

Preterm Labour Management with Glyceryl Trinitrate Patch and Isoxsuprine: A Longitudinal Study

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ABSTRACT

Introduction: Nitric oxide donors in the form of nitroglycerine and β -mimetic drugs (Isoxsuprine hydrochloride) are commonly used in managing preterm labour. It is one of the most challenging obstetric complications encountered by obstetricians, as well as preterm neonates for paediatricians. Preterm labour refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of the cervix between 20 and 37 weeks of gestation.

Aim: To compare the effects of transdermal Glyceryl Trinitrate (GTN) with Isoxsuprine in terms of maternal complications, perinatal outcomes, and their tocolytic effectiveness.

Materials and Methods: A hospital-based longitudinal study was conducted in the Department of Obstetrics and Gynaecology at JNU Medical College and Research Centre, Jaipur, Rajasthan, India. The study duration of the study was one year, from March 2022 to February 2023. A total number of 100 cases of preterm labour were enrolled and equally divided into two groups: Group A (GTN patch) and group B (Isoxsuprine) with a defined dosing schedule. Singleton pregnancies with intact membranes and gestational age of 26-36 weeks were included in the study, meeting the diagnostic criteria for preterm labour. Both the groups received pharmacological intervention, and outcome measures such as success rate of treatment (i.e., prolongation of labour), maternal side effects, and foetal outcomes {Neonatal Intensive

Care Unit (NICU) admission and Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score) were measured and evaluated. Predefined parameters and other data were tabulated in Microsoft Excel and statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20.0. The Chi-square test was applied to identify significant differences.

Results: The incidence of preterm labour was highest in the age group of 21-30 years (76% in Group A and 70% in Group B) among patients treated with nitroglycerine and isoxsuprine, respectively. The mean prolongation of pregnancy in the nitroglycerine group was 21.42 days, and in the isoxsuprine group, it was 16.22 days ($p=0.042$). The most common side effect in the nitroglycerine group was headache (60%), while in the isoxsuprine group, it was maternal hypotension (24%). The mean APGAR score in Group A and Group B was 8.18 and 8.06, respectively. It was observed that 24% of newborns in the nitroglycerine group and 36% in the isoxsuprine group required NICU admission. The success rate was 90% in the nitroglycerine group and 80% in the isoxsuprine group.

Conclusion: Both drugs were effective in prolonging pregnancy for the first 48 hours, but nitroglycerine was found to be slightly better in terms of success rate. Nitroglycerin was more acceptable to patients with preterm labour, as it did not have to be administered through painful injections

Keywords: Nitroglycerine, Premature birth, Tocolysis adverse effects, Tocolytic therapy

INTRODUCTION

Preterm labour is a challenging obstetric complications encountered by obstetricians, as are preterm neonates for paediatricians [1]. It not only causes psychological trauma for the mother but also present a major health problem in terms of loss of life, long-term disability (such as cerebral palsy, blindness, deafness, and chronic lung disease), and healthcare costs [2]. It occurs in 5%-10% of pregnancies and is a leading cause of neonatal morbidity and mortality [3]. Preterm labour refers to the onset of uterine contractions, with sufficient strength and frequency to effect progressively dilate and effacement of the cervix, between 20 and 37 weeks of gestation [4]. In the majority of cases, the aetiology of preterm labour is idiopathic [2]. Factors that contribute to an increased incidence of preterm labour include a previous history of preterm labour, abortion, asymptomatic bacteriuria or recurrent urinary tract infections, smoking habits, and low socioeconomic and nutritional status. Maternal factors such as preeclampsia, antepartum haemorrhage, premature rupture of membranes, polyhydramnios, uterine anomalies like cervical incompetence, and malformation of the uterus also play a role. Surgical and medical illnesses like acute fever, acute pyelonephritis, diarrhoea, acute

appendicitis, and abdominal operations increased the incidence of preterm labour [3].

The inhibition of uterine contractions remains the mainstay of the management of preterm labour management. The management may include bed rest, hydration, sedation, and tocolytic drugs. Tocolytic drugs are pharmacological agents that relax the uterine muscle fibres, inhibiting uterine contractions and preventing preterm labour. They act through various mechanisms to decrease the availability of intracellular calcium ions, thereby inhibiting actin-myosin interaction [5]. Various tocolytics such as β -adrenergic agonists (terbutaline, ritodrine, isoxsuprine), calcium channel blockers (nifedipine), Magnesium Sulphate ($MgSO_4$), indomethacin, atosiban, and Nitric Oxide (NO) donors (NO donor) have been used [6,7]. β -sympathomimetic agents include terbutaline, ritodrine, isoproterenol, isoxsuprine, hexaprenaline, and salbutamol. These drugs are structurally similar to the endogenous catecholamines epinephrine and norepinephrine. They act as tocolytics by stimulating the β receptors present in the myometrium, activating the enzyme adenylyl cyclase, thereby increasing in intracellular cyclic Adenosine Monophosphate (cAMP). This, in turn, decreases the intracellular calcium and directly phosphorylates of myosin light chain kinase,

leading to its inactivation. The final result is the disruption of actin-myosin interaction thereby, inhibiting muscle contractility [8].

Nitric oxide donors activate guanylyl cyclase and increase the synthesis of cyclic 3, 5-guanosine monophosphate, which causing the relaxation of smooth muscles. This effect is similar to endogenously synthesised nitric oxide from L-arginine in the presence of the NO synthase enzyme. Nitric oxide concentration is increases during pregnancy to maintain a quiescent uterus, and decreased production occurs during labour, which explains the role of nitroglycerine in preterm labour. Nitroglycerine and GTN are used as a sources of NO donors. They are available in various forms such oral tablets, sustained-release tablets, Intravenous (i.v.) injections, lingual sprays, transdermal patches, and buccal tablets [9,10]. Effective management of preterm delivery is a very essential measure to reduce perinatal mortality. Various tocolytics have been tried to prevent preterm birth. Efforts have been made to establish the least cumbersome method with minimal side effects, allowing patients to remain ambulatory [11,12].

The aim of the study was to compare the efficacy of transdermal GTN with isoxsuprine in preterm labour in terms of maternal complications and perinatal outcome.

MATERIALS AND METHODS

A hospital-based longitudinal study was conducted in the Department of Obstetrics and Gynaecology at JNU Medical College and Research Centre, Jaipur, Rajasthan, India. The study lasted for one year, from March 2022 to February 2023. Approval for the study was obtained Institutional Ethics Committee letter no. (IEC No. JNUIMSRC/IEC/2022/15). A total number of 100 cases of preterm labour were enrolled in the study. The sample size was calculated considering the estimated proportion of preterm labour cases in the population, with a 95% confidence level and an expected the proportion of approximately 0.5 (50%), with a margin of error of 0.1 (10%). These patients were divided into two groups, A and B, using alternate case random allocation, after obtaining informed written consent.

Inclusion criteria: Patients with singleton pregnancy, intact membranes, and a gestational age of 26-36 weeks. Additionally, patients, had to meet the diagnostic criteria for preterm labour, which included experiencing painful uterine contractions of four or more in 20 minutes or eight or more in one hour, along with cervical dilatation of more than 1 cm and cervical effacement of over 80% [4].

Exclusion criteria: Patients with maternal factors such as gestational age exceeding 36 weeks, vaginal bleeding or leaking, evidence of chorioamnionitis, polyhydramnios, cardiac problems, diabetes, or cervical dilatation exceeding 3 cm. Patients with severe Intrauterine Growth Restriction (IUGR), multiple pregnancies, or congenital malformations were also excluded from the study.

The Sample size calculation was based on the advice of a statistician. The sample size was calculated considering the estimated proportion of preterm labour cases in the population, with a 95% confidence level and an expected the proportion of approximately 0.5 (50%), with a margin of error of 0.1 (10%).

Study Procedure

A total number of 100 cases of preterm labour were enrolled and were equally divided into two groups:

Group A: This group included 50 cases where a GTN patch (nitroderm TTS 5) was applied after the diagnosis of preterm labour. After prehydration with 1000 mL of Ringer’s Lactate (RL) or normal saline infusion, a GTN patch was applied on the anterior abdominal wall. The patch released nitroglycerine at a rate of 0.2 mg/hour and was applied only for 12 hours. Afterward, the patients received a tablet of nitroglycerin (2.6 mg) twice a day for one week.

Group B: This group included 50 cases, where isoxsuprine treatment was initiated. An injection of isoxsuprine 40 mg in 500 mL of RL was given as an infusion at a rate of 0.08 mg/minute infusion. The infusion rate was increased upto 0.24 mg/min until uterine contractions ceased or side effects occurred. Once the contractions stopped, the intravenous infusion was discontinued, and patients were maintained on oral isoxsuprine 10 mg every eight hours for up to seven days.

In each case, 12 mg of betamethasone was administered Intramuscular (IM) at the beginning of treatment, and the same dose was repeated after 12 hours. Maternal pulse, Blood Pressure (BP), uterine contractions, and foetal heart rate were recorded every 15 minutes for the first two hours and then every 30 minutes for upto four hours. Treatment was discontinued in both groups if there was, maternal tachycardia (pulse rate >120/min), a drop of BP by 15 mmHg or more from baseline diastolic BP, or signs and symptoms of pulmonary oedema (breathlessness, cough with expectoration).

The outcome measures were as follows:

- Successful tocolysis (GTN patch/isoxsuprine): Pregnancy continued for atleast 48 hours after starting the drug.
- Failed tocolysis: Delivery occurred within 48 hours or rescue tocolysis was required.
- Side effects of GTN Patch/isoxsuprine: Headache, tachycardia, vomiting, heaviness in lower limbs, local reaction, and hypotension.
- Perinatal outcome: Admission to the Neonatal Intensive Care Unit (NICU) and APGAR score.

Both groups received pharmacological intervention, and outcome measures in terms of the success rate of treatment, maternal side effects, and foetal outcomes (NICU admission and APGAR score) were measured and evaluated.

STATISTICAL ANALYSIS

Predefined parameters and other data were tabulated in Microsoft Excel. Statistical analysis was performed using SPSS version 20.0. Continuous variables were summarised as mean and Standard Deviation (SD). The Chi-square test was applied to identify significant differences.

RESULTS

A total of 4,679 deliveries were included in the study, out of which 379 presented with preterm labour. This accounts for an incidence of preterm labour of 8.10%. Among them, 100 eligible patients were included. The study found that the majority of patients (76% in group A and 70% in group B) were between 21 and 30 years of age [Table/Fig-1].

The majority of patients in both groups were multigravida, with 50% in group A and 40% in group B [Table/Fig-2].

Age group (in years)	Group A (n=50) n (%)	Group B (n=50) n (%)	Mean±SD	p-value
<20	7 (14)	11 (22)	24.96±4.5 23.58±3.97	0.149
21-30	38 (76)	35 (70)		
31-40	5 (10)	4 (8)		
>40	0	0		
Total	50 (100)	50 (100)		

[Table/Fig-1]: Distribution of patients according to maternal age. Chi-square test was applied

Gravidity distribution	Group A (n=50) n (%)	Group B (n=50) n (%)	p-value
Primigravida	6 (12)	13 (26)	0.149
Second	19 (38)	17 (34)	
Multigravida	25 (50)	20 (40)	

[Table/Fig-2]: Distribution of patients according to gravidity distribution.

In group A, 36% of preterm labour patients belonged to the gestational age range of 32.1-34 weeks upon admission. On the other hand, in group B, the majority of patients (36%) were between 28.1-30 weeks of gestational age at the time of enrollment [Table/Fig-3].

Gestational age (in weeks)	Group A (n=50) n (%)	Group B (n=50) n (%)	Mean±SD	p-value
26.0-28	1 (2)	3 (6)	32.88±2.01 31.45±2.26	0.001
28.1-30	7 (14)	18 (36)		
30.1-32	11 (22)	11 (22)		
32.1-34	18 (36)	14 (28)		
34.1-36	13 (26)	4 (8)		

[Table/Fig-3]: Distribution of patients according to gestational age at presentation.

In the present study, 26% of patients in group A and 24% in group B had a history of one or more previous abortions, which was statistically non-significant. It was observed that 50% of patients in group A and 14% in group B had a history of one or more previous preterm deliveries, which was statistically significant (p-value 0.001). The mean cervical length in group A was 1.97 cm, and in group B it was 1.81 cm. The majority of patients (78%) in both groups had a cervical length between 1-1.5 cm. In group A, 92% and in group B, 88% of patients had cervical dilatation of <2 cm. The mean prolongation of pregnancy after the therapeutic intervention in group A was 21.42 days, while in the isoxsuprine group it was 16.22 days [Table/Fig-4].

Gestational age prolongation	Group A (n=50) n (%)	Group B (n=50) n (%)	Mean±SD	p-value
≤24 hours	3 (6)	5 (10)	21.42±11.20 16.22±15.67	0.042
25-48 hours	2 (4)	5 (10)		
3-7 days	8 (16)	11 (22)		
8-14 days	9 (18)	10 (20)		
>14 days	28 (56)	19 (38)		

[Table/Fig-4]: Distribution of patients according to prolongation of pregnancy.

Headache was the most common adverse effect in the nitroglycerine-treated group (60%), whereas it was observed in only 18% of the isoxsuprine group. In the isoxsuprine-treated group, hypotension was the most common (24%) side effect [Table/Fig-5].

Side effects	Group A (n=50) n (%)	Group B (n=50) n (%)	p-value
Headache	30 (60)	9 (18)	0.002
Maternal tachycardia	5 (10)	11 (22)	0.098
Palpitation	4 (8)	9 (18)	0.168
Hypotension	5 (10)	12 (24)	0.018
Nausea	2 (4)	9 (18)	0.064
Vomiting	0	0	0.652
Dizziness	4 (8)	0	0.024
Foetal tachycardia	0	0	0.001

[Table/Fig-5]: Distribution of side effects of drugs in preterm labour patients.

The APGAR score in the present study shows that 88% of babies delivered in group A and 82% in group B had scores between 7-10. The mean APGAR score in group A and group B was 8.18 and 8.06, respectively [Table/Fig-6].

APGAR score at five minutes	Group A (n=50) n (%)	Group B (n=50) n (%)	Mean±SD	p-value
0-3	0	0	8.18±1.4 8.06±1.53	0.693
4-6	6 (12)	9 (18)		
7-10	44 (88)	41 (82)		

[Table/Fig-6]: Distribution of patients according to APGAR score at five minutes.

The mean baby weight in the nitroglycerine group was 2.52±0.46 kg, and in the isoxsuprine group it was 2.3±0.25 kg among the studied

preterm patients. However, this difference was not statistically significant (p-value-0.48). A higher percentage of neonates (36%) required NICU admissions in the isoxsuprine group compared to the nitroglycerine group (24%) [Table/Fig-7].

The mean delay in pregnancy was 21.4 days in group A, which was lower in group B (16.22 days) as shown in [Table/Fig-8].

NICU admission	Group A (n=50) n (%)	Group B (n=50) n (%)	p-value
Required	12 (24)	18 (36)	0.85
Not required	38 (76)	32 (64)	

[Table/Fig-7]: Distribution of patients according to NICU admission. NICU: Neonatal intensive care unit

Delivery	Group A (n=50) (Mean±SD)	Group B (n=50) (Mean±SD)	p-value
Gestational age at delivery	35.44±1.69	33.69±2.24	0.001
Delayed by (days)	21.4±11.2	16.22± 15.67	0.032

[Table/Fig-8]: Comparison of the effect of treatment in patients of preterm labour.

The success and failure of treatment were assessed in terms of prolongation of pregnancy by >48 hours. The success rate was 90% in the nitroglycerine group and 80% in the isoxsuprine group, which was statistically significant (p<0.01) [Table/Fig-9].

Treatment response	Group A (n=50) n (%)	Group B (n=50) n (%)	p-value
Success	45 (90)	40 (80)	0.01
Failure	5 (10)	10 (20)	

[Table/Fig-9]: Treatment success and failure.

DISCUSSION

The lack of reliable and effective methods to predict or prevent preterm labour has resulted in very little change in the incidence of preterm deliveries over the last 40 years [7]. Clinicians often face the dilemma of managing established preterm labour with various pharmacological agents that may lack uterine specificity, have low efficacy, or potentially cause serious side effects for the mother and foetus. Commonly used measures include tocolytic drugs, corticosteroids, and antibiotics. Various tocolytics used are β -adrenergic receptor agonists, calcium channel blockers, cyclooxygenase inhibitors, NO donors, oxytocin receptor antagonists, and magnesium sulfate [12]. The incidence of preterm deliveries during the study period was 8.10%, which is comparable to other studies as the worldwide incidence of preterm deliveries varies between 6% and 15% [1,2,13]. The mean age in the present study is similar to the mean age of patients in Rita D and Haripriya V, Jaju PB, Kaur P et al., and Raymajhi R and Pratap K studies [14-17]. The mean age was higher in Lee HH et al., El-Sayed YY et al., and Kashanian M et al., studies, possibly because women in developed countries conceive at a comparatively later age than those in developing countries [13, 18,19]. Fifty percent of group A and 40% of group B patients were multigravidas, which is comparable to the findings of studies by Rita D and Haripriya V, Smith GN, and Tambe S and Alnure Y, where preterm labour was more common in multigravida patients due to their history of previous preterm labour [14,20,21]. According to Purisch SE and Gyamfi-Bannerman C, the incidence of preterm labour in subsequent pregnancies after one preterm birth rises to 14.3%, and after two preterm births, it increases to 28% [22].

The majority of women in the present study are at risk of preterm delivery. Cervical dilatation upon admission is inversely related to the onset of preterm labour. The present study is comparable to a study by Romero JA et al., in which a cervical length >2.5 cm is a strong predictor of preterm birth [23]. The mean age of presentation with preterm labour was 32.88 weeks in group A and 31.45 weeks in group B. The mean gestational age at delivery in group A was 35.44 weeks, while in group B it was 33.69 weeks, which is

S. No.	Success rate with GTN patch in various studies				The success rate of isoxsuprine in various studies			
	Authors	Place of the study	Year	Success rate (%)	Authors	Place of the study	Year	Success rate (%)
1.	Sarbhaj V et al., [29]	Delhi, India	2018	88	Sarbhaj V et al., [29]	Delhi, India	2018	76
2.	Tambe S and Alnure Y [21]	Pune, India	2015	96	Tambe S and Alnure Y [21]	Pune, India	2015	94
3.	Rita D and HariPriya V [14]	Karnataka, India	2021	86	Rita D and HariPriya V [14]	Karnataka, India	2021	90
4.	El-Sayed YY et al., [18]	California, USA	1999	37.5	Giorgino FL and Egan CG [8]	Padova, Italy	2010	92.5
5.	Kashanian M et al., [19]	Tehran, Iran	2014	98.3	Jaju PB [15]	Karnataka, India	2021	100
6.	Kaur P et al., [16]	Punjab, India	2021	95	Raymajhi R and Pratap K [17]	Kathmandu, Nepal	2003	70
7.	Mahajan B et al., [24]	Jammu, India	2000	90	Yogol NS et al., [27]	Kathmandu, Nepal	2009	78
8.	Ray N and Kshirsagar N [26]	Maharashtra, India	2022	80	Alavi A et al., [30]	Iran	2015	88.5
9.	Present study	Jaipur, India	2022	90	Present study	Jaipur, India	2022	80

[Table/Fig-10]: The success rate of GTN and isoxsuprine in various other studies [8,14-19,21,24,26,27,29,30].
GTN: Glyceryl trinitrate

consistent with other studies [16,20,24]. In the present study, the mean prolongation of pregnancy in group A was 21.42 days, while in the isoxsuprine group it was 16.22 days. In the study by Tambe S and Alnure Y, the mean duration of prolongation of pregnancy in the nitroglycerin group was 25.72 days, and in the isoxsuprine group, it was 20.34 days, which was slightly higher compared to the present study [21].

Headache was the most common adverse effect in the nitroglycerine-treated group (60%), while in the isoxsuprine-treated group, hypotension was the most common (24%) side effect. Various other studies also reported headache as the most common side effect of the nitroglycerine-treated group [16,18,19,25]. In comparison, isoxsuprine side effects commonly related to the cardiovascular system, such as hypotension, tachycardia, and palpitations, similar to other studies of isoxsuprine [8,17,21,26,27].

Neonatal complications like Intraventricular Haemorrhage (IVH), sepsis, jaundice, and birth asphyxia were less common in the nitroglycerine-treated group than in the isoxsuprine-treated group. Smith GN et al., also reported that neonatal complications were less common in the nitroglycerine-treated group [20,28]. This may be due to the prolongation of pregnancy and improved blood flow to the placenta caused by nitroglycerine. The success rate was 90% in the nitroglycerine group and 80% in the isoxsuprine group, which was statistically significant (p<0.01). Various other studies with treatment success rates have been tabulated in [Table/Fig-10] [8,14-19,21,24,26,27,29,30] for comparison with the present study.

In conclusion, preterm labour is a challenging problem in obstetrical practice. It is a major public health concern in terms of loss of life, long-term disability, and healthcare costs. In the past, the management of preterm labour was mainly conservative, but with the invention of newer tocolytics, a new breakthrough has emerged.

Limitation(s)

The present study not being a randomised controlled study means that the chances of selection bias cannot be entirely excluded.

CONCLUSION(S)

Both drugs are effective in prolonging pregnancy for the first 48 hours, but nitroglycerine was found to have a slightly better success rate compared to isoxsuprine. Transdermal nitroglycerin appears to be better tolerated by patients, with fewer side effects than isoxsuprine, except for headaches. Nitroglycerin was more acceptable to patients with preterm labour, as it did not require painful injections for administration. Therefore, transdermal nitroglycerin seems to be a safe, cost-effective, non-invasive method for treating preterm labour.

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