Original Article

Role of Nifedipine as Tocolytic Agent in Preterm Labour

Ammara Niaz, Mubashra Naz, Saadia Khanum

ABSTRACT

Objectives: To determine the efficacy of nifedipine as tocolytic agent in preterm labour.

Study Design: Quasi experimental study. **Settings:** Allied Hospital/ Divisional Head Quarter Hospital affiliated with Punjab Medical College, Faisalabad. **Duration:** from 2008 to 2009. **Methodology:** Sixty patients following inclusion and exclusion criteria on the basis of history and clinical examination were selected. Capsule nifedipine 10 mg (powder form) was administered sublingually every 15 minutes and no more 40 mg in 1 hour. Maintenance dose of slow release nifedipine (60-160mg) was administered orally twice daily for next 48 hours when the patient responded to initial sublingual regimen. Main outcome measures including arrest of pre-term labour and secondary outcome measures like maternal hypotension, tachycardia, headache, flushing, nausea and vomiting were observed. Blood pressure of all patients was measured every 15 minutes as long as they were in pre-term labour and 4 hourly during next 24 hours. Fetal heart rate and uterine contractions were recorded during whole study period. SPSS version 10 was used to analyze descriptive statistics like frequencies and percentages. **Results:** Successful tocolysis occurred in 80 % of cases. The incidence of maternal side effects was very low of 60 patients only eight (13%) had side effects including hypotension (5%) 6 patients developed tachycardia (10%), headache occurred in 6 patients (10%). Only one patient had nausea (1.6%) and two suffered flushing (3.3%). **Conclusion:** The results of study indicated that nifedipine is an effective tocolytic agent with low side effect profile.

Keywords: tocolysis, pre-term labour, nifedipine

INTRODUCTION

Preterm labour is defined as onset of labour after the age of viability (24weeks) and before 37 completed weeks of pregnancy. In developed countries the incidence of preterm labour varies between 10 to 12 % and its contribution to neonatal morbidity and mortality varies between 50-70% .[1]

Pre term delivery is one of the major cause of perinatal mortality and morbidity like respiratory distress syndrome, neonatal jaundice, sepsis, cerebral palsy, developmental delay, chronic lung disease, visual and hearing loss.

Corresponding Author:
Dr. Ammara Niaz
Senior Registrar, Obstetrics & Gynaecology
Punjab Medical & Dental College, Faisalabad
Tel. +92 301-7070156
E-mail: ammaraniazrehman@gmail.com

Management of all these complications in neonates consumes more than 35% of the health resources.[2] About 85% of deaths in structurally normal infants are due to prematurity.[3]

Preterm birth is the single most important determinant of adverse infant outcome in terms of both survival and quality of life. During the last 2 to 3 decades there is hardly any change in the perinatal mortality rather it has climbed up in the recent past.[4]

The etiology of preterm labour is unknown in more than 50% of the cases. Some maternal factors implicated in preterm labour include age <18 and >35 years, poverty, short stature, poor nutrition, BMI <18, poor weight gain during pregnancy, cigarette smoking and substance abuse. Occupational factors, psychological stress, unmarried and primigravida of African origin are also contributory factors.[5]

Owing to high morbidity and mortality associated with prematurity various remedies have been introduced in obstetrics to minimize the effects of prematurity.[6] These therapies include antenatal corticosteroids to decrease respiratory distress syndrome and tocolytic agents to arrest preterm labour. The major advantage of these tocolytic agents is to gain time to administer corticosteroids and in utero transfer of the fetus for better NIC (neonatal intensive care) facilities in phase of active preterm labour.[7] Although long term use of tocolytic agents to prolong pregnancy has been abandoned, the short term use for maximum 48 hours to administer steroid and in utero transfer is still being practiced widely.[8]

Many tocolytic agents are being used world over to arrest preterm labour. Beta sympathomimetic including ritodrine and salbutamol are signature drugs of the series. Other included in list are prostaglandin synthetase inhibitors (indomethacin), MgSO4, Calcium channel blockers and oxytocin antagonists. The perfect tocolytic that is uniformly effective with complete fetomaternal safety does not exist. Tocolytic agents differ in their cost, utero-specificity, safety, efficacy and whether they are licensed for use.

The existing evidence is populated with Ritodrine and indomethacin. Both drugs are equal in efficacy in arresting preterm labour but with long list of side effect profile both for mother and fetus.[9] The emerging drug Nifedipine from class of Ca^{++} channel blockers traditionally used as antihypertensive has gained popularity due to ease of administration, low cost and reasonable side effect profile. Although the drug is being used largely world over, the obstetricians in Pakistan and specially this part of country are not comfortable and familiar with the drug. There is not enough confidence in its use as a tocolytic agent. To bridge this gap, the study was conducted not only to determine the efficacy in our obstetric population but also to gain confidence in its use. The thin existing evidence in this part of the world regarding the use of nifedipine also paved the way for the study.

The rationale of the study was to establish the efficacy of nifedipine as tocolytic agent in pre-term labour.

MATERIALS AND METHODS

The study was conducted in Department of Obstetrics Allied Hospital, Faisalabad from 2008 to 2009.

Sixty consecutive patients presenting in labour room with preterm labour (regular uterine contractions associated with cervical changes) between 30-34 weeks of gestation were enrolled in study. Patients with multiple pregnancies (diagnosed on USG), premature rupture of membranes (confirmed on history and speculum examination) and maternal hypotension defined as Blood pressure <90/50 mmHg were excluded from study. Ethical issues were addressed by explaining patient relative innovative use of this drug as tocolytic. The study gained approval from research ethical committee of institute. Risks like possibility of maternal hypotension, palpitations, flushing, nausea and benefits that prolongation of pregnancy for at least 48 hours to administer steroids, low cost, less frequent side effects were explained to patients and informed consent was taken.

Capsule nifedipine 10mg (powder form) was administered sublingually every 15 minutes. The maximum dose did not exceed 40mg in first hour.

The maintenance dose (60-160mg of slow release nifedipine twice daily for next 48 hours) was only prescribed to those patients in which uterine contractions had stopped after the initial regime of the drug in first hour.

Main outcome measures including blood pressure was measured every 15 minutes as long as the patients were in labour and 4 hourly during next 24 hours. Fetal heart rate and uterine contractions were recorded during whole study period. All patients were given one course of betamethasone intramuscular injection 24 hours apart to promote fetal lung maturation.

Tocolysis was considered successful when uterine activity stopped (<4 contractions /hour) in the absence of cervical change for at least 48 hours. If patients continued to have uterine activity after 6 hours of administration of drug or had cervical dilation more than 2 cm after admission, tocolysis was switched off. Primary outcome measure that is arrest of preterm labour and secondary outcome measures like maternal hypotension, tachycardia, headache, flushing, nausea and vomiting were

recorded. SPSS version 10 was used to analyze descriptive statistics like frequencies and percentages.

RESULTS

Minimum age of patients in study population was 18 years and maximum was 46 years. Mean age was 30 years ± 7.3 SD.

Amongst sixty patients enrolled for study 38(64%) were unbooked and 22(37%) were booked at Allied Hospital, Faisalabad. Considering parity 10 patients (17%) were primigravidas and 50 patients (83%) were having more than 1 babies previously. (Table 1)

As far as gestational age is concerned 46 patients were below 32 weeks (77%) and 14 (23%) were more than 32 to 34 weeks. (Table 1) Forty patients (67%) had cervical dilatation of 1-2 cm at presentation while 20 patients (33%) had 2-3cm dilatation of cervix. Regarding efficacy of nifedipine as tocolytic agent, it arrested preterm labour in 48 patients (80%) and contraction remained unsettled in 12 patients (20 %). (Table 2) Overall 8 patients suffered from side effects while 52 patients had no side effects. (Table 3)

Maternal tachycardia was found in 6 patients (10%). During tocolysis hypotension was noted in 3 patients. (5%) of sixty patient 6 patients (10%) suffered from headache due to nifedipine. Only one patient had nausea (1.6%) during treatment while flushing was experienced by only 2 patients (3.2%). (Table 4)

Table 1
Baseline parameters of study population

Sr. no	Parameters		No of Patients	%Age
1	Booking status	Booked	22	36 %
		Un booked	38	63%
2	Gestation age at presentation	30-31+6 weeks	46	76.67%
		32-34 weeks	14	23%
3	Parity status	Primigravida	10	16%
		P1 to P3	32	53%
		>P3	18	30%

Table 2
Main outcome measure Efficacy of nifedipine as tocolytic
n=60

Success of tocolysis	No of cases	%Age	Frequency
Successful tocolysis	48	48	80 %
Failed tocolysis	12	12	20%

Table 3
Side effects of nifedipine

Sr. no		No of cases	Frequency	%Age
1	Over all Side effects	8	8	13.3
2	No side effects	52	52	86.6

Table 4
Distribution of various side effects in 60 patients

Sr. no	Side effects	No of cases	Frequency	%Age
1	Hypotension	3	3	5
2	Headache	6	6	10
3	Tachycardia	6	6	10
4	Nausea	1	1	1.6
5	Flushing	2	2	3.3

DISCUSSION

Preterm birth is strongly associated with neonatal death and long-term neurological morbidity. The purpose of tocolytic drug administration is to postpone threatening preterm delivery for 48 hours to allow maximal effect of antenatal corticosteroids and maternal transportation to a center with specialized neonatal care facilities.

Preterm labour and delivery are among the most challenging obstetric complications encountered by the obstetrician worldwide. In the United States, preterm delivery affects approximately 1 in 10 births and is the cause of at least 75% of neonatal deaths, excluding those related to congenital malformations.[10] According to confidential enquiry in the year 2000, 48.5% of

neonatal deaths in England and Wales are due to prematurity. Pakistan is one of the countries with a high perinatal mortality rate. A multicenter survey from hospital based facilities indicates that the overall perinatal mortality rates in Pakistan has increased to 104/1000 live births.[11]

A wide range of tocolytics have been utilized for the management of preterm labor. Calcium channel blockers, namely nifedipine, gained popularity as tocolytic due to the oral route of administration, availability of immediate- and slow-release preparations, the low incidence of maternal adverse effects associated with its use, and the fact that it is cheap.[12]

The perfect tocolytic that is uniformly effective with complete fetomaternal safety does not exist. Tocolytic agents differ in cost, utero-specificity, safety, efficacy and whether they are licensed for use.

This study was designed at Allied Hospital affiliated with Punjab Medical College Faisalabad which is a major referral center for the population of this area. For nifedipine, concerns have been raised about unproven safety, lack of placebo-controlled trials, and its off-label use.[13]

Considering the main outcome measure that is successful tocolysis, the result are comparable to the study conducted at Emek Medical Center, in Israel by Salim et al in which successful tocolysis was observed in 89% of patients at 7 days.[14]

The results are also supported by the study conducted in Tehran University of Medical Sciences by Kashanian et al on Comparison of the efficacy and adverse effects of nifedipine and indomethacin for the treatment of preterm labor.[15]

A multicenter comparative study held in France on Nifedipine or nicardipine in management of threatened preterm delivery demonstrated only 2% patients with side effects while in this study overall 14 % patients experienced minor side effects . The difference might be due to small sample size of this study. The low level of adverse effects in nifedipine group explains its safety. [16]

The study strengthened the existing evidence on the safety of nifedipine which supported by the study of Laohapojanart N in Bangkok.[17]

The success of nifedipine in reducing uterine contractions for effective tocolysis has been appreciated by world authorities as well. RCOG has recommended it as first line tocolytic drug showing its comparable effectiveness with atosiban (oxytocin receptor antagonist). The main reason for considering it as first line is its low side effects profile seen in mother which is also established in my study. Over all side effect profile of nifedipine is much lower than the traditional tocolytic agents like ritodrine and indomethacin.[18]

The study strengthened the existing evidence as the drug is cost effective, easy to administer, easily available and no storage problems. The drug can be reliably used to arrest preterm labour

CONCLUSION

Nifedipine is an effective oral tocolytic and a rational alternative to other tocolytic agents in the management of preterm labour. The drug is cost effective, easy to administer, easily available, and no storage problems. The drug can be reliably used to arrest preterm albour with good side effect profile and it is a promising alternative to traditional beta sympathomimetic drug with serious maternal side effects .

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AUTHORS

- **Dr. Ammara Niaz**
  Senior Registrar, Department of Obstetrics & Gynaecology
  PMC/Allied Hospital, Faisalabad
- **Dr. Mubashra Naz**
  Assistant Professor, Gynaecology
  University Medical & Dental College, Faisalabad
- **Dr. Saadia Khanum**
  Post Graduate Trainee, Gynaecology
  Allied Hospital, Faisalabad

Submitted for Publication:	24-04-2013
Accepted for Publication: After minor revisions	16-05-2013