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# Prophylactic Oral Nifedipine to Reduce Preterm Delivery: A Randomized Controlled Trial in Women at High Risk

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## ABSTRACT

**Objective:** to evaluate the efficacy of prophylactic nifedipine versus placebo in reducing spontaneous preterm delivery in asymptomatic women at high risk for preterm delivery.

**Background:** Preterm birth (before 37 completed weeks of gestation) is a major cause of death and a significant cause of long-term loss of human potential. Prophylactic nifedipine in reducing spontaneous preterm delivery in asymptomatic women at high risk for preterm deliver

**Patients and methods:** A Prospective randomized double-blinded study was carried out on 120 pregnant women at high risk of preterm labor (5 cases lost in follow-up), (5 discontinued before 28 days because they had preterm delivery or drug side effects) which attended from the Obstetrics and Gynecology outpatient clinic in Minoufia University Hospital during the period from March 2016 to August 2017. Detailed history, laboratory investigations, obstetric and ultrasound follow up study were done.

**Results:** there was no significant difference ($P > 0.5$) between nifedipine and placebo groups regarding maternal age, gestational age, parity, Previous preterm labor and Inter pregnancy interval (years). While, there was statistically significant difference ($P \leq 0.05$) regarding mode of delivery, delivery time and medications side effects, neonatal respiratory distress and neonatal Intensive care unit (NICU) admission in both group. Additionally, onset of labor between 34-37 week was significantly less frequent in nifedipine group than placebo group.

**Conclusion:** we found that the superiority of nifedipine as prophylactic tocolosysis in the mean prolongation of pregnancy compared to that of placebo in high risk women for preterm labor, it has better effect on neonatal outcomes, fewer maternal side effects. We would only comment that nifedipine looks like a promising drug in this regard and further large studies are required to establish this fact.

**Keywords:** Tocolysis, Nifedipine, Perinatal Outcome, preterm.

## INTRODUCTION

**Preterm birth**, defined as birth occurring between 26 and 36 completed weeks of gestation is a major contributor to perinatal morbidity and mortality [(1)]. The rate of preterm birth is increasing across low- and middle-income countries, affecting 8.6% of births in high-income countries and between7.4% to 13.3% in low- and middle- income countries [(2)].There are several possible pathways which lead to spontaneous preterm birth, four of these pathways are supported by a considerable body of clinical and experimental evidence: excessive myometrial and fetal membrane over-distention, decidual hemorrhage, precocious fetal endocrine activation, and intrauterine infection or inflammation [(3)].These pathways may be initiated weeks to months before clinically apparent preterm labor.

The tocolytics which have been most widely tested are the betamimetics ritodrine, salbutamol and terbutaline [(4)]. Betamimetics have a high frequency of unpleasant, sometimes severe maternal side-effects including tachycardia, hypotension, tremulousness and a range of biochemical disturbances. Furthermore, betamimetics have been associated with at least 25 maternal deaths mainly from pulmonary oedem.There is a need therefore for an effective tocolytic agent with less sideeffects than the betamimetics [(5)]. A meta-analysis reported that calcium channel blockers decrease the number of preterm births within 7 days of first administration and before 34 weeks of gestation in women with preterm labor, with improvement in some neonatal outcomes. Moreover, they have been associated with fewer adverse drug reactions than have other tocolytic agents (mainly beta-mimetics), so reducing the need for treatment suspension [(6)].

Calcium channel blockers (CCB) are non-specific smooth muscle relaxants, predominantly used for the



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treatment of hypertension in adults. They exert their tocolytic effect by preventing the influx of extracellular calcium ions into the myometrial cells. They have been demonstrated *in vitro* to have potent relaxant effect on human myometrium [7]. The most widely used and studied CCB is nifedipine which (like nicardipine) belongs to the dihydropiridine group. Nifedipine was first reported in 1980 in an observational study to be an effective tocolytic agent with minimal side-effects [8].

## PATIENTS AND METHODS

A Prospective randomized double-blinded study was carried out on 120 pregnant women at high risk of preterm labor (5 cases lost in follow-up), (5 discontinued before 28 days because they had preterm delivery or drug side effects) which attended from the Obstetrics and Gynecology outpatient clinic in Minoufia University Hospital during the period from March 2016 to August 2017.

**Ethical consideration:** All participants were volunteers. All of them signed a written informed consent with explaining the aim of study before the study initiation. Approval was obtained from ethical committee in Faculty of Medicine, Menoufia University.

### Sampling methods

Sample size was calculated using computer sample block randomization type. During the pre-selection visit, exclusion and inclusion criteria were applied; with recording of full medical history, findings on abdominal and local examination, and on ultrasonographical examination, along with results of investigations.

Subjects included in the study were randomized divided into 2 groups as follow:

**Group A:** include 55 pregnant patient who at high risk for preterm labor they received placebo, the placebo contained folic acid (Folac 400 lg; NBS Italia, Perugia, Italy).

**Group B:** include 55 pregnant patient who at high risk for preterm labor they received nifedipine 20 mg tablets (Epilat Retard ®, EIPICO, Egypt) once daily for 28 days.

### *Inclusion criteria*

Patients with single fetus with an ultrasonographic cervical length (UCL) of ≤25 mm between 24 and 32 weeks of gestation (determined by the date of the last menstruation period and confirmed by early ultrasound), without uterine contractions.

### *Exclusion criteria*

Gestational age of <24 weeks or >32 weeks, cervical cerclage, maternal pathologies, fetal growth restriction and/or any other fetal morbidity, any previous hospitalization for threat of preterm delivery, or previous tocolytic treatment, the presence of significant uterine contractility (four or more contractions every 20 min recorded by external tocodynamometer) and/or known hypersensitivity to nifedipine.

All pregnant women who fulfill the eligibility criteria were subjected to:

*History taking*Personal history: with emphasis on name, age, occupation, residency and special habits. Present history: with emphasis on history of onset, course and duration of labor pains, vaginal gush of fluid, vaginal discharge, vaginal bleeding, or febrile illness. Past history: with particular emphasis on history of medical disorders, abdominal surgeries, drug therapy or allergy or history of intake of other tocolytic drugs. Family history: For any similar condition. Obstetric history: with emphasis on history of previous preterm labour, previous abortion, previous full-term deliveries, mode of delivery and fetal outcome. Menstrual history: for estimation of gestational age using Naegeles rule, provided that she had regular cycles for the last three months before she got pregnant and was not taking contraceptive pills during this period and she was sure of her dates.

*General examination:* To exclude any medical disease with special attention to blood pressure, pulse and temperature, pressure.

*Abdominal examination:* with emphasis on the fundal height, clinically estimated fetal weight and presence of uterine contractions.

*Pelvic examination:* to assess the state of membranes and exclude their rupture through examination with a sterile Cusco speculum, to exclude vaginal bleeding.

*Sonographic assessment:* To estimate the gestational age, amount of liquor and to exclude placenta previa, placental abruption and major fetal congenital anomalies. Several ultrasound parameters were used to estimate gestational age including biparietal diameter (BPD), head circumference (HC), and femur length (FL) Cervical length.

Non-stress test to ensure reassuring fetal wellbeing.

***Statistical Analysis***

Results analyzed and tabulated using Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS v. 16. (SPSS Inc., Chicago, IL, USA). Two types of statistics were done: Descriptive: e.g. Percentage (%), mean, median and stander deviation. Analytical: includes: Chi-Squared ($\chi 2$), Wallis analysis of variance for comparing categorical data and Person correlation coefficient (r) for correlation between two dependents quantitative not normally distributed variable. A value of P  0.05 was indicated statistically significant.

**RESULTS**

Maternal age (year) of the studied patients ranged from 18 to 42 years, with mean 27.47 ± 6.588 year in Nifedipine group, and from 19 - 43 years, with mean 28.73 ± 6.5years in placebo group. Also, there was statistical no significant difference (P > 0.5) between the two-studied group (Nifedipine and placebo) regarding Maternal age, and Gestational age on first visit (week). (Table 1). There was statistically significant difference (P ≤ 0.05) regarding regarding mode of delivery, delivery time and medications side effects. The percentage of full term in nifedipine group and placebo group was (58.2%) and (10.9%) respectively. The percentage of preterm in nifedipine group and placebo group was (41.8%) and (89.1%) respectively. The P value <0.0001 shows statistically significant difference between two groups.Headache was higher in the placebo group (25.5%) compared to nifedipine group (7.3%). Hypotention was higher in the nifedipine group (70.9%) compared to placebo group (5.5%) (Table 2). Also, there were statistical significant differences (P < 0.05) between nifedipine and placebo regarding neonatal respiratory distress and neonatal ICU admission. neonatal ICU admission was less frequent in nifedipine group than placebo group. (Table 3).

**Table 1**: Comparative study between the studied groups as regard maternal age, parity, Occupation, Previous preterm labor Gestational age and Interpregnancy interval (years).

| | | **Medication** | | **P-value** |
|---|---|---|---|---|
| | | **Nifedipine N=55, No (%)** | **Placebo N=55. No (%)** | |
| Age | Min-Max<br>Mean ± SD | (18 - 42)<br>27.47 ± 6.588 | (19 - 43)<br>28.73 ± 6.5 | 0.425 |
| **Occupation** | No | 34 (61.8%) | 37(67.3%) | 0.839 |
| | Yes | 21(38.2%) | 18(32.7%) | |
| **Socioeconomic state** | High | 18(32.7%) | 16(29.1%) | 0.680 |
| | Low | 37(67.3%) | 39(70.9%) | |
| **Parity** | MG | 37 (67.3%) | 38 (69.1%) | 0.838 |
| | PG | 18 (32.7%) | 17(30.9%) | |
| **GA** | Min-Max<br>Mean ± SD | (27.0 - 32.0)<br>29.6±1.6 | (26.0 - 32.0)<br>30±1.7 | 0.153 |
| **Interpregnancy interval (years)** | Min-Max<br>Mean ± SD | (2-8)<br>3.22±1.4 | (1-8)<br>3.34±1.6 | 0.732 |
| **Previous preterm** | 0 | 0(0.0%) | 2(3.6%) | 0.304 |
| | 1 | 10(18.2%) | 13(23.6%) | |
| | 2 | 25(45.5%) | 18(32.7%) | |
| | 3 | 2(3.6%) | 5(9.1%) | |
| | PG | 18(32.7%) | 17(30.9%) | |
| **Vaginal infection** | No | 4 (7.3%) | 4(7.3%) | 1 |
| | Yes | 51(92.7%) | 51(92.7%) | |
| CX length | Min-Max<br>Mean ± SD | (1.5 - 2.5)<br>2.17 ± 0.07 | (1.4 - 2.5)<br>2.13 ± 0.31 | 0.269 |

GA: Gestational age SD: Stander deviation P: P value **NS:** statistically non-significant

**Table 2**: Comparative study between the studied groups as mode and time of delivery and the side effects of the used mediations in nifedipine and placebo groups.

| | | Medication | | P-value |
|---|---|---|---|---|
| | | **Nifedipine N=55 N0 (%)** | **Placebo N=55 N0 (%)** | |
| **Mode of delivery** | c.s | 33 (60.0%) | 20 (36.4%) | 0.013* |
| | NVD | 22(40.0%) | 35(63.6%) | |
| **Delivery time (weeks)** | before 37 w | 23(41.8%) | 49(89.1%) | <0.0001* |
| | after 37 w | 32(58.2%) | 6(10.9%) | |
| | Min-Max<br>Mean ± SD | (34 - 38)<br>36.55 ± 0.919 | (33 - 38)<br>34.69 ± 1.451 | <0.0001* |
| **Medications side effects** | Dizziness | 0(0.0%) | 10(18.2%) | 0.001* |
| | Fatigue | 0(0.0%) | 16(29.1%) | <0.0001* |
| | Flushing | 6(10.9%) | 0(0.0%) | 0.012* |
| | Headache | 4(7.3%) | 14(25.5%) | 0.01* |
| | heartburn | 0(0.0%) | 7(12.7%) | 0.011* |
| | hypotension | 39(70.9%) | 3(5.5%) | |
| | tachycardia | 4(7.3%) | 5(9.1%) | 0.728 |
| | No | 2(3.6%) | 0(0.0%) | 0.691 |

**Table 3**: Comparative study between nifedipine and placebo as regards to neonatal respiratory distress ,neonatal mortality

| | | Medication | | P-value |
|---|---|---|---|---|
| | | **Nifedipine N=55, N0 (%)** | **Placebo N=55, N0 (%)** | |
| **Neonatal admissions to NICU** | No | 50(90.9%) | 26(47.3%) | <0.0001* |
| | Yes | 5(9.1%) | 29(52.7%) | |
| **Neonatal respiratory distress** | No | 50(90.9%) | 24(43.6%) | <0.0001* |
| | Yes | 5(9.1%) | 31(56.4%) | |
| **Neonatal mortality** | No | 55(100.0%) | 46(83.6%) | 0.002* |
| | yes | 0(0.0%) | 9(16.4%) | |

**Table 4**: neonatal outcome of the patients delivered before and after 37 w in the nifedipine group.

| | | Delivery time | | P-value |
|---|---|---|---|---|
| | | before 37 WKs, n=21 | after 37 WKs, n=32 | |
| Neonatal admissions to NICU | No | 18 | 32 | 0.006* |
| | | 78.3% | 100.0% | |
| | Yes | 5 | 0 | |
| | | 21.7% | 0.0% | |
| Neonatal Respiratory distress | No | 18 | 32 | 0.006* |
| | | 78.3% | 100.0% | |
| | Yes | 5 | 0 | |
| | | 21.7% | 0.0% | |
| Neonatal mortality | No | 23 | 32 | --- |
| | | 100.0% | 100.0% | |

## DISCUSSION

This study was carried out on 55 women who received oral nifedipine for prevention of preterm labour, their mean age was (27.47 ± 6.588) years, mean gestational age (29.6±1.6) days, as well as 55 women who received placebo their mean age was (28.73 ± 6.5) years, mean gestational age (30±1.7) days. There were no statistically significant differences between the two groups as regards the age, parity and gestational age. These findings are in agreement with those obtained by **Sarah and Doaa** [9] who compared nifedipine and progesterone in inhibiting threatened preterm labor and found that there was no statistically significant difference between nifedipine and progesterone groups about the maternal age. The percentage of multigravida in nifedipine group and placebo group was (67.3%) and (69.1%) respectively. There was non-statistical significant difference between the nifedipine and placebo groups regarding parity.

The percentage of full term in nifedipine group and placebo group was (58.2%) and (10.9%) respectively. The percentage of preterm in nifedipine group and placebo group was (41.8%) and (89.1%) respectively. The P value <0.0001 shows statistically significant difference between two groups. In addition, **Paptsonis *et al***. [10] reported that the mean prolongation of pregnancy 39.2 days with nifedipine versus 22.1 days with ritodrine concluded that calcium antagonists significantly reduced perinatal morbidity and that the number of maternal side effects was statistically lower compared with B2 sympathomimetics.

Also these results parallel to the findings of **Chawanpaiboon *et al***. [11]. They recorded that pregnant patients in the nifedipine group mostly delivered at a gestational age after 37 weeks, which indicated the efficacy of nifedipine when compared to other interventions.

In contrast to our study **Sarah and Doaa** [9] reported that mean prolongation of pregnancy duration was more with transdermal nitroglycerin, NTG (30.13±3.06 days) compared to that of nifedipine (29.57±3.65 days).

Regarding mode of delivery, the current study showed that vaginal delivery percentage was (40.0%) and (63.6%) in nifedipine and placebo respectively, while, cesarean percentage was (60.0%) and (36.4%) in nifedipine and placebo respectively, which was statistically significant in both studied group.

The neonatal outcomes in terms of respiratory distress was higher in placebo group (56.4%), than nifedipine group (9.1%). There was statistically significant difference between both groups. This is in agreement with study established by **Dhawle *et al***. [12], that reported an incidence of RDS 17.1% in the transdermal nitroglycerin group and 9.3% in the nifedipine group, and the difference was not statistically significant. A study carried out in 2001 by **Tsatsaris** [13] showed similar results. Additionally, our present study revealed that neonatal ICU admission was less frequent in nifedipine group (9.1%) than placebo group (52.7%) and the difference between them was reached to significant level.

In the present study headache was higher in the placebo group (25.5%) compared to nifedipine group (7.3%). Hypotention was higher in the nifedipine group (70.9%) compared to placebo group (5.5%). There was statistically significant difference between both groups. In the present study, although hypotension was clinically recorded, it was not associated with significant maternal or fetal morbidity. These findings are in agreement with those obtained by **Kashanian *et al***. [14] they observed that nifedipine was associated with side effects in 40% of patients as compared to 17.5% with atosiban. They also found the incidence of hypotension with nifedipine to be (70.9%).

## CONCLUSION

The present study has clearly shown the superiority of nifedipine in the mean prolongation of pregnancy compared to that of placebo in high risk women for preterm labor, it has better effect on neonatal outcomes, fewer maternal side effects. On the basis of this study nifedipine appears to be safe and well tolerated, non-invasive and effective method of preventing uterine contractions in high risk women for preterm labor.

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