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Effectiveness of Nifedipine in the Treatment of Threathened Preterm Labour

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ABSTRACT

Background: Preterm birth is one of the most important and major causes of perinatal morbidity and mortality wordwide. Strategies should be adopted to decrease the incidence of pre-term labour and delivery to avoid the associated drastic fetal and neonatal consequences.
Objective: To evaluate the effectiveness of Nifedipine in the treatment of spontaneous preterm labour.
Material and Methods: This is a Randomised control trial which was conducted in the department of Obstetrics and Gynecology, Hayatabad Medical Complex, from 1st June 2022 to 30th November 2022. Total 50 pregnant women with singleton pregnancy with threatened preterm labor between 28 and 34 weeks of pregnancy on LMP were included.
Results: Total 10 (20.0%) patients had a delay in delivery up to < 2 days while 40 (80.0%) patients had a delay in their deliveries for > 2 days, therefore, effectiveness of Nifedipine in the treatment of spontaneous threatened preterm labor was achieved in 40 (80%) patients in terms of delay in their deliveries.
Conclusion: This study demonstrated that Nifedipine successfully delayed spontaneous preterm labor for > 48 hours and thus gave sufficient time for in utero transfer and corticosteroid effect.
Keywords: Nifedipine, Preterm labor, Tocolysis.

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INTRODUCTION

Treathened preterm labour is a condition in which regular uterine contractions occur, at least 1 contraction occuring every 10 minutes lasting for atleast 30 seconds before 37 completed weeks of gestation and in the absence of cervical dilation, or before the fetus is considered viable (now defined in the UK as 24 complete weeks of gestation from the date of the last menstrual period, assuming a 28-day menstrual cycle).1,2 In the industrialized world, preterm birth is a leading cause of infant mortality and morbidity. The projected annual rate of preterm births in Europe is roughly 400,000, with a prevalence of 5.8%. Of these, over 100,000 preterm births may be avoided with better antenatal care including timely interventions. Pakistan has a very high perinatal mortality rate of 96.0 deaths per every 1,000 live births, especially when compared to affluent nations (India 48.6, Burma 57.2, Indonesia 45 and Thailand 28.3).3,4 Fifteen to twenty percent of preterm and very low birth weight babies who make it to adulthood may suffer from some form of severe neurological damage or disability, while the remaining infants may have varying degrees of minor hearing or intellectual deficiencies.5,6 There is a reduced risk of Respiratory Distress Syndrome (RDS) following a 24 48 hours delay in delivery, although this delay is only statistically significant after 48 hours.7 Preterm labour should be delayed by at least 48 hours if pharmacological treatment is to be considered successful.8,9 Nifidipine (Adalat) is a calcium channel blocker that acts by causing relaxation of the smooth mucles cells all over the body including smooth muscles of the uterus. Its main use uptil now has been in the management of hypertension and angina. When used in preterm labour it relaxes the uterine wall muscles by preventing calcium from moving into the smooth muscle cells of the uterus making it less able to contract. Maternal side effects include irregular heartbeat, low blood pressure, and other metabolic abnormalities 10,11. Tocolytically, Nifedipine is superior.12 Despite some unwanted effects, Nifedipine is generally well tolerated and is continued by most patients.13,14

The scientific rationale of the study is centered around addressing the significant issue of preterm birth, a leading cause of perinatal morbidity and mortality worldwide. It aims to assess Nifedipine's effectiveness in delaying spontaneous preterm labor by over 48 hours, minimizing risks and enabling necessary interventions. With high perinatal mortality rates in Pakistan and worldwide implications, the research addresses the urgency. Through a randomized trial, it seeks to offer empirical proof of Nifedipine's efficacy, potentially providing a valuable intervention for enhancing neonatal outcomes and decreasing preterm birth-related burdens.

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MATERIAL AND METHODS

This was a randomized trial study conducted at the department of Obstetrics & Gynecology, Hayatabad Medical Complex, Peshawar from 1st June 2022 to 30th November 2022, after permission from institutional ethical review board via notification No. 1140, Dated January 6th 2023. A total of 50 patients were enrolled in the research group. The sample size was determined considering statistical factors such as research objectives, desired confidence level, expected effect size, data variability, chosen statistical test, and desired power level. Calculations were based on established formulas and statistical software. Potential attrition was also considered. This approach ensures reliable and robust results without unnecessary resource wastage. As our population group to be studied was small so we used a simple random sampling method. All patients who were admitted to labour room via emergency with the diagnosis of threatened preterm labour were included in the study group. Threatened preterm labor (TPL) is the progression of cervical dilatation and ripening caused by regular uterine contractions occurring before 37 weeks of pregnancy, which may result in preterm birth.[19] A 4th year resident assessed these patients for the confirmation of threatened preterm labour and their enrollment in the study group after fulfillment of inclusion and exclusion criteria. A 4th-year resident's involvement in the study is based on their advanced medical training and experience. They possess clinical expertise to accurately assess patients for conditions like threatened preterm labor, as required by the study's criteria. This level of training allows them to autonomously contribute to patient assessments under supervision, benefiting both patient care and research outcomes. Additionally, their involvement aligns with their training needs and promotes a collaborative learning environment. The following inclusion criteria were to be fulfilled.

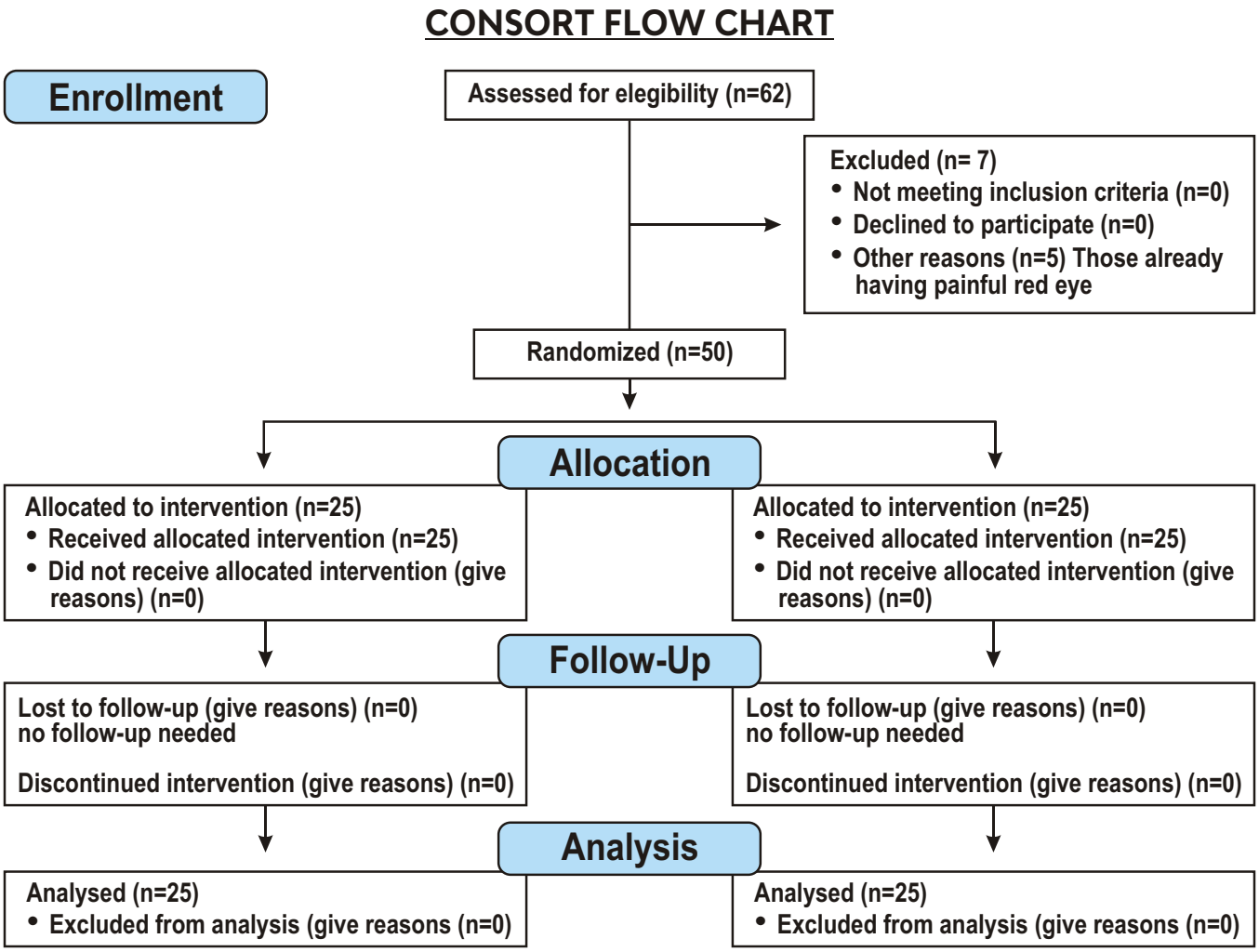


Figure 01: Consort chart for randomized control trial

Inclusion criteria
Patients with singleton pregnancies with the diagnosis of threathened preterm labour i.e atleast 1 contraction in every 10 minutes lasting for atleast 30 seconds, cervical dilatation of less than 3 cm, with intact membranes between 28 and 34 weeks of gestation on LMP.[19]

Exclusion criteria
Fetal malformations, fetal death, placental abruption, preeclampsia, amniotic fluid abnormalities severe maternal heart disease, liver dysfunction, hypotension, concomitant use of beta agonists or intravenous antihypertensive medications, and allergy to Nifedipine.

Each patient had an Obstetric ultrasound to determine the baby's viability, as well as the gestational age and cervical length. Oral tablets were used to deliver the extended-release form of Nifedipine. Tablet Adalat Retard (Nifedipine) 20 mg was used to initiate Nifedipine tocolysis. A similar dose was repeated after 30 minutes if uterine contractions persisted. If the second dose did not cease contractions, a third dose of 20 mg was given at 30-minute interval up to a maximum of 60 mg in the first hour of treatment. After initial contraction ceasing maximum dose of Nifedipine 60mg, maintenanc therapy was started with tablet Nifidipine 20mg one tablet administered every 8 hourly for 48-72 hours after the third dosage. In the research, the highest daily dose was 60 milligrams. The mother's vitals (blood pressure, heart rate, uterine contractions, and fetal heart rate) were checked before treatment, every 30 minutes for the first hour of treatment, every hour for the next four hours, and every 24 hours thereafter. All patients were given 2 doses of injection Betamethasone 12mg each 24 hours apart to aid in fetal lung maturation and were required to stay in the hospital for at least three days. Women whose uteruses remained inactive for longer than this time frame were discharged and told to stay in bed. When labour was postponed with tocolysis for at least 48 hours, it was deemed a success. The statistical plan involved collecting patient data from records and vital signs, maintaining data accuracy through structured protocols. Analysis included summarizing patient characteristics, comparing groups, and using statistical tests like t-tests and chi-square. Time-to-event analysis and multivariate techniques were employed as needed. The plan specified hypotheses, variables, a 0.05 significance level, imputation for missing data, and potential adjustments for multiple tests. Interpretation considered the research context. Collaboration with a statistician ensured plan validity.

RESULTS

Total number of patients was 50. No patient was lost to follow-up. Mean and SDs for age was 27.00±4.42 years. Mean and SDs for gestational age was 31.20±1.65 weeks. Mean and SDs for gravidity was 2.76±0.822. Mean and SDs for parity was 1.76+0.82. Distribution of cases according to age are shown in table 01.

Table 01. Distribution of cases according to age

Age Groups	Frequency	Percent
< 30 Years	37	74.0%
> 30 Years	13	26.0%
Total	50	100.0%

37 (74.0%) patients were recorded in ≤ 30 years age group while 13 (26.0%) patients were recorded in > 30 years age group.

Table 02. Uterine Contractions Before and After Treatment (n=50)

Uterine Contractions	Before Treatment	After 24 Hours of Treatment	After 48 Hours of Treatment
0	-	58 (56%)	44 (88%)
1	-	3 (6%	5 (10%)
2	21 (42%)	13 (26%)	01 (2%)
3	22 (44%)	4 (8%)	-
4	07 (14%)	2 (4%)	-

Table-02 shows uterine contractions before and after treatment at 24 hours and 48 hours, 21 (42%) patients had 2 uterine contractions, 22 (44%) patients had 3 uterine contractions while 07 (14%) patients had 4 uterine contractions before treatment. After 24 hours of treatment, 58 (56%) patients had 0 uterine contractions, 03 (6%) patients had 1 uterine contraction, 13 (26%) patients had 2 uterine contractions, 4 (8%) patients had 3 uterine contractions while 2 (4%) patients had 4 uterine contractions. Similarly, after 48 hours of treatment, 44 (88%) patients had 0 uterine contractions, 05 (10%) patients had 1 uterine contraction while 01 (2%) patient had 2 uterine contractions. Figure 01 shows frequency of delay and deliveries in terms of days.

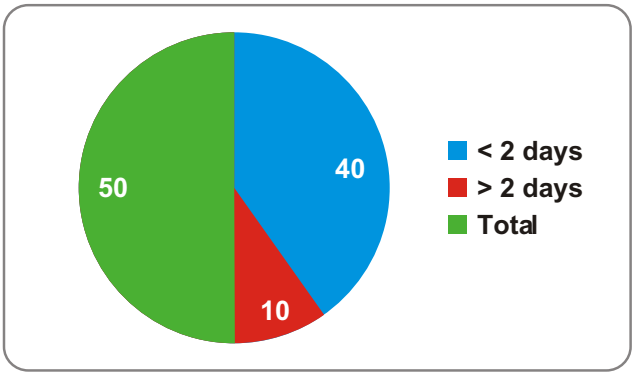


Figure 01.
Delay in Delivers in terms of days (n=50)

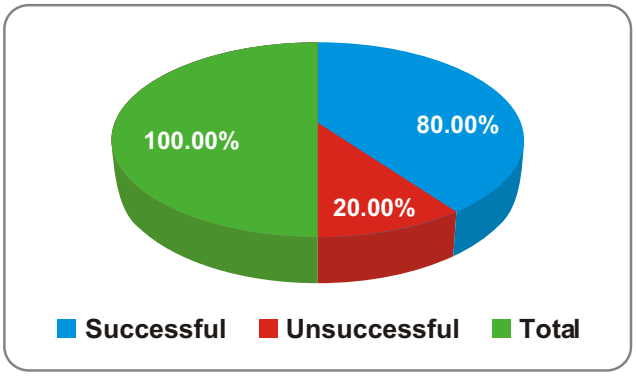


Figure 02.
Effectiveness of Nifedipine (n=50)

Figure 02 shows effectiveness of Nifedipine in the treatment of spontaneous threathened preterm labor, which showed effectiveness in 40 (80%) patients in terms of delay in their deliveries for > 48 hours.

DISCUSSION

The study's important findings include the clinicodemographic characteristics of the study population, with mean age of 27.00 years and mean gestational age of 31.20 weeks. Age distribution revealed that 74% of patients were < 30 years old. Uterine contractions were assessed before treatment and at 24 and 48 hours post-treatment, with varying patterns observed. Additionally, a graphical representation displayed the delay in delivery, indicating that 80% of patients experienced delays of > 2 days. Notably, Nifedipine showed effectiveness in delaying deliveries for over 48 hours in 80% of cases, underscoring its potential in treating spontaneous threatened preterm labor.

Unfortunately, no drugs or other interventions have proven to be completely successful in blocking preterm labor. As per clinicodemographic details of patients, mean and SDs for age was 27.00±4.42 years. Mean and SDs for gestational age was 31.20±1.65 weeks. Mean and SDs for gravidity as 2.76±0.822. Mean and SDs for parity was 1.76+0.82. 37 (74.0%) patients were recorded in ≤ 30 years age group while 13 (26.0%) patients were recorded in > 30 years age group. Similar demographic characteristics were reported by Qurat-Ul-Ain[2] Moreover, Glyceryl trinitrate's effect on preterm labor was observed by Mariam Malik of Allama Iqbal Hospital in Lahore. Those patches had to be taken off because they were causing people to experience side effects like headaches and heart palpitations. Glyceryl trinitrate's safety in preterm labor,[13,14] needs more research. Table-III shows delay in delivery in term of days, 10 (20.0%) patients had delay in delivery up to < 2 Days while 40 (80.0%) patients had delay in their deliveries > 2 Days and table-IV shows effectiveness of nifedipdine in treatment of spontaneous preterm labor, which showed effectiveness in 40 (80%) patients in terms of delay in their deliveries. These findings were inconsistent to the results from a study conducted at King Edward Hospital in Lahore showed that ritodrine was effective in delaying labour by 72 days in 88.2% of women, but 9 women discontinued treatment due to adverse effects. Both the mother and the unborn child are at risk if this continues. Another study from the Karachi Baqai Medical University Institute established polytherapy, or the use of many tocolytic drugs despite the use of a single preventative treatment. According to their findings, polytherapy is preferable than monotherapy but necessitates patient agreement. According to the American College of Obstetricians and Gynecologists, there is a risk of

maternal problems while using tocolytic medicines (1995). One must not undervalue its significance. For instance, in Jackson, Mississippi, tocolysis ranked as the third highest cause of adult respiratory distress syndrome and death among pregnant women over a 14-year span. In the United States, sympathomimetic compounds like terbutaline and ritodrine have been approved by the Food and Drug Administration as the go-to tocolytic medications. When given intravenously, these medications quickly induce a tocolytic effect. Pulmonary edoema, myocardial ischemia, and foetal cardiotoxicity are only a few of the potentially fatal side effects of -mimetic medications on the mother and unborn child. Increased heart rate, tremors, anxiety, palpitations, and insomnia are some of the less severe adverse effects. If a mother experience any of these adverse effects, she may need to decrease her dosage or stop taking the medication altogether[17]. Table-II shows uterine contractions before and after treatment at 24 hours and 48 hours, 21 (42%) patients had 2 uterine contractions, 22 (44%) patients had 3 uterine contractions while 07 (14%) patients had 4 uterine contractions before treatment. After 24 hours of treatment, 58 (56%) patients had 0 uterine contractions, 03 (6%) patients had 1 uterine contraction, 13 (26%) patients had 2 uterine contractions, 4 (8%) patients had 3 uterine contractions while 2 (4%) patients had 4 uterine contractions. Similarly, after 48 hours of treatment, 44 (88%) patients had 0 uterine contractions, 05 (10%) patients had 1 uterine contraction while 01 (2%) patient had 2 uterine contractions.

Nifedipine was usually administered sublingually, starting at a dose of 20 mg. In this trial, however, we chose to give Nifedipine orally rather than sublingually (where it would have a shorter duration of action) due to the potential for adverse effects. Minor adverse effects, such as headaches, were reported in our study. These unwanted effects went away on their own after a few hours and required no treatment. Children who delivered after 48 hours of tocolytic treatment and were given steroids had high Apgar scores at birth and did not need to be admitted to the intensive care unit. Babies who were born within 24 hours were the only ones who needed to be admitted to the neonatal critical care unit. Nifedipine has not been shown to have any serious side effects in newborns in previously conducted clinical investigations. There was no difference in newborn outcomes between the Nifedipine and ritrodine groups in four investigations, whereas two other studies reported considerably larger neonates in the Nifedipine group. When used as directed, Nifedipine looks to be one of the most effective and safest tocolytic medicines on the market.

In this study, table-II shows uterine contractions before and after treatment at 24 hours and 48 hours, 21 (42%) patients had 2 uterine contractions, 22 (44%) patients had 3 uterine contractions while 07 (14%) patients had 4 uterine contractions before treatment. After 24 hours of treatment, 58 (56%) patients had 0 uterine contractions, 03 (6%) patients had 1 uterine contraction, 13 (26%) patients had 2 uterine contractions, 4 (8%) patients had 3 uterine contractions while 2 (4%) patients had 4 uterine contractions. Similarly, after 48 hours of treatment, 44 (88%) patients had 0 uterine contractions, 05 (10%) patients had 1 uterine contraction while 01 (2%) patient had 2 uterine contractions, therefore, during the study we noted that Nifedipine did not show any serious side effects and effectively delayed spontaneous preterm labor.

Table-03 shows delay in delivery in term of days, 10 (20.0%) patients had delay in delivery up to ≤ 2 Days while 40 (80.0%) patients had delay in their deliveries > 2 Days.

Table-IV shows effectiveness of Nifedipine in treatment of spontaneous preterm labor, which showed effectiveness in 40 (80%) patients in terms of delay in their deliveries for > 48 hours.

Finally, in view of the above, we concluded that Nifedipine effectively suppressing contractions for more than 48 hours, allowing for corticosteroid impact and intrauterine transport to hospital with infant care facilities, was made possible by Nifedipine.

Limitations of study

Small sample size and single centered study were main limitations of this study; therefore, large multicentered randomized control trials shall be carried out to gain robust results and generalize it to the overall population of this province.

CONCLUSION

This study demonstrated that Nifedipine successfully delayed spontaneous preterm labor for more 48 hours and thus gave sufficient time for an intrauterine or corticosteroid transfer effect.

Conflict of Interest
Authors declare no conflict of interest

Grant Support and Financial Disclosure
NIL

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DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

AUTHOR'S CONTRIBUTION
The following authors full fill authorship criteria as per ICMJE guidelines;

Ali S, Sadaf R:	Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Rauf B, Iqbal K:	Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Farhad U:	Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Kishwar N:	Analysis and interpretation of data, critical revision,final approval, agreed to be accountable for all the work.

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