DOI: https://doi.org/10.54393/pjhs.v5i11.2111

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Comparison of Fetomaternal Outcomes in Nifedipine Combined with Sildenafil Citrate Versus Nifedipine Alone for the Management of Threatened Preterm Labour

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ARTICLE INFO

Keywords:
Nifedipine, Sildenafil Citrate, Neonatal Intensive Care, Preterm Delivery

How to Cite:
Faiz Rasul, H. M., Shahzad, Q., Kanwal, S., Aslam, A., Shaukat, F., & Inam, I. (2024). Comparison of Fetomaternal Outcomes in Nifedipine Combined with Sildenafil Citrate Versus Nifedipine Alone for the Management of Threatened Preterm Labour: Fetomaternal in Nifedipine Combined with Sildenafil Citrate Versus Nifedipine . Pakistan Journal of Health Sciences, 5(11), 248-252. https://doi.org/10.54393/pjhs.v5i11.2111

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Received Date: 24th August, 2024
Acceptance Date: 16th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Sildenafil, a smooth muscle relaxant, has been explored as an adjuvant to delay the onset of preterm labor. By inhibiting uterine contractions, it helps prolong pregnancy and improve fetal outcomes. **Objectives:** To evaluate the effects of Nifedipine on the mother and fetus during impending preterm labour, alone or with sildenafil citrate. **Methods:** The quasi-experimental trial was conducted at Sir Ganga Ram Hospital Lahore. Patients were randomly assigned to receive either 20 mg Nifedipine orally (stat dose) followed by 10 mg every 8 hours with 25 mg sildenafil citrate orally at 8-hour intervals or 20 mg without sildenafil citrate. The medication therapy lasted 72 hours. Chi-square and independent sample t-tests were used to compare groups in SPSS version 26.0. **Results:** Baseline age, gestational age and parity were similar in both groups ($p>0.05$). With mean gestational age at delivery 34.47 ± 2.18 weeks, the frequencies of term, preterm and very preterm were 15.0%, 77.5% and 7.5%, respectively. Nifedipine with Sildenafil citrate group had significantly higher term deliveries (30.0% vs. 0.0%; p-value=0.002) and normal weight births (35.0% vs. 5.0%; p=0.005) compared to Nifedipine alone group; however maternal readmission and neonatal intensive care unit admission rates were not statistically different between groups ($p>0.05$). There was no mortality feto-maternal observed. **Conclusions:** It was concluded that oral sildenafil citrate combined with Nifedipine is an effective option as tocolytic therapy for threatened preterm labour. The prolongation of pregnancy will improve fetal weight, and reduce neonatal intensive care unit admissions and preterm deliveries with minimum maternal and fetal side effects.

INTRODUCTION

Delivery that occurs between 24 and 37 weeks into the gestational period is considered preterm. Details from 2010 data revealed that 14.9 million neonates were born preterm, with 1.6 million being born very preterm, despite several measures to lower its prevalence [1]. As a result, finding a suitable therapy for impending preterm labour and pregnancy lengthening is an urgent matter [2]. When compared to other risk factors, preterm delivery has the greatest impact on the likelihood of prenatal morbidity and death, low birth weight at delivery, and admission to the neonatal intensive care unit (NICU) [3]. Delaying birth for 48 to 72 hours with tocolytic treatment allows for the administration of corticosteroids, which decrease respiratory morbidity and the need for neonatal intensive care unit stays [4]. There are no known therapies that can reduce these complications at this time. As a tocolytic treatment, calcium channel blockers such as nifedipine might be utilized. The medicine Nifedipine is preferred for threatening preterm labour (PTL) due to its minimal adverse effects compared to other tocolytics, according to many reviews. These side effects include headache, tachycardia, palpitation, and others [5, 6]. Sildenafil citrate is a cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE)-5 inhibitor. It enhances smooth

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DOI: https://doi.org/10.54393/pjhs.v5i11.2111

muscle relaxation, reduces intracellular calcium levels, reduces the sensitivity of contractile elements too and can be beneficial in inhibiting threatened preterm labour (PTL) with positive maternal and fetal effects [7]. The tocolytic effects of sildenafil citrate and the fetomaternal effects of a combination of nifedipine and sildenafil citrate for the treatment of PTL without significant side effects have only been somewhat investigated in existing research.

This study aims to compare the efficacy of Nifedipine alone with that of this combination in preventing preterm delivery and enhancing feto-maternal outcomes over longer pregnancies.

METHODS

The quasi-experimental trial was conducted at Sir Ganga Ram Hospital Lahore from February to December 2021. Ethical approval of the study was taken from the Institutional Review Board with letter No. 33-Res-Publication-Gynae/ERC. Informed consents were taken from all patients. The calculation of the sample size was based on the prevalence of 18%, the margin of error was 10%, and the confidence interval was 95%. Data were collected by using survey forms. All patients were enrolled once written consent from them was obtained. A nonconsecutive sampling technique was used. Patients detailed demographics including age, parity, gestational amenorrhea, and blood pressure, pulse, uterine contractions, fetal heart rate were recorded after taking written and informed consent. Patients with no consent, hypersensitivity to Sildenafil and Nifedipine, and medical disorders were excluded from the study. Patients were randomly allocated into two equal groups. Group A received (1) Nifedipine 20 mg orally (Stat dose) followed by 10mg every 8 hours with oral administration of Sildenafil citrate (25 mg at 8 hourly intervals). Group B received Nifedipine alone. Medications were continued for 72 hours. During the therapy during admission maternal pulse, blood pressure, uterine contractions, and fetal hearts were recorded every 30 min. the interval for the first 4 hours, then 2 hourly for the rest of the admission period. Patients were discharged on vaginal Progesterone therapy with a weekly follow-up plan. If a patient had preterm contractions again, readmission and treatment were repeated. At every follow-up visit, feto-maternal assessment was done with fetal heart rate, uterine contractions, and side effects of medications, Fetomaternal outcome was recorded at the time of delivery including fetal weight (kg), NICU admission, gestational age at the time of delivery and number of readmissions with threatened PTL was recorded. Statistical Packages for Social Sciences (SPSS) version 26.0 was used to analyze data. Mean and standard deviation calculated for quantitative variables like age parity, gestational age, fetal weight (Low birth weight: A fetal weight of less than 2,500 grams (5 pounds, 8 ounces) Very low birth weight: A fetal weight of less than 1,500 grams (3 pounds, 5 ounces), NICU admission, maternal readmissions. Comparisons between groups were done by Chi-square and independent sample t-test. Data were presented in tables and graphs. p-value≤0.05 was taken as significant.

RESULTS

The data obtained from a total of 40 pregnant women with threatened preterm labor including 20 women in the Nifedipine with Sildenafil citrate group and 20 in the Nifedipine alone group were subjected to final analysis. The mean age of the study population was 27.55 ± 2.79 years and ranged between 21 and 34 years. The overall mean gestational age at enrollment was 30.90 ± 1.94 weeks and ranged between 28 and 35 weeks. At baseline, there were no statistically significant differences between the Nifedipine with Sildenafil citrate group and Nifedipine alone group in terms of age (p-value 0.912) gravida (p-value 0.414), para (p-value 0.265), abortus (p-value 0.896) and gestational age (p-value 0.369) (Table 1).

Table 1: Maternal Factors and Their Association with Umbilical Cord Coiling Pattern

Variables	Total (n=40)	Nifedipine with Sildenafil (n=20)	Nifedipine alone (n=20)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (Years)	27.55 ± 2.79	27.50 ± 2.80	27.60 ± 2.85	0.912
Gravida	3.40 ± 1.37	3.55 ± 1.35	3.25 ± 1.40	0.414
Gestational Age On Enrollment (Weeks)	30.90 ± 1.94	30.55 ± 1.96	31.25 ± 1.92	0.369

Using the median age, the study population was categorized into two age groups i.e. ≤28 years and >28 years. The participation of women ≤28 years was twice as high as that of women >28 years (70.0% vs. 30.0%). However, both age groups were almost equally distributed in Nifedipine with Sildenafil citrate group and Nifedipine alone group at baseline (p-value 0.731) (Figure 1).

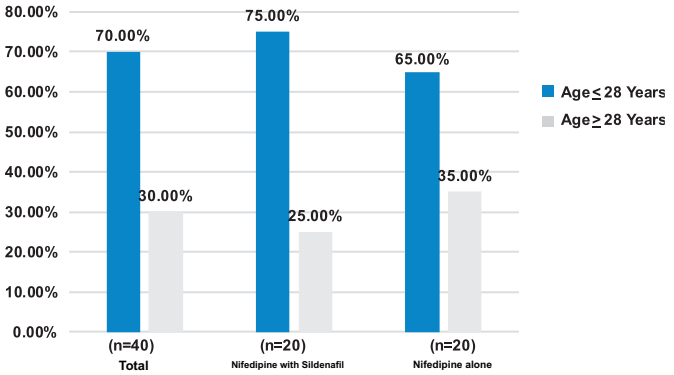

Figure 1: Age Distribution of Study Population at Baseline

Overall, there was no primigravida woman. The frequencies of women with gravida 2, 3, 4 and 6 were 35.0%, 20.0%, 30.0% and 15.0%, respectively (Figure 2).

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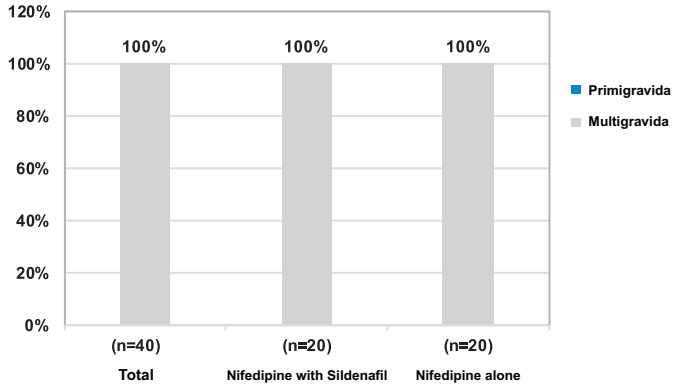

Figure 2: Gravida Status of Study Population at Baseline

The overall frequencies of primipara and multipara women were 35.0% and 47.5%, respectively. All paras were almost equally distributed in Nifedipine with Sildenafil citrate group and Nifedipine alone group at baseline (p-value 0.636)(Figure 3).

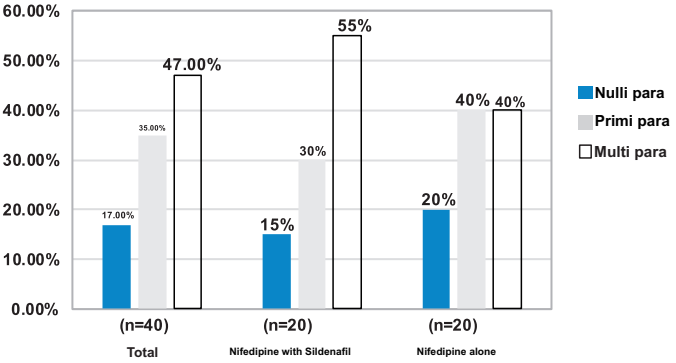

Figure 3: Para Status of Study Population at Baseline

The feto-maternal outcomes at follow-up included preterm delivery, readmission, fetal birth weight and NICU admission. The overall mean gestational age at delivery was 34.47 ± 2.18 weeks and ranged between 30.0 and 38 weeks; and the overall frequencies of term, preterm and very preterm were 15.0%, 77.5% and 7.5%, respectively. The comparison between groups showed that all term deliveries (n=6) were occurred in Nifedipine with Sildenafil citrate group; all very preterm deliveries (n=3) were in Nifedipine alone group; and the difference was statistically significant (p-value=0.002). Total 95.0% women were readmitted; however, the readmission rates were same in both groups (p-value=1.000). The overall mean FBW was 2.02 ± 0.42 kilograms and ranged between 1.3 and 2.8 kilograms; and the overall frequencies of normal weight, low-weight and very low-weight births were 20.0%, 70.0% and 10.0%, respectively. The comparison between groups showed that 7 out of 8 normal weight births occurred in Nifedipine with Sildenafil citrate group; all very low-weight births (n=4) were in Nifedipine alone group; and the difference was statistically significant (p-value 0.005). Total 70.0% neonates were admitted to NICU. The frequency of NICU admission was lower in Nifedipine with Sildenafil citrate group than of Nifedipine alone group (60.0% vs. 80.0%), but the difference was not significant (p-value=0.301), frequency of low Apgar score in Nifedipine group was insignificantly higher (0.297)(Table 2).

Table 2: Fetomaternal Outcomes at Follow-Up

Variables		Total (n=40)		Nifedipine with Sildenafil (n=20)		Nifedipine Alone (n=20)		p-value
Gestational Age on Delivery (Weeks)	Mean ± SD	34.47 ± 2.18		35.25 ± 2.22		33.70 ± 1.89		0.043
	Term	06	15.0%	06	30.0%	0	0.0%	0.002
	Preterm	31	77.5%	14	70.0%	17	85.0%	
	Very preterm	03	7.5%	0	0.0%	03	15.0%	
Read -mission	Yes	38	95.0%	19	95.0%	19	95.0%	1.000
	No	02	5.0%	01	5.0%	01	5.0%	
Fetal Birth Weight (Kg)	Mean ± SD	2.02 ± 0.42		2.23 ± 0.37		1.80 ± 0.35		0.001
	Normal	08	20.0%	07	35.0%	01	5.0%	0.005
	Low	28	70.0%	13	65.0%	15	75.0%	
	Very low	04	10.0%	0	0.0%	04	20.0%	
NICU Admission	Yes	28	70.0%	12	60.0%	16	80.0%	0.301
	No	12	30.0%	08	40.0%	04	20.0%	
Low Apgar Score	Yes	24	60.0%	10	50.0%	14	70.0%	0.297
	No	16	40.0%	10	50.0%	06	30.0%	

DISCUSSION

Sildenafil, which has various long-term uses, may have beneficial effects on fetomaternal outcomes when administered to treat impending preterm labour. Therefore, the purpose of this randomized experiment was to determine if this medication was beneficial. Recent research has demonstrated that when it comes to treating threatening PTL, a combination of Sildenafil Citrate and Nifedipine has a more effective tocolytic effect than Nifedipine alone. There was a decrease in prenatal mortality and morbidity, as seen by fewer NICU admissions, an increase in neonatal birth weight within 7 days following delivery, and fewer births while hospitalized. Multiple published trials related to this drug (Sildenafil citrate) were done in the last two years, besides the result of the meta-analysis done by Paauw *et al.*, showed that the effect of Sildenafil citrate has the potential to improve fetal growth with the prolongation of pregnancy and agreed to current trial [8]. Present study confirms that sildenafil significantly increases the growth rate and belly circumference in the von Sharami et al., experiment. In the current study, the overall mean FBW was 2.02 ± 0.42 kilograms and ranged between 1.3 and 2.8 kilograms; and the overall frequencies of normal-weight, low-weight and very low-weight births were 20.0%, 70.0% and 10.0%, respectively [9]. Babies born to mothers who took sildenafil citrate had a significantly higher birth weight (222.58 g, ranging from 27.75 to 417.41 g) and were less likely to require admission to

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DOI: https://doi.org/10.54393/pjhs.v5i11.2111

the neonatal intensive care unit (31.4% vs. 44.1%). Very small (p=0.043) [10-12]. The present study has shown a reduction in NICU admission with prolongation of pregnancy with Sildenafil citrate although the admission rates were not statistically different between groups (combined drug versus single drug), A Total of 70.0% of neonates were admitted to NICU. The frequency of NICU admission was lower in the Nifedipine with Sildenafil citrate group than in the Nifedipine alone group (60.0% vs. 80.0%), but the difference was not significant (p-value 0.301), see Table 2. However, the Karya *et al.*, trial has shown the Sildenafil treatment was associated with increased fetal AC growth (odd ratio, 12.9, 95% confidence interval, 1.3, 126 compared with institutional sildenafil – Naïve early-onset intrauterine growth restriction (IUGR) control) [13]. A review by Aggarwal *et al.*, has shown a reduction in preterm deliveries with a prolongation of pregnancy of (14 days)[14]. Another study by Manouchehri *et al.*, concluded, fewer deliveries within 7 days of admission (9.1 vs. 20.3%) with Sildenafil citrate and these findings are matched with the results of the present study [15]. This shows the mean gestational age at delivery was 34.47 ± 2.18 weeks, and the frequencies of term, preterm and very preterm were 15.0%, 77.5% and 7.5%, respectively. In curent study, the dose of Sildenafil citrate and trial with mild side effects were selected. It shows that the maternal readmission rate was 77%, while in the current trial, 95% of women were readmitted, however, readmission rates were the same in both groups (Sildenafil Citrate and Nifedipine versus Nifedipine alone) with minimal side effects [16-18]. Facial flushing was the most often reported adverse effect (48%), followed by nasal congestion, dry mouth, and headaches; nevertheless, no woman was readmitted because of serious side effects associated with sildenafil medication [19, 20]. It should be mentioned that study was unable to determine if the medicine had any long-term impacts on children since no research included long-term follow-up of babies. Sildenafil, on the other hand, might be a novel treatment for several severe obstetric disorders, including preeclampsia and IUGR, due to its safety during pregnancy and the lack of evidence of teratogenic effects. Despite these findings, there is a need for further randomised controlled studies including the same pregnancy illnesses using comparable methods required to prove the progression of placental insufficiency to higher birth weight for the fetus.

CONCLUSIONS

It was concluded that oral Sildenafil citrate combined with Nifedipine is an effective option as tocolytic therapy for threatened preterm labour. The study findings indicated that prolonging pregnancy through the use of sildenafil led to significant improvements in fetal outcomes. By delaying the onset of preterm labor, sildenafil allowed further fetal development, resulting in increased fetal weight, which reduced the risks associated with low birth weight, such as respiratory distress and feeding difficulties. Additionally, the study showed a decrease in NICU admissions, as babies born closer to full term typically experienced fewer complications. The use of sildenafil was found to have minimal maternal and fetal side effects, making it a safe and effective method for managing threatened preterm labor.

Authors Contribution

Conceptualization: HMFR
Methodology: HMFR, QS, FS
Formal analysis: HMFR, AA
Writing review and editing: QS, FS, SK,II

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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