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Original Research Article

Effect of oral nifedipine or combined with sildenafil citrate for management of threatened preterm labour randomized trial

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ABSTRACT

Background: In developing countries, preterm birth is a leading cause of neonatal and infant illness and mortality. In southern India, there is an increase in preterm delivery and the prevalence is about 5-8%. It is related with severe suffering for both women and babies as well as long-term disabilities; hence interventions to prevent preterm birth are critical. The threatened preterm labor can be postponed by using "tocolytic" therapy in order to transfer the patient to a center with a neonatal intensive care unit or administer corticosteroids. It helps in the prevention or treatment of respiratory morbidity.
Aims: To assess the efficacy of nifedipine combined with sildenafil citrate and nifedipine alone in threatened preterm labor and also to determine the maternal and perinatal outcome.
Materials and Methods: The final analysis comprised a total of 60 subjects. There were 30 people in Group A (Nifedipine) and 30 people in Group B (Sildenafil +Nifedipine).
Results: The mean age of the participants was identified as 21.07 ± 3.31 years and 22.87 ± 3.15 years in group A and B respectively. The cause of preterm was identified as idiopathic in the majority of the women in group A with 83.33 and in group B with 70% and 16.67%. Maternal side effects in group A were tachycardia, palpitations, nausea, and vomiting with 26.67%, 3.33%, and 16.67%, while in group B, tachycardia, facial flushing, palpitations, and headache were identified with 10%, 6.67%, 10%, 6.67%. Respiratory distress syndrome, Neonatal intensive care unit admission, perinatal death, alive and healthy neonates were identified with 16.67%, 23.33%, 20%, and 53.33% in group A, whereas it was identified with 23.33%, 36.67%, 3.33%, and 56.67% respectively. The rate of success was higher with group B (93.3%) as compared in group A (50%).
Conclusion: The combination of sildenafil citrate and nifedipine is more effective than nifedipine alone in avoiding approaching preterm labor.

1. Introduction

Threatened preterm labor occurs when regular uterine contractions occur at least once every 10 minutes and last for more than 30 minutes before the 37^{th} week of pregnancy without the cervix dilation. [1]

Preterm labor is the onset of regular painful uterine contractions with effacement and dilatation of the cervix prior to the completion of 37 weeks of pregnancy, starting on the first day of the last menstrual period and lasting after viability. It causes 75% of neonatal mortality and 50% of long-term morbidities such as respiratory distress and neurodevelopmental impairment. [2]

Premature birth is the leading cause of neonatal and newborn mortality in developing countries. To reduce perinatal mortality and morbidity, public health educational initiatives, lifestyle modification, obstetric protocols of treatment, and early diagnosis of threatened preterm labor

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are used as preventive measures.[3]

The main goal of obstetrician is to delay delivery for at least 24-48 hours in order to give adequate time for corticosteroids to be administered which aids in lowering the newborn complications.

Nifedipine is a prototype of dihydropyridines with a rapid onset and a short duration of action. It inhibits voltage-dependent L-type calcium channels decreasing calcium influx into the cells resulting in smooth muscle relaxation.

In a meta-analysis, nifedipine was identified as more effective and safer than other traditional tocolytics, whereas, another meta-analysis study concluded it as a drug of choice for threatened preterm labor.[4]

Sildenafil prevents the degradation of second messenger 3',5' cGMP by the enzyme PDE-5. The vasodilator effect of sildenafil citrate on uterine and myometrial vessels can cause an increase in the uterine flow and endometrial thickening. It has the ability to promote nitric oxide synthesis, as well as vascular system relaxation and vasodilation.

2. Need of the Study

Tocolytics are used to buy time for steroids for fetal lung maturity in preterm labour.[5]

Nifedipine has a significant effect in prolongation of pregnancy, therefore, combining with sildenafil can help to reduce perinatal outcome.[6]

Till date, no additional intervention has been advantageous. A few studies have found the tocolytic effect of combining nifedipine and sildenafil citrate in women who are at risk of threatened preterm labor advantageous.[7]

As per literature, there is paucity of studies conducted, as a result, the goal of this study is to see if combining nifedipine with sildenafil has a better effect than nifedipine alone in terms of preventing threatening preterm labor and enhancing perinatal outcomes.

3. Aims and Objectives

1. To assess the efficacy of nifedipine combined with sildenafil citrate in preventing the progress of threatened preterm labor.
2. To evaluate the efficacy of nifedipine alone for preventing the progress of uterine contraction in threatened preterm labor.
3. To determine the maternal and perinatal outcome among the groups using nifedipine alone and nifedipine combined with sildenafil citrate.

4. Materials and Methods

4.1. Study site

Department of Obstetrics & Gynecology RL JALAPPA and Research Center attached to Sri Devaraj Urs Medical College, affiliated to Sri Devaraj Urs Academy of higher Education and Research Tamaka, Kolar- 563101.

4.2. Study population

All the eligible pregnant women admitted to labor room with threatened preterm labor at R.L JALAPPA Hospital attached to Sri Devaraj Urs Medical College were considered as the study population.

4.3. Study design

Randomized Trial

Group A: Nifedipine

Group B: Sildenafil+Nifedipine

4.4. Sample size: (Formula to compare two independent means)

The sample size was calculated assuming the expected mean and standard deviation of the birthweight of group A as 1500 and in group B as 1900 grams with standard deviations of 400 and 600 as per the previous study by MA Maher et al.[8] The other parameters considered for sample size calculation included were 80% power of study and 5% two-sided alpha error. The required sample size was calculated using the following formula as proposed by Kirkwood BR et al.[9]

Formula used for sample size calculation

$N = \frac{(u+v)^2(\sigma_1^2+\sigma_0^2)}{(\mu-\mu_0)^2}$

N = Sample size

μ_1, μ_0 = Difference between the means (μ_1 = 1500 and μ_0 = 1900)

σ_1, σ_0 = Standard deviations (σ_1 = 400 and σ_0 = 600)

u = Two-sided percentage point of normal distribution corresponding to 100%-the power=80%, u=0.84

v = Percentage point of normal distribution corresponding to (two-sided) significance level (Significance level = 5%, v=1.960)

The required sample size as per the above-mentioned calculation was 26 in each group. To account for a non-participation rate/loss-to-follow-up rate of about 11%, another 4 subjects will be added to sample size. Hence, the final required sample size would be 30 subjects in each group.

4.5. Sampling method

All eligible subjects were recruited into the study consecutively by convenient sampling.

4.6. Study duration

The data collection was done between January 2020-June 2021 for a period of 1 year 5 months.

4.7. Inclusion criteria

1. Age: 18-35 years, gestational age 28-37 weeks.
2. Singleton pregnancy.
3. No vaginal discharge.

4.8. Exclusion criteria

1. Cervical dilatation
2. Cervical length>15mm on TVS
3. Chorioamnionitis (unexplained fetal tachycardia or maternal temperature)
4. Maternal complications like eclampsia, HELLP syndrome
5. Bronchial asthma, cardiac or thyroid disorder.

4.9. Ethical considerations

The approval was obtained by the Institutional ethics committee. Informed written consent for all study participants and only those participants who gave consent were included in the study. Risks and benefits involved in study; the voluntary nature of participation was explained to the participants before obtaining consent. The confidentiality of the participants was maintained.

4.10. Data collection tools

All relevant parameters were documented in a structured study proforma.

4.11. Methodology

Pregnant women hospitalized to labor room were recruited for the study

General examination includes

1. Maternal pulse rate.
2. Blood pressure.
3. Uterine contraction.
4. Fetal heart rate.

4.12. Routine examination

1. Complete blood count.
2. Serology: HIV and Hepatitis-B.
3. Bleeding time.
4. Clotting time.
5. Random blood sugar.
6. Transvaginal ultrasound- cervical length more than 15 mm, diagnostic for preterm labor.

Transvaginal ultrasound examination is done prior to randomization by chit system. Chit system was,

1. The first group had received nifedipine alone and
2. "Second group had received nifedipine along with sildenafil citrate per vaginal. Nifedipine 20mg orally stat dose followed by 10mg orally every 6-8hours at the same time as vaginal administration of sildenafil citrate 25mg at 8^{th} hourly interval every 6-8hrs.
3. Each woman was followed up until delivery, and the outcome was recorded.
4. The success of tocolysis was considered at the end of 48hours, after the onset of tocolysis
5. Tocolysis was considered as failed if uterine quiescence was not stopped, despite a maximum dose of delivery or when the patient delivered within 48hours of initiation of therapy.

4.13. Statistical methods

Maternal side effects and neonatal outcomes were considered as primary outcome variables. The study group (Group-A vs. Group-B) was considered as the primary explanatory variable. Skewed distributed quantitative variables were summarized by the median and interquartile range. Data was also represented using appropriate diagrams like Error bar diagram, Stacked bar diagram, and cluster bar diagram. All Quantitative variables were checked for normal distribution. For normally distributed Quantitative parameters, mean values were compared between study groups using an independent sample t-test(2-groups). For non-normally-distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2-groups). Categorical outcomes were compared between study groups using the Chi-square test/Fisher's Exact test (If overall sample size was <20 or if expected number in any one of the cells is <5, Fisher's exact test was used.). P-value<0.05 was considered statistically significant. Data were analyzed by using coGuide software, V.1.03.

5. Results

The final analysis comprised a total of 60 subjects. Group A (Nifedipine) were 30 participants, and Group B (Sildenafil+Nifedipine) were 30 participants.

Average age of participants in study group-A was 21.07±3.31, and group B was 22.87±3.15 years. There was a statistically significant difference between mean age between study groups(P-Value=0.035)

Among the population in group-A, 14(46.67%) participants were age group between 18-20years, 12(40%) participants between 21-25years and 4(13.33%) participants were ≥26 years. Among the population in group-B, 8(26.67%) participants belonged to the age group up to 20 years, 16(53.33%) participants between 21-25years, and 6(20%) participants belonged ≥26years. There was no statistically significant difference in the age group between

the study group (P-value = 0.271).

Among the participants, there were 8(26.67%) booked and 22(73.33%) unbooked pregnancies in group-A, and 15(50%) each in group-B. No statistically significant difference between the two groups booked/unbooked (P-value=0.063).

Among the participants, the gravida was primigravida in 26(86.67%) participants and Multigravida for 4(13.33%) participants in group-A, and it was primigravida for 22(73.33%) participants and multigravida for 8(26.67%) participants in group-B. There was no statistically significant difference in gravida between study groups (P-value=0.197).

Among the participants, 2(40%) in group-A and 6(75%) in group-B had previous history of PTB. There was no statistically significant difference in previous history of PTB between the study groups (P-value=0.293).

In group-A, the median period of gestation was 32.50(30,34) weeks, ranging from 24-35 weeks. In group-B, the median period of gestation was 34(31,34.25) weeks, ranging from 29-35 weeks. No statistically significant difference was observed between the study groups (P-value=0.208).

Among the participants, gestational age was 24-30 weeks for 9(30%) participants in group-A and 6(20%) in group-B; the gestational age was 31-32 weeks for 6(20%) participants in group-A and 5(16.67%) in group-B, the gestational age was 33-35weeks for 15(50%) participants in group-A and 19(63.33%) in group-B. There was no statistically significant difference between study groups (P-value=0.559). (Table 1)

In group A, the median prolongation of pregnancy was 2(2,5) days, ranging from 1-15 days. While in group-B, it was 7(2.75, 20) days, ranging from 1-28 days. Statistically significant difference was observed in median prolongation of pregnancy between the study groups (P-value <0.001).

Among the participants, the cause of preterm was Cervical incompetence for 1(3.33%) participant in group-A and 2(6.67%) participants in group-B, Idiopathic for 25(83.33%) participants in group-A and 21(70%) in group-B, Lower Genital Tract Infection for 4(13.33%) participants in group-A and 5(16.67%) in group-B and Urinary Tract Infection for no participant in group-A and 2(6.67%) participants in group-B. (Table 2)

Among the participants, the maternal side effect was tachycardia for 8(26.67%) participants in group-A and 3(10%) in group-B, Facial Flushing for no participants in group-A and 2(6.67%) in group-B; Palpitations for 1(3.33%) participant in group-A and 3(10%) in group-B, headache for no participants in group-A and 2(6.67%) in group-B and nausea and vomiting for 5(16.67%) participants in group-A and no participant in group-B. No statistically significant difference was observed between the study groups(P-Value>0.05). (Table 3)

In group-A, the mean birth weight was 2090±372.64 grams, ranging from 1200-3200grams and 2381.67±492.44 grams, ranging from 1600-3400grams in group-B. Statistically significant difference was observed (P-Value=0.012). (Table 4)

Among the participants, neonatal complications were respiratory distress syndrome for 5(16.67%) participants in group-A and 7(23.33%) in group-B; NICU admission for 7(23.33%) participants in group-A and 11(36.67%) in group-B; alive and healthy for 16(53.33%) participants in group-A and 17(56.67%) in group-B; perinatal death for 6 (20%) participants in group-A and 1(3.33%) in group-B. No significant difference was observed in any of the neonatal complications (p-value>0.05). (Table 5)

Among the participants, Betnesol was given to 25(83.33%) participants in group-A and 29(96.67%) in group-B. No statistically significant difference was observed between the study groups (P-value=0.195). (Table 6)

In group A, cervical length was 32(31,33) units, ranging from 21-35 and was between 32(31.75,34) units, ranging from 21-36 in group-B. No statistically significant difference was among the participants, cervical score was 21-25 for 1(3.33%) participant in group-A and 2(6.67%) in group-B; 26-30 for 2(6.67%) participants in group-A and no participant in group-B; 31-36 for 27(90%) participants in group-A and 28(93.33%) in group-B.

Among the participants, nifedipine loading dose was 20mg for 15(50%) participants in group-A and 12(40%) in group-B, 30mg for 7(23.33%) in group-A and B; 40mg for 8(26.67%) participants in group-A and 11(36.67%) in group-B. (Table 7)

Analysis of tocolytic effect in the two groups showed that in subgroup-B 93.3% success rate upto 1week was seen. (Table 8)

6. Discussion

In developing nations, preterm birth is a leading cause of neonatal and infant illness and mortality. Major goal of an obstetrician is to postpone premature delivery for administration of corticosteroids.

Tocolytics delay threatened preterm labor so the patient can be transferred to a center with a NICU, or corticosteroids can be given. Nifedipine has been found to be more effective and safer than ritodrine. This study was conducted to compare the effects of nifedipine and sildenafil citrate combination with nifedipine alone for threatened preterm labor.

A total of 60 subjects were included of which Group A (Nifedipine) were 30 participants, and Group B (Sildenafil+Nifedipine) were 30 participants.

In the present study, mean age of participants was identified as 21.07±3.31 in group A, and 22.87±3.15 years in group B.

Table 1: Comparison of gestational age (weeks) between study groups (N=60)

Gestational age (weeks)	Study Group		Chi-square	P-value
	Group-A(N=30)	Group-B(N=30)		
24-30weeks	9(30%)	6(20%)		
31-32weeks	6(20%)	5(16.67%)	1.161	0.559
33-35weeks	15(50%)	19(63.33%)		

Table 2: Comparison of causes of preterm between study groups (N=60)

Cause of preterm	Study Group	
	Group-A(N=30)	Group-B(N=30)
Cervical Incompetence	1(3.33%)	2(6.67%)
Idiopathic	25(83.33%)	21(70%)
Lower Genital Tract Infection	4(13.33%)	5(16.67%)
Urinary Tract Infection*	0(0%)	2(6.67%)

*No statistical test was applied-due to 0 subjects in the cells

Table 3: Comparison of maternal side effects between study groups (N=60)

Maternal side effect	Study Group		Chi-square	P-value
	Group-A(N=30)	Group-B(N=30)		
Tachycardia	8(26.67%)	3(10%)	2.783	0.095
Facial Flushing	0(0%)	2(6.67%)	*	*
Palpitations	1(3.33%)	3(10%)	†	0.612
Headache	0(0%)	2(6.67%)	*	*
Nausea and vomiting	5(16.67%)	0(0%)	*	*

*No statistical test was applied due to 0 subjects
†Fishers exact test was used

Table 4: Comparison of mean of birth weight (grams) between study groups(N=60)

Parameter	Study group(Mean± SD)		P-value
	Group-A(N=30)	Group-B(N=30)	
Birth weight (grams)	2090±372.64	2381.67±492.44	
Minimum	1200	1600	0.012
Maximum	3200	3400	

Table 5: Comparison of neonatal complication between study groups (N=60)

Neonatal complication	Study Group		Chi-square	P-value
	Group-A(N=30)	Group-B(N=30)		
RDS	5(16.67%)	7(23.33%)	0.417	0.519
NICU	7(23.33%)	11(36.67%)	1.270	0.260
Alive and healthy	16(53.33%)	17(56.67%)	0.067	0.795
Perinatal death	6(20%)	1(3.33%)	*	0.103

* Fisher's exact test was used

Table 6: Comparison of Betnesol between study groups (N=60)

Betnesol	Study Group		Fisher-exact P-value
	Group-A(N=30)	Group-B(N=30)	
Yes	25(83.33%)	29(96.67%)	0.195
No	5(16.67%)	1(3.33%)	

Table 7: Comparison of nifedipine loading dose (mg) between study groups (N=60)

Nifedipine loading dose(mg)	Study Group		Chi-square	P-value
	Group-A(N=30)	Group-B(N=30)		
20	15(50%)	12(40%)		
30	7(23.33%)	7(23.33%)	0.807	0.668
40	8(26.67%)	11(36.67%)		

Table 8: Comparison of outcome between study groups (N=60)

Parameter	Study Group		Chi-square	P-value
	Group-A(N=30)	Group-B(N=30)		
Success	15(50%)	28(93.3%)	13.871	<0.001
Failure	15(50%)	2(6.6%)		

Shoukat F et al.[3] performed a randomized controlled in which 30.67±3.90 and 29.95±4.32 years were the mean age in the nifedipine and combination group.

In another study by Yousef Abou-Elwan El-Sayed et al.[10] on 192 women the mean age was 30.6±4.9 and 31.3±6.1 (years) in the nifedipine and combination group.

Elkattan R. et al.[11] performed a prospective study on 88 women in which 26.75years and 26.55years were identified as mean age in the nifedipine and sildenafil groups, respectively.

Above studies showed an increased mean of age compared to our study.

In the present study, majority of the participants in group A belonged to age <20years with 46.67%, followed by age between 21-25years with 40%. Whereas, in group B majority of participants belonged to age between 21-25years with 53.33%, followed <20years with 26.67%.

In this study, there were 26.67% booked and 73.33% unbooked pregnancies in group A and 50% each in group B.

In this study, majority of the participants in groups A and B belonged to primigravida with 86.67% and 73.33%, respectively. Urmila Karya et al.[12] conducted a prospective randomized study on 80 women in which majority of the participants in the nifedipine and combination group belonged to multigravida with 65% and 62.5%, respectively, which was contradictory to our study.

In the current study, 40% of the participants in group A had history of preterm birth, whereas; it was 75% in group B. In Elham Mohammadi et al.[13] the history of preterm birth was 9.1% in the nifedipine group while it was 21.2% in combination group which was less as compared to our study.

The median period of gestation was 32.50(30,34) weeks in group A while it was 34(31,34.25) in group B. In Shoukat F, et al.[3] study 29.58±2.05 and 31.23±2.16 were identified as the mean period of gestation in the nifedipine and combination group which was a decreased mean as compared to our study.

Most of the women had gestational ages between 33-35weeks in groups A and B with 50% and 63.33%, respectively. In Urmila Karya et al.[12] study majority of participants had gestational age between 32-34 weeks in the nifedipine and combination group with 60% and 55%, respectively, which resembles our study.

In the current study, median prolongation of pregnancy was observed as 2(2,5) days in group A, and 7(2.75,20) in group B. Saima Ayub et al.[14] performed a study on 176 women in which majority of participants had prolongation of pregnancy between 48hours-1week in nifedipine group with 37.50% followed by >1week with 30.68% while, in sildenafil group majority of the women had >1week prolongation of pregnancy with 32.95% followed by 48hours-1week with 20.65% which are similar to our study.

The cause of preterm was identified as idiopathic in majority in group A with 83.33%, followed by infection with 13.33% and was 70% and 16.67% in group B, respectively.

Maternal side effects in group A were tachycardia, palpitations, nausea, and vomiting with 26.67%, 3.33%, and 16.67%, while in group B, tachycardia, facial flushing, palpitations, and headache were identified with 10%, 6.67%, 10%, 6.67%. In Urmila Karya et al.[12] study, facial flushing, palpitations, headache, and nausea were the side effects identified within the nifedipine group with 22.5%, 10%, 25%, and 7.5%, and was 42.5%, 7.5%, 40%, and 5% respectively which resembles our study.

In the current study, the birth weight was 2090±372.64 in group A and was 2381.67±492.44 grams in group B. Elham Mohammadi et al.[13] conducted a randomized study on 139 women in which 1609.0±204.3 and 2154.5±221.3 (grams) were the mean birth weight identified in the nifedipine and combination group which was a decreased mean birth weight compared to our study.

In the current study, respiratory distress syndrome, NICU admission, perinatal death, alive and healthy neonates were 16.67%, 23.33%, 20%, and 53.33% in group A, and was 23.33%, 36.67%, 3.33%, and 56.67% respectively in group B. In Urmila Karya et al.[12] study the respiratory distress and perinatal death were 22.5%, 35%, and 12.5% in the nifedipine group and was 10%, 22.5%, and 5% in the combination group.

Abd El-Naser et al.[15] performed a study on 300 pregnant women in which respiratory distress, sepsis, perinatal mortality were 7.40%, 4.20%, and 1.06%, while it was 8.30%, 4.10%, and 2.08% in the sildenafil group.

Our study showed similar neonatal outcomes to these studies.

Betnesol was given to 83.33% and 96.67% participants in group A and B.

In the current study, cervical length was 32(31,33) in group A. Majority of the participants had a cervical score between 31 to 36 in group A and group B with 90% and 93.33%, respectively. In Elham Mohammadi et al.[13] 29.50±3.51 and 28.62±3.90(cm) were identified as the mean cervical length in the nifedipine and combination group which was a decreased mean as compared to our

study.

In the current study, the nifedipine loading dose was 20mg for majority of women in groups A and B with 50% and 40%, respectively. The rate of success was higher with group B (93.3%) than with group A (50%).

7. Conclusion

An ideal tocolytic agent should be safe, well tolerated, easily administered, rapidly absorbed and should relax myometrium to prevent threatened preterm labor.

Effect of tocolytic is intensified through the synergistic effect of sildenafil citrate with nifedipine combination.

In our study, a combination of sildenafil citrate and nifedipine was found to be more beneficial than nifedipine alone.

The combination has better efficacy in maternal and neonatal outcome, compared to nifedipine alone.

8. Limitations

The study was performed in a single center. So, more studies are required with a fixed dose of the drug and on a larger scale.

9. Recommendations

Larger studies at multiple centers are required to gain a better understanding of the benefit of this therapeutic intervention. Adverse effects of this combination regimen on fetus and mother as a prophylactic agent in preterm labor can also be determined.

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