

Clinical Evaluation of Transdermal Nitroglycerine in Preterm Labor in Tertiary Care Teaching Hospital in North India

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Abstract- Research: Effect of various tocolytics in preterm labour is varied and also the side effects. Thus in this study comparison between Transdermal Nitroglycerine (NTG) and Isoxsuprine was done to assess the same.

Material & Methods: This study was conducted in the Department of Obstetrics & Gynecology, CSM Medical University, Lucknow. A Prospective comparative study, 100 women of preterm labour were enrolled after the informed consent, amongst them 50 women received Inj. Isoxsuprine 5 mg intramuscular (Group-I) and 50 women received Transdermal Nitroglycerine patch (NTG 10) on the abdominal wall (Group-II).

Result: Successful tocolysis (Inj. Betamethasone 12mgm intramuscular 2 doses 24 hours apart) was achieved in 98% of Group-II as and 84% of patients in Group-I which was statistically significant ($p=0.014$). In group-I 28% women delivered after 37 weeks where as in group-II 50% delivered after 37 weeks which was statistically significant. ($p=0.024$) In group-I 16% neonates developed RDS whereas in Group-II 2% developed RDS which was not significant ($p=0.307$) Headache was found to be the persistent side effect in all subjects of Group-II as compared to none in Group-I. ($p<0.001$)

CONCLUSION:

This randomized prospective comparative study lends support to the proportion that Transdermal Nitroglycerine may be promising safe, effective, well tolerated, cost effective and non invasive method of tocolysis.

Index Terms- Transdermal Nitroglycerine, Isoxsuprine, and Preterm labour

I. INTRODUCTION

Premature birth is the single largest cause of perinatal morbidity and mortality in non anomalous infants. About 70-80% of perinatal deaths occur in preterm infants.¹ Almost two third of deaths in preterm infants occurs in those born at less than 28 weeks of gestation.² In practical terms, preterm birth after 32 weeks of gestation are known to have improved survival and less morbidity due to rapid advances in perinatal and neonatal medicine in recent decades.³

The major neonatal morbidity includes respiratory distress syndrome, intraventricular hemorrhage. Patent ductus arteriosus, sepsis, necrotizing, enterocolitis, periventricular leukomalacia and retinopathy of prematurity.⁴ On the long term basis the

preterm infants are found to be more at risk for neurodevelopmental handicaps like cerebral palsy, hearing loss, and blindness. Also a wide spectrum of intellectual impairments may be present.⁵ The non neurologic long term sequelae can be chronic pulmonary disease or the compromise in over all growth of the preterm baby.⁶

According to World Health organization (WHO) preterm is defined as a gestational age of <37 completed weeks (259 days) from the first day of the last menstrual period.⁷ The tocolysis used to prevent preterm labour basically aims at prolonging the pregnancy at least for 48-72 hours, so as to provide adequate time to administer two doses of corticosteroid which would help in preventing respiratory distress syndrome in the newborn if delivery occurs within 7 days of steroid administration. It will also provide opportunity to transfer the woman to a higher medical centre where adequate NICU facilities can be provided to the neonate as and when required.⁸

Over the few years a variety of tocolytic drugs (Isoxsuprine, Ritodrine, Nifedipine) with different pharmacological action have been used to suppress preterm labor. With the use of these drugs considerable adverse maternal effects. (like pulmonary oedema, arrhythmia, myocardial ischemia) and fetal effects (like hyperglycemia, hypokalemia, neonatal hypoglycemia & paralytic ileus) were reported.²

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.⁹ In transdermal drug administration the drug is delivered at a constant and predictable rate so a smooth plasma concentration of the drug is reached without fluctuations.

In this study Transdermal Nitroglycerine delivery system, Nitroglycerine patch-10 (NTG patch-10) was used which contains 50 mg nitroglycerine with contact surface of 20 sqcm & rate of release of nitroglycerine 0.4 mg/hour. This study was done to compare the efficacy in terms of achievement of successful tocolysis and prolongation of pregnancy with the use of Isoxsuprine vs Transdermal Nitroglycerine patch and their side effects and patients' acceptability.

II. METHODS

This study was carried out in the department of Obstetrics & Gynaecology, C.S.M. Medical University Lucknow (A tertiary care teaching hospital). In the study period of one year total 134

women with preterm labour pain were assessed. In this prospective comparative study after taking informed consent, detailed history and clinical examination one hundred patients of preterm labour were enrolled. Women with singleton pregnancy between the gestational age of 24-37 completed weeks with threatened preterm labour pains or established preterm labour according to definition of A.C.O.G. (1997) (uterine contractions of 4 in 20 minutes or 8 in 60 minutes, cervical dilatation of >1cm, cervical effacement of 80% or greater) were included in this study.(fig.1)

Women with active labour, preterm premature rupture of membrane, chorioamnionitis, severe hypertension. Eclampsia, antepartum haemorrhage, fetal distress, severe IUGR, lethal congenital anomaly, intrauterine death, sensitivity or contraindication to tocolysis were excluded from this study. In group-I, 50 patients received Isoxsuprine injection intramuscularly every 8 hourly till 24 hours of uterine relaxation followed by tab Isoxsuprine 10 mg orally every 8 hourly for one week. In Group-II, 50 Patients received Transdermal Nitroglycerine patch (NTG -10) releasing nitroglycerine at the rate of 10 mg per 24 hours which was applied on the anterior abdominal wall. If no change in contractions occurred or there was an increase in intensity, frequency or duration of contractions after one hour of placement of first NTG Patch, one additional NTG Patch of same dose was applied, and then both patches were continued for 24 hours. If still contractions unchanged or increased at the end of four hours, all the patches were removed. Such patients were grouped under failed tocolysis. Twenty four hours after initiation of treatment, the patches were removed and replaced by the same number of patches for the next 24 hours. (Figure 2)

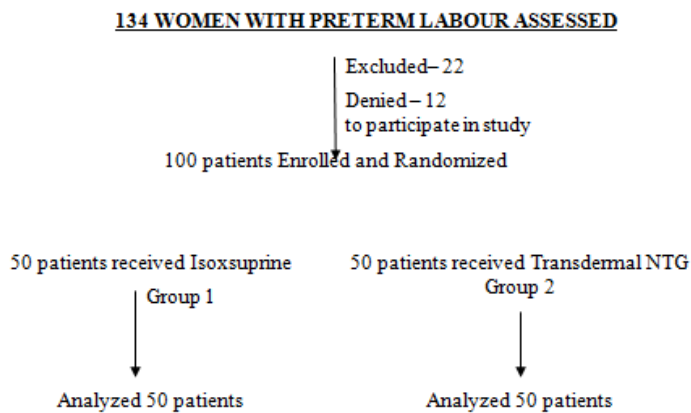
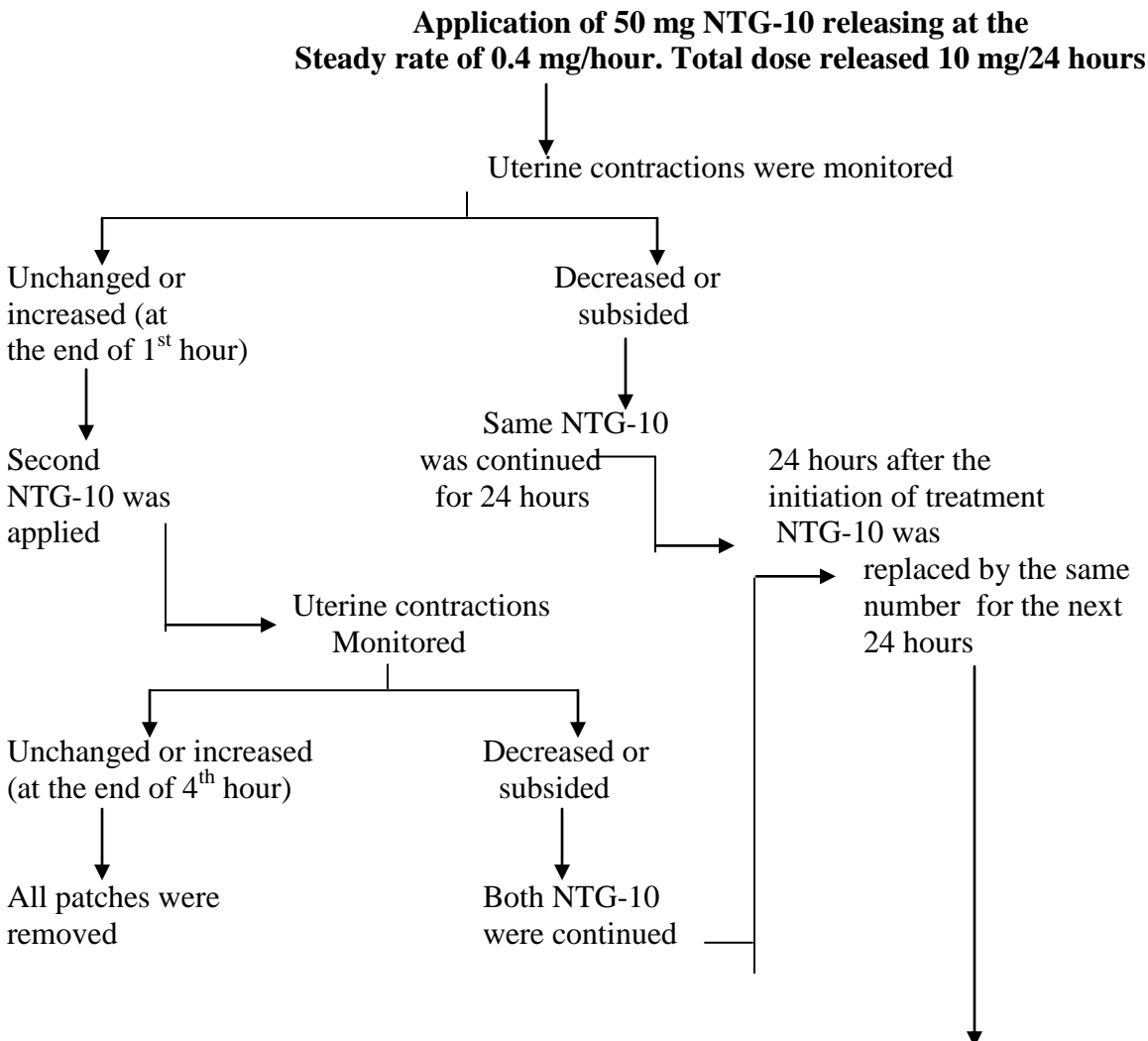


Fig. 1: Participant flow through the study.



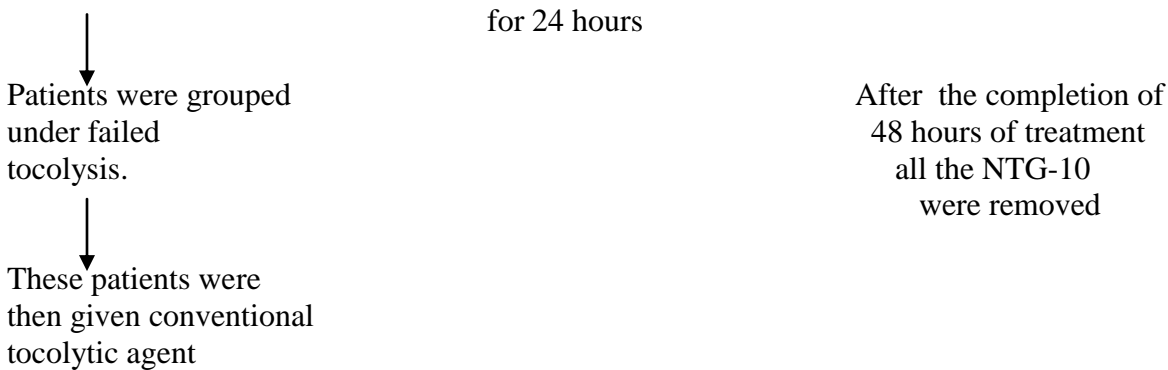


Fig. 2: Intervention strategy in Group-II patients

Maternal outcome were measured in terms of successful tocolysis, duration of prolongation of pregnancy, completion of course of maternal steroids, gestational age at delivery, mode of delivery and adverse drug reactions. **Fetal outcomes** were measured in terms of NICU admission and neonatal death.

The Ethical clearance for this study was given by Intuitional ethics committee, Office of the Research Cell, CSMMU (erstwhile King George's Medical University, Lucknow, U.P. (Ref. Code: XXX I ECM-II B/P3 dated 09/09/2008) for conducting and publishing the present work.

The demographic profile of women in the both the groups is shown in Table 1

The data so obtained was subjected to statistical analysis and tabulated Parametric comparison of proportions has been made using chi-square test for proportions. The confidence level of the study was kept at 95% hence a "P" value less than 0.05 indicated a statistically significant difference.

III. RESULTS

Both groups were age & parity matched. Participant flow through the study has been shown in Fig.-1. In the current study it was observed that in Group-II, 50% women delivered at the gestational age of more than 37 weeks as compared to 28% women in Group-I ($p=0.024$) (Table-2). In Group-II, 98% women had attained successful tocolysis as compared to 84% women in Group-I ($p=0.014$) (Table-2).

In the present study we also compared the duration of prolongation of pregnancy in both the groups. It was observed that in Group-I, 16% women delivered within 48 hours of start of tocolytic therapy as compared to only 2% women in group-II ($p=0.008$). The duration of prolongation of pregnancy exceeded 7 days in 60% women of Group-II. The duration of prolongation of pregnancy exceeded more than 7 days in higher percentage of cases in Group-II as compared to Group-I although the difference were not statistically significant because of small sample size ($P=0.161$) (Table-2). In Group-I, 81.25% of women of gestational age <34 weeks with preterm labour pain completed the course of steroid (Inj. Betamethasone 12 mg intramuscular given 24 hours apart), while in Group-II, 88.89% of women were able to complete the course of steroids. However the difference between the two groups was not statistically significant. ($P=0.010$) (Table-2)

The comparison of mode of delivery (vaginal/cesarean) between the two groups was not statistically significant ($P=0.79$) (Table-2).

We also assessed the clinical side effects of Transdermal Nitroglycerine and Isoxsuprine. In the present study headache occurred in 100% women of Group-II while none in Group-I ($p<0.001$) complained of headache. On visual analogue scale the severity of pain in Group-II was found to be mild in 70% of women and moderate in 30% of women. However, none of the women suffered from severe headache. Palpitation and tachycardia were observed in all 100% women of Group-I while none of the women of Group-II had such complaints ($p<0.001$). Other side effects were not observed in either of the two groups (Table-3).

We there after examined the neonatal outcome measures in the present study. In Group-I 16% neonates had Apgar Score <7 at 5 minutes and thus required resuscitation while in Group-II only 2% neonates had Apgar Score <7 at 5 minutes and required resuscitation. 10% neonates in Group-I and 2% neonates in Group-II developed respiratory distress syndrome, 6% neonates in Group-I required NICU admission and mechanical ventilator as compared to 2% neonates in Group-II. 4% neonates were recovered in Group-I and 6% of neonates expired while in Group-II only 2% of neonates expired. Although the neonatal death in group-I was not statistically significant as compared to group-II but neonatal complications were much higher in group-I as compared to group-II. (Fig.-3)

IV. DISCUSSION

In 1961 first beta sympathomimetic drug that was used to inhibit preterm labour was Isoxsuprine. However in light of unpleasant side effects and efficacy, many studies have shown it to have limited therapeutic value. Thus still researches are ongoing in search of a safe and effective agent. Recently various studies done worldwide on NO donors such as NTG suggest that these are equally or more efficacious in comparison to betamimetics and have fewer side effects.

Graeme N. Smith et al.¹⁰ did not find any significant reduction in delivery within 48 hrs with the use of Nitroglycerine. However in the current study, we found a significant reduction ($p>0.008$) in delivery within 48 hrs with the use of NTG as compared to Isoxsuprine. Similarly John Patrick et al.¹¹ found successful

tocolysis with NTG in all 100% cases. Similarly C Lees M.B. et al.¹² also found successful tocolysis in all 20 episodes (13 women of preterm labour) with the NTG group.

Duckitt Thornton S et al.¹³ found that significant number of pregnancies were prolonged beyond 37 wks of gestational age with the use of Transdermal NTG as compared to other tocolytics. In the present study 50% of women delivered after 37 wks of gestational age when NTG was used as tocolytic agent. Thus our results were quite comparable.

In the present study headache was the universal side effect with the NTG as also stated by Duckitt Thornton S et al.¹³ that women were more likely to experience headache with the use of NO donors. Tachycardia and palpitation were universally seen in all women of Isoxsuprine group. Rayamajhi R et al.¹⁴ also found the higher rate of such complications with Isoxsuprine. Similarly Rebecca et al.¹⁵ reported significantly more cardiovascular side effects with betamimetics and minimal adverse effects with NTG group. However in our study no adverse cardiovascular side effects occurred in NTG group.

The primary goal for the use of tocolytic agents is to improve neonatal outcome. In the present study there was a trend towards a reduction in the incidence of Respiratory Distress Syndrome with the use of Nitroglycerine.

Only one neonate in group II died due to RDS in whose mother NTG tocolysis was not successful. In group-I 16% who

had not completed successful tocolysis (Isoxsuprine group) only 10% neonates developed RDS and out of these 6% neonates died. Our results are in corroboration with Graeme Smith, et al.¹⁰ where none of the neonates suffered from RDS in NTG tocolysis group.

However in study conducted by Gill A et al.¹⁶ no significant difference in terms of neonatal morbidity and mortality was found between NTG and β 2 agonist tocolytic therapy.

This randomized prospective comparative study lends support to the proportion that Transdermal Nitroglycerine may be promising safe, effective, well tolerated, cost effective and non invasive method of tocolysis. However before its widespread use can be recommended, large multicenteric trials are needed to assess optimal dosage, dosage regimes, overall efficacy and fetal safety.

V. CONCLUSION

This randomized prospective comparative study lends support to the proportion that Transdermal Nitroglycerine may be promising safe, effective, well tolerated, cost effective and non invasive method of tocolysis.

Table-1: Demographic characteristics of participants

		Group -1 Isoxsuprine		Group -2 Transdermal NTG	
		N	%	N	%
1.	Age (years)	25.68 +3.84 (Mean± SD)		25.92 + 3.68 (Mean± SD)	
2.	Parity				
	0	22	44	22	44
	1	16	32	15	30
	2	11	22	11	22
	>3	1	2	2	4
3.	History of Preterm Labour				
	Present	5	10	3	6
	Absent	45	90	47	94
4.	History of Recurrent Pregnancy loss				
	Present	4	8	2	4
	Absent	46	92	48	96
5.	Vaginal Culture				
	Positive	2	4	1	2
	Negative	48	96	49	98
6.	Urine Culture				
	Positive	2	4	1	2
	Negative	48	96	49	98

Table-2: Maternal Outcome

	Group -1 Isoxsuprine		Group -2 Transdermal NTG		P value
	N	%	N	%	
Gestational Age At Delivery (weeks)					
> 37	14	28	25	50	0.024
35-37	20	40	16	32	0.405
33-34	11	22	7	14	0.298
29-32	5	10	2	4	0.24
< 28	0	0	0	0	-
Successful Tocolysis					
Yes	42	84	49	98	0.014
No	8	16	1	2	
Duration of Prolongation of Pregnancy (Hours)					
<48	8	16	1	2	0.008
48-<72	7	14	4	8	0.505
72-<96	10	20	13	26	0.476
96-<7days	2	4	2	4	1
>7days	23	46	30	60	0.161
Completion of course of Maternal steroids(<34weeks)					
Yes	13 of 16	81.25	8 of 9	88.89	0.010
Negative	3 of 16	18.75	1 of 9	11.11	
Mode of Delivery					
Vaginal	42	84	41	82	0.79
Caesarean	8	16	9	18	

Table 3: Clinical Side Effects

Side Effects	Group I (Isoxsuprine) (n=50)		Group II (Transdermal Nitroglycerine) (n=50)		Statistical Significance	
	No.	%	No.	%	χ^2	P value
Headache	0	0	50	100	100	<0.001
Flushing	0	0	0	0	-	-
Palpitation	50	100	0	0	100	<0.001
Tachycardia	50	100	0	0	100	<0.001
Hypotension	0	0	0	0	-	-
Pulmonary oedema	0	0	0	0	-	-
Arrhythmia	0	0	0	0	-	-
Myocardial infarction	0	0	0	0	-	-

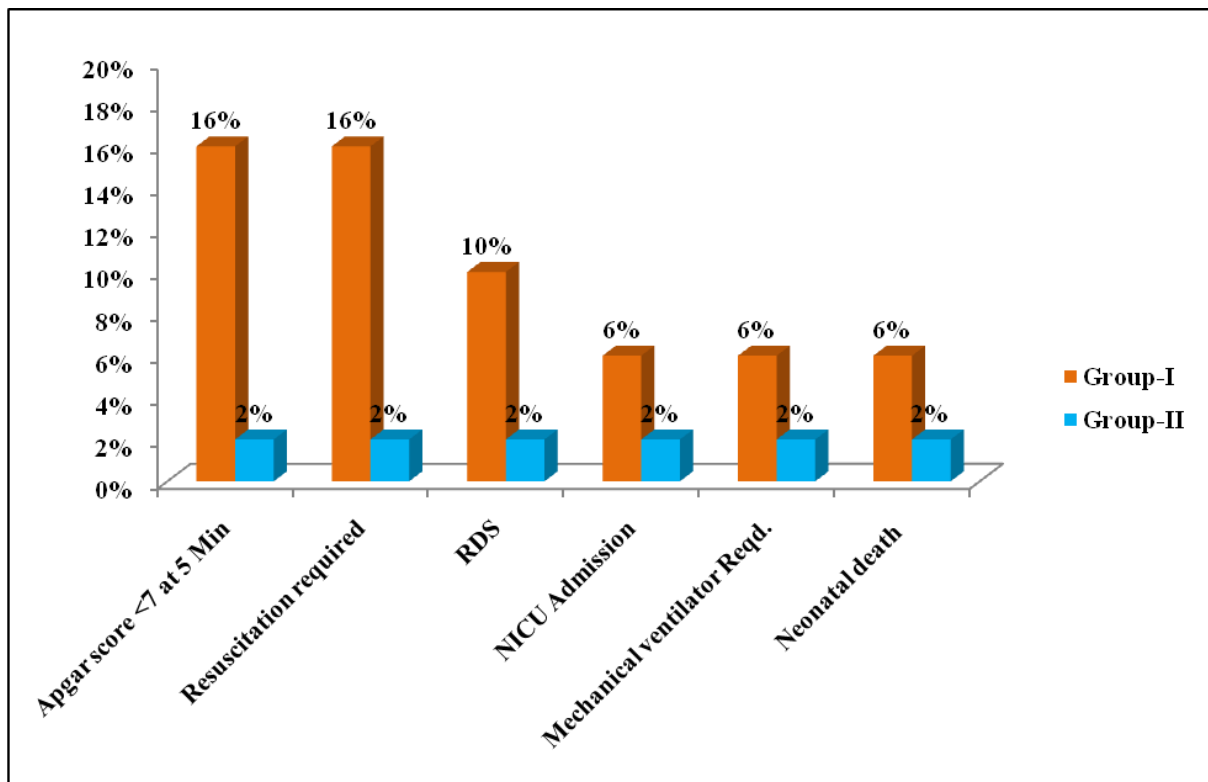


Figure 3: Neonatal Outcome

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