TO COMPARE THE EFFECTIVENESS OF NIFEDIPINE AND GLYCERYL TRINITRATE PATCH IN PREVENTION OF PRETERM LABOUR

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ABSTRACT

Objective: To assess the effectiveness of Nifedipine and Glyceryl trinitrate patch in prolonging the pregnancy for more than 48 hours.

Methodology: This was a randomized control study. Fifty patients with preterm labour meeting the inclusion criteria were inducted in study and randomly allocated to the treatment group A (Nifedipine) and group B (Glyceryl trinitrate patch, GTN). After taking consent from the patients, all the details were documented on a proforma and tocolysis was started with either of these tocolytics according to a preset protocol.

Results: Nifedipine was found to be more effective than GTN, as prolongation of pregnancy beyond 48 hours was more frequent (74 %) with nifedipine than GTN (40%) with P value <0.05 . Similarly prolongation beyond 7 days was also more frequent (32%) with nifedipine as compared with GTN (24%). Most common adverse effect found with nifedipine was headache followed by palpitations and hypotension. GTN patch had a better side effect profile with most of the patients being asymptomatic. Fetal distress was noticed more in GTN group as compared with nifedipine.

Conclusion: Nifedipine, as a tocolytic, is found to be more effective in pregnancy prolongation when compared with Glyceryl trinitrate but has frequent maternal adverse drug effects. Glyceryl trinitrate patch is well tolerated by the patients with preterm labour with relatively fewer side effects.

Key Words: Preterm labour, Nifedipine, Glyceryl trinitrate

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INTRODUCTION

A wide range of tocolytics (drugs used to suppress uterine contractions) have been tried to stop preterm labor due to significant risks of prematurity, neonatal morbidity and mortality. These tocolytic agents include atosiban, magnesium sulphate, betamimetics, calcium channel blockers, nitric oxide donors. These have been used and trials are going on to select an ideal tocolytic which is highly effective in stopping the contractions with minimal adverse effects for baby and the mother. Women most likely to benefit from use of a tocolytic drug are those needing transfer to a hospital which can provide neonatal intensive care and those who have not yet completed a full course of corticosteroids[1].

The currently available data are suggestive of deleterious fetal effects of MgSO4 in the setting of preterm labor to the extent that some authorities are recommending abandoning it for routine use as a tocolytic therapy.

Nifedipine and atosiban have comparable effectiveness in delaying birth for up to seven days[2]. Atosiban is not freely available in local settings although it is highly recommended. Use of betamimetics is limited due to significant adverse effects.

Calcium channel blockers (nifedipine) have the ability to inhibit contractility in smooth muscle cells. Nifedipine is commonly used in pregnancy for the treatment of pre-eclampsia (elevated blood pressure), but normotensive women show a minimal drop in blood pressure. Nifidipine has similar tocolytic activity with less side effects than betamimetics[3]. Oral nifedipine could be a suitable alternative for magnesium sulfate with the same efficacy and side effects in the management of preterm labor[4]. There is uncertainty about the value of atosiban (oxytocin receptor antagonist) and nifedipine (calcium channel blocker) as first-line tocolytic drugs in the management of preterm labor[5].

Nitric oxide donars (Glyceryl trinitrate Patch or GTN patch) are also undergoing trials after encouraging preliminary reports[6]. GTN patch has been shown to inhibit

preterm births leading to reduced perinatal morbidity and mortality[7].

Nifedipine and Glyceryl Trinitrate are both relatively cost effective, readily available in our set up so we will try to sort out which will be more effective regarding tocolytic therapy. Tocolytic therapy is specifically initiated to gain some time for in-utero transfer and steroid administration for fetal lung maturity. An ideal tocolytic is yet to be identified which effectively stops uterine contractions and have safety for mother and fetus[7].

The data generated may help in managing patients presenting with threatened preterm delivery and will find which one of these two groups (nifedipine and GTN) is more effective and safe.

METHODOLOGY

It was an analytical study in which 50 patients with preterm labour were randomly allocated to one of the two groups. Group A with 25patients were given tocolysis with nitroglycerine patch while the group B with were given nifidipine tocolysis. The study was carried out in Deptartment of obstetrics/Gynae, Lady reading hospital, Peshawar from September 2014 till September 2015.

The ethical committee of PGMI Lady reading hospital approved this study. It was a randomized clinical trial. Those women fulfilling the inclusion criteria were included in study. Eligible women were all pregnant women diagnosed with preterm labor, between 28 and 34 weeks+5days of gestation with singleton pregnancy. Whereas those with multiple pregnancy, preterm rupture of membranes or showing signs of chorioamnionitis were not included in the study. Patients with congenital fetal malformations or a non-reassuring fetal heart rate, which need delivery anyways, were excluded from the study. Hypotension is supposed to be the known side effect of both of the tocolytics under the study therefore patients already presenting with hypotension were not enrolled in the trial and were given some alternative tocolysis for stopping the uterine contractions. The operational definition of preterm labour was the presence of 4 uterine contractions or more over 30 minutes, each lasting at least 30 seconds, with a cervical change (dilatation of 0-4 cm and effacement of at least 50%)[8].

After taking consent from the patients, all the details were documented on a proforma and tocolysis was started with either of these tocolytics according to a preset protocol.

The protocol for Nifedipine tocolysis was to initiate with a 10 mg capsule (available with trade name nifidil) which was repeated every 15 min for one hour and then nifedipine maintenance dose was 10 mg every eight hourly for 48 hours. Glyceryl trinitrate patch (deponit patch) with a dose of 5 mg was applied as a single patch (over the abdomen) which was repeated after 12 hours. Thus two deponit patches 12 hours apart were applied.

Before giving tocolysis, blood pressure (BP) and maternal heart rate were recorded and a fetal cardiograph with a CTG (cardiotocograph) machine was done to rule out a non-reassuring CTG. The blood pressure was measured every 15Minutes for an hour and then every 6 hours.

The collected data were analyzed by using statistical tools (SPSS Version 16) using descriptive statistics (mean, standard deviation and confidence interval) and the chi square test to compare the efficacy and adverse maternal and fetal outcomes. The p-value less than 0.05 was considered as significant.

RESULTS

The two study groups were comparable regarding demographic variables in terms of age and parity. The mean gestational age of fetuses with preterm labour was 32 weeks ±2.19 ranging from 28 weeks to 34 weeks ±5 days .

Prolongation of pregnancy beyond 48 hours was more with Nifedipine (74%) than GTN (40%). (table 2)

Similarly prolongation beyond 7 days was also more frequent with Nifedipine(32%) as compared with GTN (24%). (table 1)

Most common adverse effect found with Nifedipine was headache (32%) followed by palpitations and hypotention. GTN patch had a better side effect profile with 48% patients being asymptomatic ,however ,headache was the most frequent complaint with it (table 3). Hypotention was more common in patients treated with nifedipine as compared with GTN.

Fetal distress was noticed more in GTN group (44%) as compared with nifedipine group (16%) and subsequently higher neonatal admissions to ICU and early neonatal deaths (table 4)

DISCUSSION

Preterm labour leading to a premature baby have grave consequences which increase neonatal morbidity and mortality. Tocolysis aims at delaying delivery so as to reduce these complications and to gain time for administration of steroids to attain fetal lung maturity.

Nifedipine (calcium channel blocker used as a tocolytic) lowers the blood pressure in hypertensive patients but in normotensives, drop in blood pressure is not marked. Studies have shown that the uteroplacental blood flow to the baby is not decreased with nifedipine although it readily crosses placenta. However, some studies have documented severe hypotention with fe-

tal death with nifedipine tocolysis[9]. These studies raise concerns regarding safety of nifadipine. Yet there is a comparable efficacy of nifedipine with atosiban and magnesium sulfate[3,10].

Glyceryl trinitrite patch is also being used as a tocolytic, favored by its easy application and fewer side effects but some studies have questioned its efficacy . In literature it is even reported that the effect of GTN in the treatment of preterm labour is similar to the placebo without any serious complication[11].

Our study was undertaken to come up with efficacy and safety of nifedipine and Glyceryl trinitrate in management of preterm labour.

The primary outcome measure was to arrest preterm labor which was defined as prevention of delivery for 48 hours with uterine quiescence. The secondary outcome measures were patients remaining undelivered 7 days after tocolysis, maternal adverse drug reactions, fetal distress with subsequent NICU admissions and neonatal death.

Regarding the duration of tocolysis, the recommended dosage for GTN patch is 2 patches applied 12 hours apart which cannot be continued for 48 hrs. However, in research settings different dosage regimens could be tried both for GTN and nifidipine to find out most effective dose with minimal side effects.

Table 1: Efficacy of Glyceryl trinitrate and Nifedipine in delaying uterine contractions

Drug used for tocolysis	Delivery time	Frequency	Percent
Glyceryl trinitrate patch	delivery in 24 hours	11	44
	delivery in 48hours	4	16
	delivery in 7 days	4	16
	delivery more than 7 days	6	24
	Total	25	100
Glyceryl trinitrate patch	delivery in 24 hours	5	20
	delivery in 48hours	2	8
	delivery in 7 days	10	40
	delivery more than 7 days	8	32
	Total	25	100

Table 2: Efficacy of Glyceryl trinitrate and Nifedipine in delaying uterine contractions for 48 hours

Drug used for tocolysis	Efficacy modified		Total	P value
	delivery within 48 hours	delivery after 48 hours		
Glyceryl trinitrate patch	15	10	25	0.023
Nifedipine	7	18	25	

Table 3: Frequency of fetal distress with Glyceryl trinitrate and Nifedipine

Drug used for tocolysis	Fetal Distress	Frequency	Percent	P value
Glyceryl trinitrate patch	No fetal distress	14	56	0.031
	Fetal distress	6	24	
	Early neonatal death	5	20	
	Total	25	100	
Nifedipine	No fetal distress	21	84	
	Fetal distress	4	16	
	Total	25	100	

Table 4: Adverse maternal effects with Glyceryl trinitrate and Nifedipine

Drug used for tocolysis	Adverse maternal effects	Frequency	Percent	P value
Glyceryl trinitrate patch	No side effects	12	48	0.015
	Headache	8	32	
	Nausea vomiting	2	8	
	Palpitations	1	4	
	Headache+ Hypotention	2	8	
	Total	25	100	
Nifedipine	no side effects	4	16	
	headache	8	32	
	nausea vomiting	1	4	
	palpitations	2	8	
	flushing	1	4	
	hypotention	2	8	
	headache+palpitations	2	8	
	headache+hypotention	1	4	
	hypotention+palpitations	4	16	
	Total	25	100	

Nifedipine was found to be more effective than GTN in prolongation of pregnancy beyond 48 hrs was more frequent with nifedipine (72%) than GTN (40%). Prolongation of pregnancy beyond 7 days was also more frequent with nifedipine (32%) as compared with GTN (24%). Similar results showing successful prolongation of pregnancy were shown in study by Dhawle et al [12] in which pregnancy prolongation for 48 hours was more with nifedipine as compared with GTN. Failure of acute tocolysis, defined as delivery within 48 hours, was significantly more common with GTN (31.7%) as compared to nifedipine (11.6 %) in the above mentioned study[12]. Failure of acute tocolysis in our study was similarly more with GTN (60%) as compared with nifidipine (28%).

Although nifedipine was more successful in prolongation of pregnancy but it was associated with more frequent side effects as compared with GTN. No adverse effects were found in (48%) of patients who received tocolysis with GTN as compared with (16%) of those with nifedipine tocolysis. Adverse effects of nifedipine are palpitations, dizziness, hypotension, headache, nausea and flushing. These symptoms were found either in combination or alone in more than half of patients.

In a meta-analysis, Nifedipine was associated with significantly fewer maternal adverse events than β_2-adrenergic-receptor agonists and magnesium sulfate.[13] However, in this meta-analysis, side effects of nifedipine has not been compared with GTN. This study showed that tocolysis with nifedipine is associated with more adverse effects as compared to GTN which showed fewer maternal adverse effects. In another study by Malik[14], nifedipine tocolysis was preferred over salbutamol due to its rapid and effective action, its simplicity of administration and safety. Calcium channel blockers reduced the number of women giving birth within seven days of receiving treatment (relative risk (RR) 0.76; 95% confidence interval (CI) 0.60 to 0.97) when they compared it with salbutamol[1].

Regarding fetal condition in using these tocolytics, it was found that more cases of fetal distress followed by neonatal intensive care unit (NICU) were noticed with GTN tocolysis as compared with Nifidepine. It should also be kept in mind that tocolysis is being used for preterm babies who are already prone to get admitted in NICU for prematurity and problems related to prematurity. Thus giving higher nursery admission rates as compared to term babies.

Thus the primary outcome measure of prolongation of pregnancy was more successful in nifedipine than Glyceryl trinitrate with relatively higher side effects rate, however, NICU admissions and neonatal morbidity was found to be higher with nifedipine tocolysis.

CONCLUSION

Nifedipine, as a tocolytic, is found to be more effective in pregnancy prolongation when compared with Glyceryl trinitrate but has frequent maternal adverse drug effects. Glyceryl trinitrate patch is well tolerated by the patients with preterm labour with relatively fewer side effects. Further research on a larger scale is needed to be carried out to compare different dosage regimens for nifedipine to optimize its side effects while maintaining its efficacy.

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CONTRIBUTORS

SY conceived the idea, planned the study, and drafted the manuscript. SS helped acquisition of data and did statistical analysis. FZ drafted the manuscript and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.