

# Comparing the effectiveness of two different dosage regimes of oral nifedipine in the treatment of preterm labour

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## ABSTRACT

**Objective:** To compare the effectiveness and side effect of two different dosage regimes of oral Nifedipine in the treatment of preterm labour

**Methods:** A double blinded randomized controlled trial in which 86 pregnant women with preterm labour were randomized to receive either the low or high dose regimen of Nifedipine for tocolysis. Low dose of 10 mg of oral Nifedipine then 5mg every 15min for 1hr 10mg 6hly for 48hrs, while the high dose was 20 mg of oral Nifedipine followed by 10 mg every 15 minutes for 1hr then 20mg 6hourly for 48 hours. The primary outcome was defined by mean uterine quiescence time and fetomaternal side effect were compared between the groups.

**Results:** The mean uterine quiescence time for the low dose and high dose regime were comparable 13.60±11.69 hours versus 12.16±8.90 hours ( $P = 0.747$ ) respectively, there was no statistical significance difference. None of the patients in both groups needed rescue treatment. Forty patients (93%) versus 41 patients (95%) ( $P = 0.506$ ) of low and high dose respectively were able to achieve uterine quiescence within 48hours, there was no statistical significant difference. Maternal headache was higher in the high dose compared to the low dose but not statistically significant {19% vs 5% ( $p = 0.08$ )}. None of the women in both groups had fetal heart rate abnormality.

**Discussion:** The high dose regimen of oral Nifedipine for tocolysis does not have any advantage over the low dose regime in terms of effectiveness for tocolysis and in fact low dose had a lower maternal side effect.

**Key words:** Nifedipine; preterm labour; treatment.

## Background

Preterm birth is one of the most important cause of perinatal morbidity and mortality worldwide. The effective treatment of preterm labor is important, not as an end in itself, but as a means of reducing adverse events of preterm birth. Calcium channel blockers have the ability to inhibit contractility in smooth muscle cells. Consequently, nifedipine has emerged as an effective and rather safe tocolytic agent for the management of preterm labor; several studies have shown that the use of nifedipine in comparison with other tocolytics

is associated with a more frequent successful prolongation of pregnancy,<sup>[1]</sup> resulting in significantly fewer admissions of newborns to the neonatal intensive care unit (NICU),<sup>[1]</sup> and is associated with a lower incidence of respiratory distress syndrome.<sup>[1]</sup> Also nifedipine is readily available, easy to use and very cheap compared with other tocolytic drugs,

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thereby making it a very good choice in low resource settings like Nigeria.

The unequivocal impact of tocolysis in short-term postponement of delivery allowing for in-utero transfer and also allow for steroid administration before delivery has prompted many investigators to recommend focusing future trials on determining the optimal dosage regime for Nifedipine in managing preterm labor.<sup>[1,2]</sup> Also studies comparing two different dose regimens of nifedipine published in the literature are very scarce compared with studies done to compare nifedipine to other tocolytic drugs or placebo.<sup>[1]</sup> Also nifedipine is readily available and cheap making it to be a favored choice in low resource setting like Nigeria and indeed Africa. An understanding of the effective optimal dosage and adverse reaction associated with different dosage regimes will help to determine dosage protocol in the management of preterm labor.

The investigators' study would try to assess the safety profile of two different dosage regimens on the mother and the fetus by assessing a selected number of outcome variables. The data generated would be used to advocate for a change in the dosage protocol in managing patients presenting with preterm labor and would fill the existing gap in knowledge regarding the most effective and safest dose regimen of nifedipine for preterm labor.

## Method

This study was carried out at the Department of Obstetrics and Gynaecology, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife, Osun State, Nigeria. It is a double blinded randomized controlled trial.

The drug used in this study was oral Nifedipine and it comes in 10 mg and 20 mg tablet forms. Two groups investigated comprises of low dose regime receiving 10 mg of oral nifedipine stat then 5 mg every 15 min for first hour followed by 10 mg 6 hourly for 48 h and high dose regime of 20 mg of oral nifedipine stat followed by 10 mg every 15 min in the first hour then maintenance dose was be 20 mg 6 hourly for 48 hours.

### Inclusion criteria

All pregnant women with singleton fetus with preterm labor diagnosed by one uterine contraction in 10 min with intact membrane 3 between 28 and 34 weeks of gestation.

### Exclusion criteria

The following pregnant women were excluded: Multiple pregnancy, Pre labour rupture of membranes, Congenital fetal malformations, intra uterine growth restriction (IUGR),

previous tocolysis in this pregnancy, chorioamnionitis, cervical dilation >4 cm, maternal medical conditions, such as renal insufficiency, hepatic insufficiency, or myasthenia gravis. Non-reassuring fetal heart rate, maternal hypotension, defined as a blood pressure <90/50 mmHg, intrauterine fetal death, and those women who have previous allergic reaction to Nifedipine.

A total of 86 patients were recruited with each arm of the study having 43 patients. The subjects were pregnant women at gestational age of 28–34 weeks presenting at the antenatal ward with preterm labor diagnosed by one uterine contraction in 10 min with intact membrane.<sup>[3]</sup> Sampling technique was done by randomization achieved through sequentially numbered opaque envelopes, the contents were varied according to a computer generated randomization sequence prepared by an independent statistician, the numbers generated were written on two groups of envelopes and one group handed over to the hospital pharmacy, who packaged the drugs and the second group handed to the participating doctors at the admission room. As patients present at the admission room they were informed about the research work and consent taken from them, each voluntary participant was asked to pick an envelope and this envelope was presented to the pharmacy unit who in turn gave the patient a pre-packed drug inside a labeled drug envelope that correspond to the number on the envelope that the patient presented with. At the end of the study one group of patient had received 10 mg of oral nifedipine stat then 5 mg (obtained by dividing the 10 mg tablet into two equal halves) every 15 min for first hour followed by 10mg 6 hourly for 48 h.<sup>[4]</sup> While the other group had received 20 mg of oral nifedipine stat followed by 10 mg (obtained by dividing the 20mg into two equal halves) every 15 min in the first hour then maintenance dose was be 20mg 6 hourly for 48 h.<sup>[5]</sup>

The following were measured as part of the proforma as attached in appendix A. Cervical effacement and dilatation were measured by performing a vaginal examination at the admission room and the effacement done by measuring the length of the cervix palpable using the assessing middle finger in the vagina and scored as 3 cm, 2 cm, 1 cm while the cervical dilatation was scored measuring the distance between the examining fingers (middle and index fingers) when placed inside the cervix and it was scored as closed, 1 cm, 2 cm, 3 cm, 4 cm. Cardiotocography machine was used to determine the time to achieve uterine quiescence. Maternal blood pressure was taken before each dose of nifedipine was administered. Also the fetal heart rate was recorded from the cardiotocography machine before each dose of nifedipine was given to the patient. Maternal side

effect was obtained by asking if there is any from the patient before each dose of nifedipine was given. Statistical analysis: the effect of the drug and patient's sociodemographic characteristics were imputed into a proforma and this was processed into data form. The fetal heart rate was processed into normal value 120–160 b/m, tachycardial >160 b/m and bradycardia <120 b/m during data entry and statistical package for the social sciences (SPSS) version 17 was used for analysis and result tested for significance using *t*-test for continuous variable and Chi-square for categorical variable. Level of confidence was set at 95% and level of significance was set at 0.05.

## Results

A total of 86 consecutive pregnant women with preterm labor who met the inclusion criteria for this study were recruited out of 1261 admissions over the recruitment period hence preterm labor accounted for 6.8% of admissions over the study period. Of the 86 participants only 81 women (40 women in LD group and 41 women in HD group) completed the study while 5 women (3 women in LD group and 2 women in HD group) progressed in labor to delivery.

Table 1 shows the comparison of baseline characteristics between the two groups. The mean age of the subjects in the low dose group and the high dose group were  $29.23 \pm 3.9$  years vs  $28.86 \pm 3.6$  years  $P > 0.05$ , there was no significant difference in the mean age in both groups. The mean estimated gestational age at recruitment in the low dose group and high dose were  $31.72 \pm 1.9$  weeks vs  $31.05 \pm 2.4$  weeks  $P > 0.05$  respectively, there was no significant statistical difference in the mean gestational age at recruitment. The cervical dilatation, the cervical length, and the frequency of contraction at admission had same median value when compared.

Table 2 shows the comparison of the low and high dose nifedipine regimen with respect to uterine quiescence and need for rescue treatment. The mean uterine quiescence time were  $13.60 \pm 11.69$  hrs vs  $12.16 \pm 8.90$  h  $P > 0.05$  in the low and high dose regimen respectively, there was no significant difference when the two groups were compared.

The women who remained undelivered at 48 h were the patients that achieved uterine quiescence within 48 h were 41 patients (95%) vs 40 patients (93%)  $P > 0.05$  in high vs low dose regimen, respectively, there was no statistical significance difference on comparing the two groups. However, 5 patients progressed to delivery during the study out of which 3 patients (7%) vs 2 patients (5%)  $P > 0.05$  among low vs high dose groups, respectively, this shows that there

**Table 1: Comparison of baseline characteristics between the low and high Nifedipine dose regime**

	Low dose n=43	High dose n=43	<i>p</i>
Mean age (years)	29.23±3.9	28.86±3.6	0.966
Occupation [freq (%)]			
Civil servant	13(30.2%)	15 (34.9%)	
Artisan	11 (25.6%)	10 (23.3%)	
Unemployed	10 (23.3%)	8 (18.5%)	
Student	9 (20.9%)	10 (23.3%)	
Education [freq (%)]			
Tertiary	28 (65.1%)	24 (55.8%)	
Secondary	10 (23.3%)	16 (37.2%)	
Primary	5 (11.6%)	3 (7%)	
No formal education	0 (0%)	0 (0%)	
Religion [freq (%)]			
Christianity	41 (95.3%)	40 (93.0)	
Islam	2 (4.7%)	3 (7%)	
Others	0 (0%)	0 (0%)	
Mean parity (mean±SD)	1.0±1.2	0.74±1.13	0.332
Gestational age (mean±SD in weeks)	31.72±1.9	31.05±2.43	0.159
Cervical dilatation (mean±SD in cm)	1.33±0.47	1.26±0.44	0.476
Cervical length (mean±SD in cm)	2.07±0.59	2.16±0.65	0.596
Frequency of contraction (mean±SD in 10 min)	1.93±0.70	1.91±0.64	0.785

**Table 2: Comparison of the low and high dose Nifedipine regime with respect to uterine quiescence and need for rescue tocolysis**

	Low dose (n=43)	High dose(n=43)	<i>P</i>
Time to achieve uterine quiescence (mean±SD hours)	13.60±11.69	12.16±8.90	0.747
Number Undelivered at 48 h			
freq (%)	40 (93%)	41 (95%)	0.506
Failed to treatment			
Freq (%)	3 (7%)	2 (5%)	0.645
Need for rescue treatment			
Freq (%)	0 (0%)	0 (0%)	

was no significant difference in the number of women that progressed to delivery between the two groups. None of the patient needed rescue treatment.

Table 3 shows comparison of fetomaternal side effects between the low and high nifedipine dose regimen. All (100%) the patients in both groups had a normal fetal heart rate changes at the end of the study. However the only maternal side effect recorded in this study was headache in which 2 patients (5%) vs 8 patients (19%),  $P > 0.05$  on correction using fisher exact, in low and high dose respectively, this shows that there was no significant statistical difference in the maternal side effect experienced by the women.

Table 4 shows the odd ratio and 95% confidence interval for outcome predictors of uterine quiescence at 48 h (OR 1.66,

**Table 3: Comparison of fetomaternal side effect between the low and high dose regime of Nifedipine**

	Low dose (n-43) Frq(%)	High dose (n -43) Frq(%)	P
Fetal heart rate			
<120	0	0	0.152
120-160	43	43	
>160	0	0	
Maternal side effect			
Hypotension	0 (0%)	0 (0%)	0.04
Tachycardia	0 (0%)	0 (0%)	
Headache	2 (5%)	8 (19%)	
Flushing	0 (0%)	0 (0%)	
Dizziness	0 (0%)	0 (0%)	
Nausea	0 (0%)	0 (0%)	
Palpation	0 (0%)	0 (0%)	
Vomiting	0 (0%)	0 (0%)	
Others	0 (0%)	0 (0%)	

**Table 4: Odds ratio and confidence interval of both low and high dosage regime outcome**

Outcome	Df	OR	95%CI	
			LOWER	UPPER
Uter. quicent at 48 h	1	1.66	0.24	11.68
Side effect	1	2.14	0.95	4.81
Uter. Quicent at 12 h	1	1.52	0.51	4.52

95%CI 0.24 to 11.68) and at 12 h (OR 1.52, 95% CI 0.51 to 4.52) which shows that there was no advantage of the high dose regimen over the low dose regimen. Also the maternal side effect (OR 2.14, 95%CI 0.95 to 4.81) showed that there was no difference in both arms of the treatment.

## Discussion

The dosage regimen of oral nifedipine had been varied from one researcher to another, there was no particular regimen used and there appears to be no consensus on the ideal regimen. The present study compared two of the previously tested regimens of nifedipine in the treatment of preterm labor, therefore the two regimes were compared with respect to their efficacy and side effects. The high dose was recommended by Bracerol *et al.*<sup>[5]</sup> and the low dose was recommended by Papatsonis *et al.*<sup>[4]</sup>

The present study found no statistically significant difference between the two regimes with respect to efficacy and side effect.

Nifedipine has been used and strongly recommended to inhibit uterine contraction for over 30 years and used as effective tocolytic to delay delivery for at least 48 h to allow corticosteroid administration to take effect or to allow for transfer of patient to tertiary care center with neonatal intensive care facility.<sup>[6]</sup>

The mean ages of women in this study in the low dose was  $29.23 \pm 3.9$  years and high dose was  $28.86 \pm 3.6$  years which is comparable to the study of Ghazi A *et al.*<sup>[7]</sup> Also in this study most of the patients were of low parity which is contradictory to the results found in the study of copper L *et al.*<sup>[8]</sup> where the incidence of preterm labor was high in high parity women. This maybe due to the fact that all the patients in this study were low parity or may be due to the fact that more of the high parity women deliver at home and did not come to the hospital. In the study the mean gestational age of 31 weeks at admission were similar in both groups, this means there was no bias with respect to the application of the drug regimen in both groups with respect to the gestational age. This is also comparable to the study by Weerakul W *et al.*<sup>[9]</sup> where the mean gestation age was 31.7 weeks.

This study showed that the high dose regimen had a shorter mean time to achieve uterine quiescence than the low dose group, interestingly the difference was found not to be statistically significant when compared with each other. Also there was no statistical difference in the number of women achieving uterine quiescence at 48 h when both groups were compared. This is comparable to what was obtained by Anwar *et al.*<sup>[10]</sup> in a study comparing two dose regimes of nifedipine for the management of preterm labor where the result showed that there was no significant difference in the number of women attaining uterine quiescence at 48 h between the high and the low dose of nifedipine used in that study, with the high dose group having shorter mean time to achieving uterine quiescent.

Also in this study none of the patient had a rescue treatment, the 3 patients (7%) noted in the low dose regimen with the 2 patients (5%) noted in the high dose group who did not complete the treatment with nifedipine actually progressed to active phase of labor and subsequently delivered within 6–8 h of admission. However comparing the two groups with regards to failure of treatment, there was no advantage conferred on the high dose regimen as against the low dose. This result is comparable to the study by Chawan paiboon *et al.*<sup>[11]</sup> in which there was failure of tocolysis in 2% of the study group.

Concerns about the fetal heart rate abnormality due to the effect of nifedipine on both fetal and placental circulation is yet to be confirmed in human study,<sup>[12]</sup> this was further confirmed in this study as none of the women in both groups had fetal tachycardia or bradycardia during the course of the treatment. All had a normal fetal heart rate pattern. Also this result is comparable with the study done by Tsatsaris *et al.*<sup>[12]</sup> which observed that there was no fetal heart rate abnormality noticed in all the patients studied.

Also there were concerns about the maternal side effect, nifedipine been an antihypertensive with vasodilation effect which may predispose to hypotension and other effects, interestingly none of the patients had hypotension in the two groups, this is not comparable with the study by Tsatsaris *et al.*<sup>[12]</sup> in which hypotension was second to headache in terms of maternal side effect, however a total of 679 patients were studied, the result of the side effect obtained in this study could be possibly due to small sample size. However in the study by Chawanpaiboon *et al.*<sup>[11]</sup> complications of nifedipine were not detected at all in the nifedipine study group.

The only maternal side effect recorded in this study was headache. Headache was found to be more among women that were in the high dose group which was not significant, however the headache was not that severe to require discontinuation of treatment in view of the fact that all the patients with headache tolerated the treatment well. This is comparable to the side effects noted by Anwar *et al.*<sup>[10]</sup> in which headache was the commonest side effect noted among the two groups of women that took two different regimens of nifedipine.

The result of this study showed that high dose of oral nifedipine does not seem to have an advantage over the low dose of oral nifedipine in terms of the mean time to achieve uterine quiescence and the number of women undelivered at 48 h. However, more women in the high dose regime had headache though this was not significant. None of the patient had abnormal fetal heart rate changes. Further research work with larger sample size and a much lower dose than the low dose used in this study could be explored.

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### Conflicts of interest

There are no conflicts of interest.

### Ethical approval

Obtained from OAUTHC Ethics and Research Committee with international number IRB/IEC/0004553.

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