (8)

The most common drug used to arrest preterm labour is nifedipine at a daily dose of 30-60mg daily. Various studies done worldwide have suggested that there is decrease in number of preterm deliveries within 7 days of commencement of treatment with a better fetomaternal outcome. Nifedipine has its advantages of easy administration by oral route, low neonatal complications, along with its own disadvantages also and should be used cautiously in patients with cardiovascular conditions as they may be at a risk of pulmonary oedema and cardiac failure.(1)

Studies have shown, that there is a considerable decrease in pregnant and non-pregnant myometrial contractility due to nitric oxide donation by glyceryl trinitrate. Transdermal use of nitroglycerine for management of preterm has been in use since 1996. Study done by Lees et al. back in 1994 reported that all 20 women with preterm labour enrolled in a pilot study experienced suppression of uterine contractions after the use of transdermal nitroglycerine patch, suggesting that NTG can be used as a safe and effective tocolytic agent(9). A number of studies have been reported on use of different medications for induction of labour(10-14).

Relaxation of smooth muscles of myometrium is brought by nitric oxide and CGMP. There is decreased excretion of CGMP and nitrite in early pregnancy, thus increasing their plasma levels, following which there is an increase in nitric oxide concentration in the myometrium. At the term approaches in pregnancy there is reduction in myometrial and decidual nitric oxide levels which increases their contractility.(15) Nitric oxide in NTG helps in reducing the increased contractions which occurs towards the end of term.

Conclusion:

Nitroglycerin and Nifedipine are both effective tocolytic drugs and very few studies have been done in India comparing the two. However, in this study we aim to conclude that transdermal nitroglycerine patch is more effective in the management of preterm labour as compared to oral nifedipine with less adverse effects and a better fetomaternal outcome.

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