ORIGINAL ARTICLE

Comparison between Sildenafil Citrate & Nifedipine with Nifedipine Alone for the Treatment of Threatened Preterm Labour

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ABSTRACT

Background: Pre-term labour is a serious issue that impact the both maternal and neonatal health. There is debate how to deal with this issue and multiple options are utilized. In this study the tocolytic action of nifedipine combined with sildenafil citrate (SC) versus nifedipine alone in inhibiting threatened preterm labour (PTL) is evaluated so that a drug of choice could be determined.
Methods: It was a randomized controlled trial carried out in Sir Ganga Ram Hospital, Lahore for a duration of six months. Patients were randomly allocated to receive either (1) nifedipine 20mg orally (stat dose), followed by 10mg orally every 8 hours and at the same time oral administration of SC (25mg at 8-hourly intervals) or (2) nifedipine alone. Medications were continued for 72 hours. The comparison of women who remained undelivered during hospitalization and one week after admission, was made to determine the best modality to prevent the threatened preterm labor.
Results: The baseline characteristics of participants were similar (p-value>0.05).On comparison of the both treatment groups, it was found that 121(82.9%) in the combination group and 103(70.5%) in the nifedipine alone group remained un-delivered. (P-value<0.05). Moreover, a significant difference was noted with respect to delivery at one week for both treatment group.
Conclusions: Oral SC combined with nifedipine is an effective option for tocolytic therapy for threatened PTL.
Keyword: Nifedipine, Sildenafil citrate, Pre-term delivery, Tocolytic therapy

INTRODUCTION

Preterm labor is defined as delivery of fetus after 24 weeks and less than 37 completed gestational weeks. All over the world, preterm birth is a major obstetric problem being faced in obstetric healthcare[1,2]. In developing countries, preterm birth is a major cause of neonatal and infant morbidity and mortalityl[3]. In healthcare strategies, prevention of preterm labor is the key priority to reduce the perinatal mortality and morbidity and preventive measures are superior than treatment protocols. In order to achieve the success of preventive measures for preterm labor, it is mandatory to consider multiple approaches including public health educational programs, lifestyle modification of patient, obstetric protocols of healthcare and early diagnosis of threatened and established preterm labor. It could be best of public interest to implement efficient treatment strategies for threatened preterm labour[4,5].

Despite of advanced knowledge and recent researches on myometrial physiology, the exact mechanisms responsible for threatened preterm labor and delivery is still not very clear[6].

Nifedipine is a calcium channel blocker that could be used as a tocolytic. A review had concluded that, in comparison of other calcium channel blockers, nifedipine could be used for tocolysis in prevention and treatment of threatened preterm delivery[7].

The most substantial updated Cochrane review comparing calcium to any other tocolytic agent (as beta-mimetic mainly), concluded that calcium channel blockers (Nifedipine mainly) could diminish the risk of threatened preterm labor within 7 days of administration[8].

The aim of this study is to determine the effect of sildenafil citrate as tocolytic agent in combination with nifedipine administration. Sildenafil citrate is a phosphodiesterase inhibitor and it enhances smooth muscle relaxation.In addition, Sildenafil citrate may sensitize the myometrium to other tocolytic agents and this effect can prove the superiority of combination over nifedipine alone.

MATERIAL & METHODS

This randomized controlled trial study is approved by ethical committee (IRB-ERC) of Fatima Jinnah Medical University, Sir GangaRam Hospital Lahore. All participants gave consent and filled informed consent forms. 292 patients fulfilling selection criteria were enrolled in the study from emergency and outdoor of Department of Obstetrics & Gynecology, Sir Ganga Ram Hospital, Lahore. Recruitment started for cases of threatened PTL with a singleton pregnancy between 24 and 36+6 weeks of' gestation.

Exclusion Criteria; major fetal anomalies, intrauterine fetal death, ruptured membranes, Antepartum hemorrhage, medical disorders, multiple pregnancies, polyhydramnios, cervical incompetence, pregnancy with fibroid uterus, pregnancy with urinary tract infection and bacterial vaginosis, as these factors cause increase in the risk of threatened PTL..

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Each patient underwent an ultrasound examination prior to randomization to confirm gestational age, rule out major fetal anomalies and to determine cervical measurements. Dexamethasone in a total dose of 24 mg was administered to all patients if not given in a previous admission.

Eligible women were then randomly assigned into two study groups using random number table: Group I: (combined nifedipine and sildenafil citrate) The protocol for nifedipine consists of 20mg orally stat, followed by 10mg orally every 8 hours, at the same time sildenafil citrate was administered orally in a dose of 25mg at 8 hourly intervals and both medications were continued for 72 hours as indicated. Group II: (Nifedipine alone) received therapy by nifedipine alone in the same regimen and duration described before.

During therapy, maternal (pulse rate, blood pressure, uterine contractions), as well as fetal (heart rate) monitoring was performed every 30 minutes during the first 4 hours following the start of therapy then every 2 hours during the rest of treatment period. Patients whose contractions stopped after 72 hours were observed for additional 24 hours,if they remained stable, then they were discharged and asked to come for follow up after one week. Patients were reassured that at any time if preterm contractions appeared re-admission with repeated treatment using the same drugs will be used.

For Statistical analysis, SPSS latest version 23.Inc. is used. Mean and standard deviation are calculated for quantitative variables like age, parity, gestation age at presentation. Comparison is done by chi square and t-test. P-value ≤ 0.05 will be taken as significant.

RESULTS

It was observed that there is non-significant difference in the age of the pregnant patients (p-value>0.05). Mean gestation age at the time of enrollment in the treatment groups was also statistically insignificant (p-value>0.05). Singleton parity was noted in 42(44.7%) in the combination group and 52(55.3%) in the nifedipine alone group again with statistically non significant difference (Table 1).

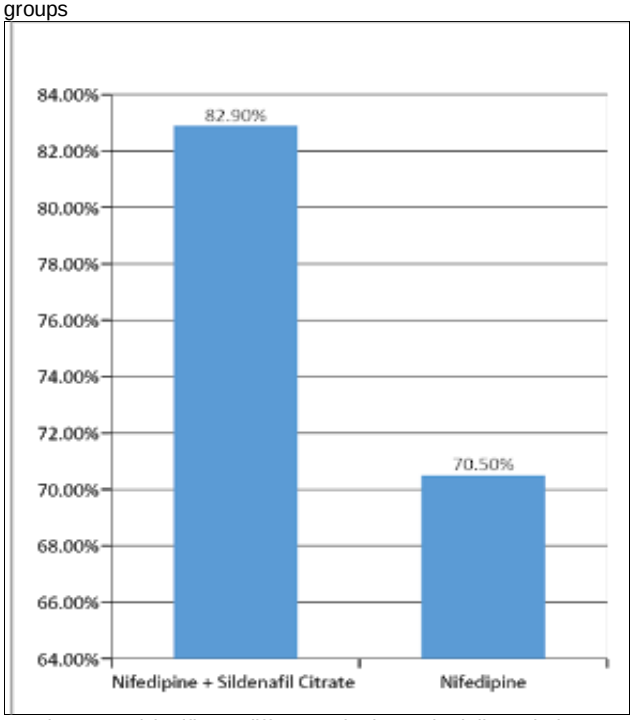
On comparison of the both treatment groups, it was found that 121(82.9%) in the combination group and 103(70.5%) in the nifedipine alone group remained un-delivered. (P-value<0.05) (Graph 1).

Table 1: Baseline characteristics of the pregnant female in the study

	Nifedipine + Sildenafil Citrate (n=146)	**Nifedipine (n=146)**	**P-value**
Mean age (Yrs)	29.95±4.32	30.67±3.90	0.14
Parity			
0	24(54.5%)	20(45.5%)	0.36
1	42(44.7%)	52(55.3%)	
2	60(54.5%)	50(45.5%)	
3	16(51.6%)	15(48.4%)	
4	4(30.8%)	9(69.2%)	
Mean gestational period	31.23±2.16	29.58±2.05	0.29

*P-value<0.05 considered significant

Graph 1: Comparison of the pre-term delivery in the both medicinal groups



P-value= 0.01(significant difference in the early delivery in between the groups)

Table 2: Impact of the parity and gestational age on the prevalence of pre term delivery

Group of parity	**Drug Groups**		**P value**
	Nifedipine + Sildenafil Citrate	**Nifedipine Alone**	
0-2 patients delivered			
Yes	21(16.7%)	38(31.4%)	0.007
No	105(83.3%)	83(68.6%)	
>2 patients delivered			
Yes	4(20%)	5(20%)	0.64
No	16(80%)	20(80%)	
Duration of pregnancy 24-32, patients delivered			
Yes	14(14.6%)	41(29.9%)	0.00
No	82(85.4%)	96(70.1%)	
>32 patients delivered			
Yes	11(22%)	2(22,2%)	0.64
No	39(78%)	7(77.8%)	

Table 3: Comparison of the treatment group for the delivery time

Patient delivered	**Drug Groups**		**P value**
	Nifedipine + Sildenafil	**Nifedipine Alone**	
24 hour delivery time			
Yes	1(100%)	0(0%)	**0.97**
No	0(0%)	1(100%)	
48 hour delivery time			
Yes	11(55%)	9(45%)	**--**
No	10(50%)	10(50%)	
72 hour delivery time			
Yes	9(31%)	20(69%)	**0.97**
No	0(0%)	1(100%)	
One week delivery time			
Yes	5(27.2%)	13(72.8%)	**0.04***
No	121(54.5%)	101(45.5%)	

*P-value <0.05 and considered significant

When impact of frequency of parity and duration of pregnancy was evaluated it was observed that there was significant difference for the pre term delivery in cases with parity <2 and duration of the pregnancy of <32 weeks as mentioned in the table 2. Furthermore, there was significant difference for the frequency of the undelivered patients at one week. (Table 3)

DISCUSSION

Preterm birth is the leading cause of perinatal morbidity and mortality and one of the leading causes of infant mortality. Despite the improvement in survival rates of preterm neonates, they are at increased risk of long-term neurodevelopmental disabilities, and respiratory and gastrointestinal complications.

The most recent substantial update of the Cochrane review regarding calcium channel blockers for tocolysis in threatened preterm labor included 12 randomized controlled trials, involving 1029 patients. This review concluded that, when compared with any other tocolytic agent (mainly beta-mimetics), calcium channel blockers (mainly nifedipine) reduce the risk of delivery within 7 days of initiation of treatment and delivery before 34 weeks of gestation with improvement in some clinically important neonatal outcomes such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal jaundice[9]. A second review from the Cochrane database on maintenance tocolysis reported that, compared with no treatment, nifedipine neither reduces the risk of preterm birth before 37 weeks of gestation nor improves neonatal outcomes[10].

Alkady M et al. worked on single drug study and selected the female with mean age who were receiving nifedipine was 26.75 years, Mean Gestational age at admission was 28.16 weeks. But he found that nifedipine did not proved a drug that could prevent labor even for 15 days.(11) This study has close age group and gestation age as noted in our study. The results of this study also supports the finding of the single drug being administered. Almost similar finding that nifedipine is effective in the prevention of threatened preterm labor was observed in other studies which were carried out on analogy of single arm study[9,12,13].

In another study, it was observed that the women who received Nifedipine combined with Sildenafil Citrate remained undelivered (81.8% v/s 68.6%, indicating that for tocolytic therapy for threatened preterm labor, Nifedipine combined with vaginal Sildenafil Citrate is an effective option. The addition of Sildenafil Citrate was also associated with fewer deliveries within seven days of admission, fewer admissions to neonatal intensive care units, fewer very preterm deliveries, and increased neonatal birth weight[14,15]. The results of this study was similar to our findings as we noted 70% female remained undelivered who were administered nifedipine while 82% in the combination group remained undelivered with a statistically significant difference.

In the study of Nijman T et el. which was a multicountry survey (from January 2015 to November 2016) 239 women with threatened PTL received either nifedipine with SC or nifedipine alone. Nifedipine combined with sildenafil citrate was associated with fewer deliveries within 7 days of admission, prolonged latency, fewer admissions to neonatal intensive care unit, fewer very preterm deliveries and increased neonatal birth weight.This showed that vaginal sildenafil citrate combined with nifedipine proved to be an effective option[16]. Similar findings were noted in the current study.

Chiossi et al. also tested the hypothesis that sildenafil citrate may potentiate the tocolytic effect of nifedipine by developing an in vitro model of myometrial biopsies from full-term non-laboring women who were scheduled for caesarean section. They concluded that sildenafil citrate, by virtue of its ability to reduce the intracellular calcium concentration, can augment the myometrial relaxing effect of nifedipine. Although these authors confirmed the potentiating efficacy of nifedipine if combined with sildenafil citrate.[17] For a superior understanding of the role of sildenafil citrate in myometrial smooth muscles, Khan et al. discovered that there is important role of potassium channel blockage in myometrial contractility and relaxation. Despite the fact that these creators didn't test the impact of sildenafil citrate on calcium channels, they recommended that it had a job[18].

Inhibition of uterine contractions has been a major component of the therapy of patients with preterm labor with the hope that inhibiting uterine contractility would prevent preterm delivery and the neonatal complications associated with the preterm onset of labor. Despite decades of basic and clinical research in tocolytic agents, it is unclear whether inhibition of uterine contractions can substantially change the prognosis of pre-term labor. It seems that tocolysis can achieve a slight prolongation of pregnancy and sometimes a reduction in neonatal morbidity, particularly when used in combination with steroids[19].

This study has limitation that it was carried out in a single center. So more studies are needed with a fixed dose of the drug and on larger scale.

CONCLUSION

Using the evidence based practices,our study offers hope that the combination of sildenafil citrate with nifedipine is superior to nifedipine alone in preventing the threatened preterm labour. Larger studies at multiple centers, are needed to confirm our findings and to gain a better understanding of the benefit of this therapeutic intervention.

Conflict of Interest: There is no conflict of interest in this study.

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