

TO KNOW THE EFFICACY OF GLYCERYL TRINITRATE PATCH AND RITODRINE AS TOCOLYTIC AGENTS: A COMPARATIVE STUDY

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ABSTRACT: BACKGROUND: Preterm labour is onset of labour between 20 weeks and 37 completed weeks of gestation. Tocolytics are pharmacological agents that relax the uterine myometrium and inhibit uterine contractions leading to abolition of preterm labour. Many tocolytic drugs have been developed and used and several experimental drugs are being evaluated. Future research is needed for development of drugs with more utero-selectivity and fewer side effects. Ritodrine hydrochloride is now considered one of the most effective tocolytic drug. However, the use of nitroglycerine patch has shown comparable results and there is a need for further critical evaluation by well-planned and well monitored studies. **AIM:** To compare the efficacy of transdermal glyceryl trinitrate and intravenous ritodrine as tocolytics. **MATERIAL AND METHODS:** The study was conducted on patients who attended Bapuji Hospital, Chigateri Hospital and women and child hospital, attached to J.J.M. Medical College, Davangere. One hundred patients who were admitted and clinically diagnosed with preterm labour were randomised either to group 1, treated with glyceryl trinitrate patch or group II, treated with ritodrine, with fifty patients in each group. **ANALYSIS:** Descriptive data that included mean, Standard deviation, percentages were determined and presented for each group. Difference between two groups was compared by Mann- Whitney test for continuous data and chi-square test for categorical data. P Value of 0.05 or less was considered for statistical significance. **RESULTS:** mean percentage prolongation of gestation with glyceryl trinitrate was 58±45.9 and with Ritodrine, it was 62±44.6. Mean absolute prolongation of gestation with glyceryl trinitrate was 3.22 weeks and with Ritodrine it was 3.18 weeks. **CONCLUSION:** Both glyceryl trinitrate and ritodrine were comparable in prolongation of gestation in patients in preterm labour, both in duration and in terms of success. The advantages of glyceryl trinitrate patch over ritodrine are lesser side effects and simplicity of administration and it also allows the patient to remain ambulatory.

KEYWORDS: Preterm labour, Ritodrine hydrochloride, Glyceryl trinitrate.

INTRODUCTION: Preterm or premature birth is the term used to define infants who are born too soon.¹ It refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of cervix between 20 and 37 weeks of gestation.² Overall incidence of preterm labour is reported to be 6-15%.³ It is a major public health problem in terms of loss of life, long term disability (cerebral palsy, blindness, deafness, chronic lung disease) and health care costs both in the developing and the developed world.² Unfortunately, the incidence of preterm labour has changed very little over the last 40 years and uncertainties still persist regarding the best strategies for its management. It has been widely recognised that

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its prevention and/ or effective management will improve neonatal outcome and will have a profound impact on societal and long term public health care costs.

Clinicians are often faced with the dilemma of managing an established preterm labour with a variety of pharmacological agents, which may lack utero-specificity, have low efficacy or potential serious side effects for the mother or the fetus. Along with bed rest, hydration and sedation, the measures that are commonly used are tocolytic drugs, corticosteroids and antibiotics. Tocolytics are pharmacological agents that relax the uterine myometrium and inhibit uterine contractions leading to abolition of preterm labour. They act through a variety of mechanisms to decrease the availability of intracellular calcium ions leading to inhibition of actin-myosin interaction. Though, in recent times, the use of tocolytic drugs has become controversial, they should still be considered if the few days gained would be put to good use such as completing a course of corticosteroids or in-utero transfer.⁴ They are not recommended after 34 weeks of gestation and currently there is no consensus regarding the lower gestational limit at which they could be used.⁵

Many tocolytic drugs have been developed and used and several experimental drugs are being evaluated. Alcohol, beta sympathomimetics, calcium channel blockers, magnesium sulphate, oxytocin antagonists, prostaglandin synthetase inhibitors, nitric oxide donors and combination of these drugs have been used for tocolysis.

Ritodrine hydrochloride is the first drug approved by the FDA for the pharmacological inhibition of preterm labour.⁶ It is a β -adrenergic stimulant but is associated with serious maternal side effects (pulmonary edema, myocardial ischemia, arrhythmia, death).⁷

Future research is needed for development of drugs with more utero-selectivity and fewer side effects. Recently, nitric oxide donors have been found to be potent uterine relaxants in vitro and transdermal nitroglycerine has been reported to be safe for the mother and the fetus, though a study concluded that there is insufficient evidence to support routine administration of nitric oxide donors in the treatment of threatened preterm labour.^{8,9,10}

Ritodrine hydrochloride is now considered to be one of the most effective tocolytic drugs. However the use of nitroglycerine patches has shown comparable results and there is a need for further critical evaluation by well-planned and well monitored studies. The aim of this study is to compare the efficacy of transdermal glyceryl trinitrate and intravenous ritodrine as tocolytics.

MATERIALS AND METHODS: One hundred patients who were admitted and clinically diagnosed with preterm labour were selected randomly after inclusion criteria were fulfilled. This study was conducted in hospitals attached to JJM Medical College, Davangere, Karnataka, India, with the duration of the study being 2 years, after approval from hospital ethical committee, with written and informed consent of the patients.

Inclusion criteria were women with singleton and multiple pregnancy with uterine contractions 2 per 10 minutes or 4 per 20 minutes between 28 to 34 weeks of gestation, cervical dilatation of 0-3 centimeters, effacement of up to 80% and intact membranes. Exclusion criteria were hypotension (blood pressure <80/50 mm Hg), fetal congenital malformations, ante-partum hemorrhage, Severe pre-eclampsia, severe anemia, rupture of membranes, fetal distress, cervical suture in situ, maternal tachycardia >100 per minute, uterine tenderness with or without

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offensive vaginal discharge, contraindications to beta agonists, non-steroidal anti-inflammatory drugs and other tocolytics.

PROCEDURE OF THE STUDY: When a case of preterm labour is admitted, detailed present and past obstetric history is taken. General physical examination including vital signs is done. Detailed obstetric, per abdomen and per vaginal examination was done. The selected patients were randomized either to group 1, treated with glyceryl trinitrate patch or group 2, treated with ritodrine.

GROUP 1: Glyceryl trinitrate patch releasing 10mg/24 hours (0.4mg/ hour) is applied transdermally to the abdomen (Fig-1 and Fig-2). If the contractions did not subside within 2 hours, then one more patch is applied. Not more than two patches per 24 hours applied. Patients are assessed every 15 min for 2 hours and then every 2 hours for 12 hours and 4th hourly for 48 hours. Treatment is discontinued if side effects were noted or if there is persistence of contractions even after 48 hours and patient allowed for delivery. If contractions subside, patient is discharged and assessed antenatally every week till delivery and readmitted if there is recurrence of contractions and treated in the same manner.

GROUP 2: Ritodrine 50mg is added to one bottle of 5% dextrose or ringer lactate solution (Fig-3, Fig-4). Initially patient is given 50 micro grams/min intravenously i.e., 8-10 drops per minute. The dose is increased by 50 micrograms per minute every 10 min until contractions stop or pulse rate >120 bpm or toxicity develops. Maximum dose is 350 micrograms per minute. When contractions subside, the drip is maintained for 12 hours and then gradually tapered. If contractions did not subside to the above dose in 1 to 2 hours then the same treatment is repeated with 100 mg in a bottle of 5% dextrose i.e., 2 ampoules at a rate of 6 drops/ minute or a maximum of 150 mg i.e., 3 ampoules at a rate of 3 drops/min. Oral tablet of 10 mg ritodrine is given 30 min prior to discontinuation of the drip and then one tablet every two hours for 24 hours and 10-20 mg every six for 7 days. Patient is discharged and assessed antenatally every week. Patient is re-admitted if there is recurrence of contractions and treated again in the same manner.

At the time of delivery, gestational age, mode of delivery, baby's weight and APGAR score are noted. All patients are given steroids as required and a 7 days course of appropriate antibiotics. If the patient is not responding to one drug, other drug may be tried.

LAB INVESTIGATIONS: Analysis of urine albumin, sugar, microscopy, culture/ sensitivity and blood for hemoglobin, grouping, Rh typing, HIV and HBsAg and USG were done in all cases.

STATISTICAL ANALYSIS: Descriptive data that included mean, standard deviation, percentages were determined and presented for each group. Difference between two groups was compared by Mann-Whitney test for continuous data and chi - square test for categorical data.

P value of 0.05 or less was considered for statistical significance.

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RESULTS: Patients in preterm labour accounted for 8.03% of the total deliveries in hospitals attached to JJM Medical College during the period of 2 years. Demographic data and baseline values in the two groups was statistically not significant (table 1). The percentage of prolongation in all women irrespective of gestational age at entry, the mean prolongation of gestation in weeks, success rate and birth weight in the two groups was found to be statistically not significant ($P > 0.05$) (table 2). Fetal side effects were noticed in both groups. However the difference in neonatal outcome in the two groups is not found to be significant (table 3). The difference in maternal side effects between the two groups is statistically significant with group II patients showing more side effects than group I patients, with a P value less than 0.05 (table 4).

DISCUSSION: Despite substantial advances in perinatal medicine, little progress has been made to reduce the frequency of preterm delivery. Inability to identify precise etiological factors for preterm labour has been the main handicap.¹¹

In the present study glyceryl trinitrate and ritodrine were not significantly different in reducing preterm delivery within any of the time limits. The number of deliveries even on the time of randomization in the glyceryl trinitrate and ritodrine groups was not significantly different. Mean absolute prolongation of gestation also did not differ significantly between the two groups. These results are in concurrence with the study done by Lee's et.al.¹²

The mean prolongation of gestation with glyceryl trinitrate in different studies varied from 32 to 35^{12,13,14} and with ritodrine it was seen to be between 27 and 36.9.^{12,15,16} In our study the values were 23 in both groups and hence both the drugs were almost equally effective in prolongation of gestation.

Success rate, that is, subsided uterine contractions and tocolysis achieved for more than 48 hours in different studies with glyceryl trinitrate varied from 84% to 100%,^{12,13,14,16} and with ritodrine it was 76% to 90%.^{12,15} In this study success rate was 92% with glyceryl trinitrate and with ritodrine it was 90%. Hence both these drugs were almost equally successful in tocolysis.

Also there was no significant difference between the birth weights obtained after tocolysis in the two groups.

Fetal side effects like respiratory distress syndrome and hyaline membrane disease and also deaths were seen in both groups without any significant difference. Similar side effects were seen in other studies as well.^{13,16}

In the present study the major side effect seen with glyceryl trinitrate was headache. Dizziness and vomiting were also seen. All the other adverse events were more frequent with ritodrine, in particular tachycardia (66%), palpitations (6%) and breathlessness (4%), all of which were infrequent or did not occur at all in the glyceryl trinitrate group. No patient in both groups had side effects severe enough to warrant stoppage of the treatment. Similar side effects were seen in other studies as well.^{12,13,17}

The action of ritodrine as a beta-adrenergic receptor stimulator is not specific to the uterus. Hence it may produce significant maternal side effects due to beta receptors stimulation of the heart like tachycardia, atrial flutter, insufficiencies, arrhythmias and ischemia.⁷ Metabolic abnormalities such as sodium retention, glucose intolerance and hypokalemia are also common. The most frequently reported life threatening complication is pulmonary edema which occurs in

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up to 5% of the cases. This incidence can go up to 20% in cases suffering from infection. In these cases, maternal morbidity sometimes leading to maternal mortality has been reported. Increased hydrostatic pressure from a combination of fluid overload, sodium retention, anaemia and decreased colloid osmotic pressure is primarily responsible.¹⁸

Pharmacological inhibition of uterine contractions could be achieved by nitroglycerin which can work as a smooth muscle relaxant when used in the form of skin patches, in patients who have premature onset of labour.¹³

Glyceryl trinitrate patches release 10mg/24 hours of nitroglycerin with a drug releasing area of 20 centimetres. The flat multilayer system is designed to deliver nitroglycerin continuously through a releasing membrane following application to the skin. The active substance penetrates the skin and thus becomes directly bioavailable to the systemic circulation at relatively constant concentrations. The main side effect of nitroglycerin patch is headache (in 30% of women), which can usually be dealt with a simple analgesic. Other rare side effects are irritation and hypotension.¹³

At doses required for tocolysis, transdermal glyceryl trinitrate had no significant cardiovascular effect on mother or the fetus. Combined with its excellent safety record, it might be an alternative to ritodrine for preterm labour. The possibility of higher doses, more equivalent to those in tocolysis studies in animals or cardiovascular medicine, might provide greater efficacy with only modest cardiovascular effects.

Beta agonists are susceptible to tachyphylaxis and reduction in tocolytic efficacy with time. After the first few days of the treatment, there is demonstrable down-regulation of myometrial beta receptors. Glyceryl trinitrates possible effect in reducing preterm delivery might hold the prospect of using it for maintenance or prophylaxis of repeat pre term labours. The advantage of glyceryl trinitrate would be once daily transdermal application at a dose unlikely to cause headache, cardiovascular disturbance or other side effects particularly related to beta agonists.¹²

Hence maternal side effects were more common in patients treated with ritodrine as compared to glyceryl trinitrate, the difference reaching statistical significance. Otherwise glyceryl trinitrate is seen to be as effective as ritodrine in tocolysis. The added advantages with glyceryl trinitrate as tocolytic over ritodrine are the simplicity of administration and early ambulation of the patient.

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	Group 1	Group 2	P
Age (years)	23.6 (4)	22.6(3.6)	0.36
Cervical dilatation at treatment	1.3 (0.9)	1.4 (0.9)	0.51
Cervical effacement at treatment	40 (26)	43 (27)	0.59
Gestational age at treatment	31.6 (2.2)	31.9 (2)	0.81
Primigravida	40%	42%	
Multigravida	68%	52%	

TABLE 1

Demographic data and baseline values (mean \pm SD) in the treatment groups.

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	Group 1	Group 2	P
Percentage prolongation of gestation	58.6(45.9)	62.1(44.6)	0.55
Mean prolongation of gestation(wks)	3.22	3.18(2.88)	0.76
Success rate	92%	90%	0.3
Birth weight	2.14(0.52)	2.04(0.49)	0.36

TABLE 2

Outcomes after treatment in each group (mean±SD).

Neonatal outcome	Group I		Group II	
	No of cases	Percentage	No of cases	Percentage
Deaths	04	08	02	04
RDS	02	04	04	08
HMD	04	08	04	08
Total	10	20	09	18

TABLE 3

NEONATAL OUTCOME:

Side effects	Group I		Group II	
	No of cases	Percentage	No of cases	Percentage
Dizziness	01	02	-	-
Headache	13	26	01	02
Nausea	02	04	01	02
Skin rash/Itching	03	06	-	-
Tachycardia	01	02	33	66
Breathlessness	-	-	12	04
Chest pain	-	-	01	02
Palpitations	-	-	03	06
Total	20		31	

TABLE 4

Maternal side effects.

Chi-square test, $P < 0.055$, Significant.

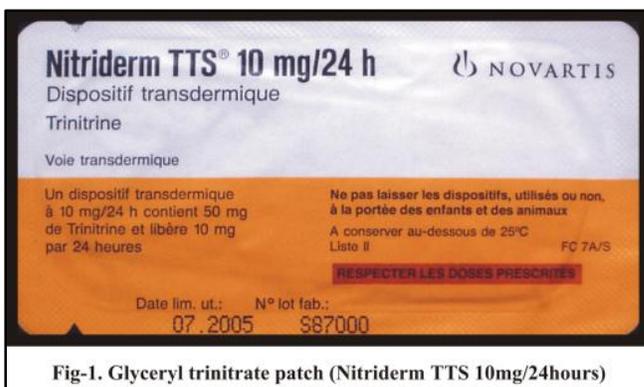


Fig-1. Glyceryl trinitrate patch (Nitriderm TTS 10mg/24hours)

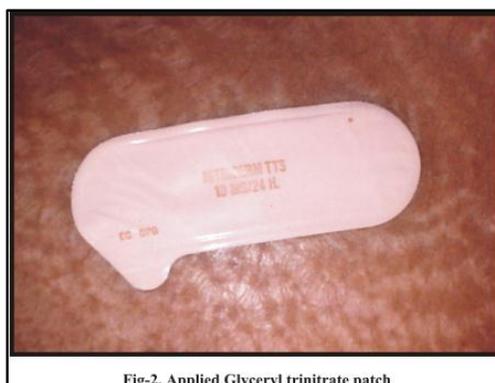


Fig-2. Applied Glyceryl trinitrate patch



Fig-3. Glyceryl trinitrate patch applied over abdomen



Fig-4. Ritrodine Hydrochloride injection (Miolene 50mg/ml ampule) and tablets (Ritrod 10mg tablet)

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