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ORIGINAL ARTICLE

Comparative Study between Nifedipine Alone Versus Nifedipine Combined with Sildenafil Citrate for Cases with Threatened Preterm Labour

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ABSTRACT

Background: Preterm labour (PTL) is any delivery after 20 weeks and before the end of 37 weeks' gestation. In PTL, using tocolytic drugs has been proven to prolong pregnancy. A commonly tocolytic drug as nifedipine, which appears to be more effective than β2-adrenergic-receptor agonists and magnesium sulfate. The aim of the present study was to study the tocolytic action of nifedipine combined with sildenafil citrate and if the combination is more effective than nifedipine alone in inhibiting threatened PTL.

Methods: This interventional study was conducted at Obstetrics and Gynecology Department, Zagazig University, from April 2019 to February 2020. Included 96 pregnant women who suffered from threatened PTL. They were divided into two classes, class (A) included 48 cases who received nifedipine only and class (B) included 48 cases who received nifedipine with sildenafil.

Results: our study showed that a statistically significant difference according to maternal heart rate and mean blood pressure before and after treatment in nifedipine with sildenafil group. But in nifedipine only group, there was no statistically significant difference according to maternal heart rate before and after treatment. There was statistically significant difference between the two studied classes in delivery 24,48 and 72 hours after admission with less early deliveries among the nifedipine with sildenafil group. Regarding mode of delivery, there was no statistically significant difference between nifedipine and nifedipine with sildenafil groups.

Conclusions: Vaginal sildenafil citrate (SC) combined with nifedipine is more effective tocolytic therapy during threatened PTL.

Key words: Nifedipine; preterm labour; sildenafil citrate; threatened preterm labour.

INTRODUCTION

Preterm labour (PTL) is any delivery after 20 weeks and before end of 37 weeks' gestation. Despite attempts aimed to decrease its incidence, statistics for 2010 appeared that 14.9 million neonates were born preterm and of these 1.6 million were born very preterm (<32 weeks' gestation). Accordingly, it is crucial to develop an appropriate approach for management of threatened PTL **[1,2]**.In PTL with cervical dilatation, the efficacy of tocolytic drugs has been proven to prolong pregnancy. A commonly used tocolytic drug is nifedipine which approve to be more effective than β2-adrenergic-receptor agonists and magnesium sulfate. Other treatments by using progesterone and bed rest were also studied **[3]**. Nifedipine is considered important tocolytic agent for the treatment of PTL. The action of nifedipine has not yet been well studied in threatened PTL. So, double-blinded placebo-controlled study was done to assess nifedipine's action in threatened PTL **[4]**.

Nifedipine, a calcium channel blocker, is mainly used to treat high blood pressure and heart disease because of its action to inhibit smooth muscle cells contraction by decreasing calcium influx into cells.

Nifedipine has emerged as an effective and safe comparing of tocolytic agent for the management of PTL. Despite its unlabeled status, several randomized studies have appeared that using of nifedipine in comparison with other tocolytic is associated with a more frequent successful prolongation of pregnancy, resulting in significantly fewer admissions of newborns to the neonatal intensive care unit. In addition, it may be associated with a lower incidence of respiratory distress syndrome (RDS), necrotizing enterocolitis, and intraventricular hemorrhage **[5].** Tocolytic therapy is used to delay delivery for 24-48 hours to give enough time for giving of corticosteroids to reduce the incidence and severity of respiratory morbidity and to allow utero transfer to a center with proper neonatal intensive care unit (NICU) facilities. No other interventions have been beneficial to the infant **[6,7].**

Calcium channel blockers such as nifedipine decrease muscle contractility by reduce calcium influx into cells. In one meta-analysis, nifedipine was more effective and safer than ritodrine, and another meta-analysis advised it as the drug of choice for threatened PTL **[8,9].** Sildenafil citrate (SC) is an effective inhibitor of cyclic guanosine monophosphate(cGMP)-specific phosphodiesterase (PDE). SC stimulate smooth muscle relaxation by inhibiting degradation of the second messenger cGMP by PDE. The relaxant action of cGMP in smooth muscle, through the enzyme protein kinase G, its downstream effector, results in decreased intracellular calcium levels and a reduced sensitivity of the contractile elements to calcium **[10]**. The danger of neonatal mortality and morbidity is low after 34 completed weeks of gestation; although a trial of acute tocolysis may be initiated; aggressive tocolytic therapy is generally not advised before 34 weeks, due to potential maternal complications. Between 24- and 33-weeks' gestation, effects of tocolytic therapy are generally accepted to outweigh the risk of maternal and/or fetal complications and these agents should be initiated provided no contraindications exist. Although aggressive tocolysis is not typically used before beyond 34 weeks' gestation, clinicians are recommended not to deliver patients at this gestation without indication because of a higher risk of neonatal morbidity in infants born at 34-36 weeks' gestation compared with deliveries at 37-40 weeks' gestation **[11,12]**. Our aim was to show whether the combination of nifedipine and SC has more effect to nifedipine alone in terms of prevent threatened PTL and improving perinatal outcomes.

METHODS

This interventional study was conducted at Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University and Fakous General Hospital (Sharkia Governorate), from April 2019 to February 2020. Included 96 pregnant women who suffered from threatened PTL. They were divided into two classes, class (A) included 48 cases who received nifedipine only and class (B) included 48 cases who received nifedipine with sildenafil. Inclusion criteria: Singleton pregnancy between 28 and 34 weeks with intact membranes. Labour was diagnosed when painful regular uterine contractions (3-5 contractions in 10 minutes for more than one hour) associated with cervical changes. Exclusion criteria were: Multiple pregnancy, advanced cervical dilation (>4 cm), with or without membranes bulging into the vagina, ruptured fetal membranes, suspected chorioamnionitis (unexplained fetal tachycardia or maternal temperature >38°C), contraindication for nifedipine and/or SC therapy, major chronic medical disorder (such as chronic hypertension, chronic renal disease, and pregestational diabetes mellitus, as these conditions may increase risk of PTL, general contraindications to tocolytic therapy, nifedipine allergy and unwillingness to be involved in this study. Written informed consent was obtained from all patients, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work was carried out for studies involving humans in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration). patients were randomly assigned in a 1:1 ratio to two study classes using a computerized random number table. All women had an ultrasound examination before randomization to confirm gestational age. Cervical assessment by transvaginal ultrasound was also done as a screening tool to determine the likelihood of birth within 48 hours of admission. Dexamethasone in a

total dose of 24 mg was given to all patients unless given before. Patients were randomly allocated to take either (1) nifedipine 20 mg orally (stat dose), followed by 10 mg orally every 6 hours at the same time as oral administration of SC 20 mg at 8-hourly intervals or (2) nifedipine alone. Medications continued for 48–72 hours. During therapy, maternal (pulse rate, blood pressure, uterine contractions) and fetal (heart rate) monitoring was done every 30 minutes during the first 4 hours following the beginning of therapy, then every 4 hours during the rest of the treatment. Patients in both classes whose contractions stopped were followed up for an additional 24 hours to determine whether contractions returned; if they become stable, they were discharged and advised to come for follow up after 1 week. All discharged patients were taken prophylactic vaginal progesterone (Cycologest 400 mg; Actavis, Ireland and NJ, USA) to inhibit recurrent PTL. In addition to progesterone treatment, all patients were advised to undergo more periods of bed rest and also learned about symptoms of PTL.

The provided antenatal care continued at 2-weekly intervals until delivery. At delivery, all data regarding labour, along with maternal and neonatal complications, were written

STATISTICAL ANALYSIS

Data was checked, entered and analyzed using SPSS version 23 for data processing. Data was expressed as number and percentage for qualitative variables and mean ± standard deviation (SD) for quantitative one. The results of the "t" value was then checked using student "t" table at degree of freedom (df=n1 +n2 – 2) to find out the level of significance (p-value).Paired T-test:- to compare quantitative normally distributed data before and after treatment.The threshold of significance was fixed at 5% level (P-value). The smaller the P value obtained the more significant are the results.

RESULTS

(Table 1) Showed that there was no statistically significant difference between the two studied groups as regard age, body mass index (BMI), gestational age on admission, cervical length on admission**,** and cervical dilatation on admission **(Figure 1).(Table 2)** Showed that there was statistically significant difference regarding maternal heart rate before and after treatment in nifedipine with sildenafil group. But in nifedipine only group, there was no statistically significant difference regarding maternal heart rate before and after treatment. Also, there was statistically significant differences regarding maternal mean blood pressure before and after treatment in nifedipine with sildenafil group. Maternal mean blood pressure decreased significantly after treatment than before treatment. But regarding nifedipine only group, there was no statistically significant difference before and after treatment.

(Table 3) Showed that there was statistically significant difference between the two studied groups in delivery 24hours after admission with less early deliveries among the nifedipine with sildenafil group. However, there was no statistically significant difference between the two studied groups in delivery 48hours after admission with less early deliveries among the nifedipine with sildenafil group. Also, there was statistically significant difference between the two studied groups in delivery 72 hours after admission with less early deliveries among the nifedipine with sildenafil group. This study shows that there was statistically significant difference between the two studied groups in cases remained undelivered till discharge with higher deliveries among the nifedipine only group.

Table 4 Showed that there was no statistically significant difference between the two studied groups in fetal heart rate and neonatal birth weight.

Table 5 Showed that there was no statistically significant difference between the two studied groups as regard fetal outcome and the occurrence of neonatal infection. This study shows that there was statistically significant difference between the two studied groups in neonatal respiratory distress with more neonatal respiratory distress among the nifedipine with sildenafil group.

Figure 2 Showed that there was no statistically significant difference between the two studied groups in neonatal incubator admission with more neonatal incubator admission among the nifedipine with sildenafil group among the least gestational age group.

Table 1. The baseline characteristics of participants

Variable	Group (A) No. (48)	Group (B) No. (48)	t-test	P
Age (years) mean ± SD (range)	29.7±4.9 (19-38)	31.3±6.1 (20-41)	0.5	0.6
BMI mean ± SD (range)	27.7±4.6 (20-36)	28.6±5.7 (19-39)	0.4	0.7
Gestational age on admission (weeks) mean ± SD (range)	30.7±2.2 (27-34)	30.4±2.1 (27-34)	0.5	0.6
Cervical length (TVU/S) mean ± SD (range)	2.6±0.5 (1.6-3.4)	2.7±0.6 (1.5-3.5)	0.5	0.6

Table (2): Comparing maternal heart rate, mean blood pressure before, and after treatment in the studied groups:

	Before treatment No. (48)	After treatment No. (48)	Paired t-test	P
Maternal heart rate				
Group (A) mean ± SD (range)	74.5±6.2 (70-100)	79.6±4.1 (71-107)	2.1	0.07
Group (B) mean ± SD (range)	75.5±8.4 (62-100)	82.3±9.1 (67-100)	3.4	0.04*
Maternal mean blood pressure				
Group (A) mean ± SD (range)	75.5±2.6 (70-95)	76.9±4.1 (71-99)	1.3	0.7
Group (B) mean ± SD (range)	76.1±4.5 (72-97)	74.3±2.3 (72-95)	2.5	0.04*

Table 3. Primary outcomes according to treatment.

	Group (A)		Group (B)		test χ^2	P	Odds (CI 95%)
	No (48)	%	No (48)	%			
Delivery 24 hours after admission							
No	37	77.1	43	89.6	3.7	0.02*	0.4 (0.1-1.2)
Yes	11	22.9	5	10.4			
Delivery48 hours after admission							
No	28	75.6	37	86.1	0.9	0.3	0.6 (0.2-1.6)
Yes	8	24.4	6	13.9			
Delivery 72 hours after admission							
No	23	82.1	35	94.6	3.8	0.03*	0.4 (0.2-1.1)
Yes	5	17.9	2	6.5			
Cases delivered from discharged to 1 week							
Yes	13	56.5	30	85.7	9.2	0.002*	4.6 (1.4-9.2)
No	10	43.5	5	14.3			
Mode of delivery							

	Group (A)		Group (B)		test χ^2	P	Odds (CI 95%)
	No (48)	%	No (48)	%			
Vaginal	19	39.6	17	35.4	1.8	0.6	
Cesarean	29	60.4	31	64.6			

Table (4): Comparison between the two studied groups as regards fetal heart rate and weight:

Variable	Group (A) No. (48)	Group (B) No. (48)	t-test	P
Fetal heart rate mean ± SD (range)	150.5±13.4 (110-166)	153.4±11.4 (115-166)	1.1	0.2
Neonatal birth weight (Kg) mean ± SD (range)	2.8±0.3 (1.4-3.9)	2.6±0.4 (1.3-3.7)	1.1	0.5

Table (5): Comparison between the two studied groups as regards fetal outcome, neonatal infection aneonatal respiratory distress

	Group (A)		Group (B)		test χ^2	P
	No (48)	%	No (48)	%		
Fetal outcome						
Normal	37	77.1	31	64.6	1.3	0.8
distressed	8	16.7	13	27.1		
Death **Intranatal** **Postnatal**	3 0.0 3	6.3 0.00 6.3	4 1 3	8.3 1.1 6.2		
Neonatal infection						
No	40	83.3	42	87.5	0.06	0.8
Yes	8	16.7	6	12.5		
Neonatal respiratory distress						
Absent	33	68.7	41	85.4	6.6	0.02*
present	15	31.3	7	14.6		

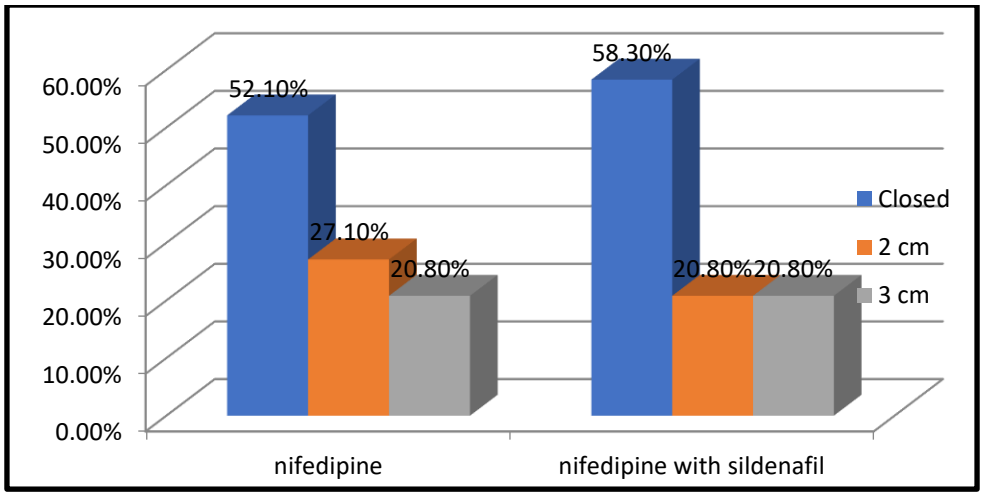

Figure (1): Bar chart for comparing cervical dilatation on admission between the two studied groups.

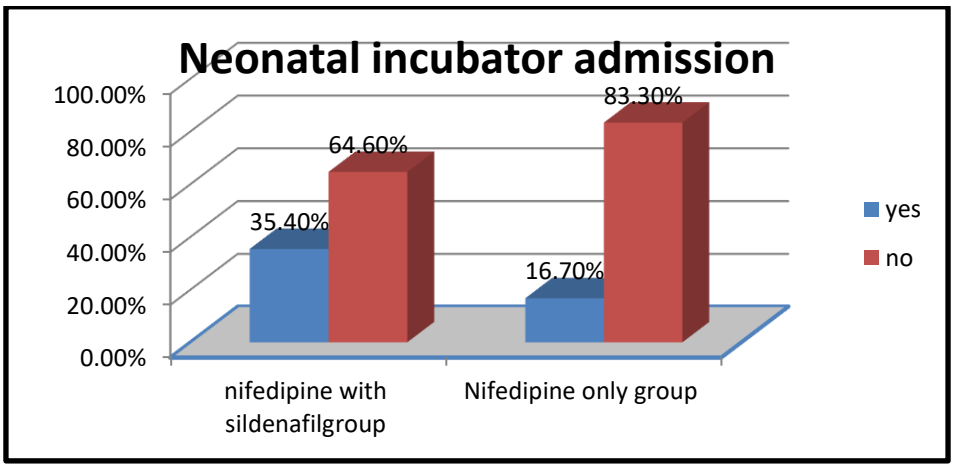

Figure (2): Bar chart for comparing neonatal incubator admission between the two studied groups**.**

DISCUSSION

Preterm birth, known as birth before the end of 37 weeks of gestation, is the single most important determinant of adverse infant production, in terms of survival and quality of life. Globally, it is the effective cause of perinatal and neonatal mortality and morbidity [13]. Preterm infants are particularly affected by complications due to impaired respiration, feeding is difficult, poor to regulate body temperature and high risk of infection [14].

Administration of tocolytic drugs can decrease the strength and times of uterine contractions. In women with acute PTL, a 2009 meta-analysis of randomized trials found that tocolytic drugs were more effective than placebo/control for delaying delivery for 48 hours (75 to 93 percent versus 53 percent for placebo/control) and for seven days (61 to 78 percent versus 39 percent for placebo/control), but not to delay delivery to 37 weeks [15]. Chiossi et al., also tested the hypothesis that SC may stimulate the tocolytic effect of nifedipine by developing an in vitro model of myometrial biopsies from full-term non-labouring women who were arranged for caesarean section. They concluded that SC, by virtue of its ability to decrease the intracellular calcium concentration, can augment the myometrial relaxing action of nifedipine. Although these compilers confirmed the potentiating action of nifedipine if combined with SC, their model was in vitro, with determination in extrapolating from in vitro testes to the in vivo situation during clinical application [16]. Our study included 96 pregnant women who suffered from threatened preterm labor. They were divided into two classes, class (A) included 48 cases who received nifedipine only and class (B) included the same number (48 cases) who received nifedipine with sildenafil. In this study there was no statistically significant difference between the two studied classes as regard age, BMI, gestational age on admission, cervical length on admission, cervical dilatation on admission. Performed a similar study from January 2015 to November 2016, 239 women were randomized: 121 given nifedipine and SC, and 118 received nifedipine alone; 226 of these completed their follow up (94.6%). No significant difference was observed between both groups as regard maternal age, parity, BMI, history of PTL, gestational age at randomization, cervical length by TVUS, total days of hospital admission, total dose of nifedipine given and compliance with progesterone therapy after discharge [17].In this study, there was statistically significant difference regarding maternal heart rate before and after treatment in nifedipine with sildenafil group. But in nifedipine only group, there was no statistically significant difference regarding maternal heart rate before and after treatment. Also, there was statistical significantly differences regarding maternal mean blood pressure before and after treatment in nifedipine with sildenafil class. Maternal mean blood pressure decreased significantly after treatment than before treatment. But regarding nifedipine only class, there was no statistically significant difference before and after treatment. In a study by Maher et al., and in time of maternal adverse events, the nifedipine–SC class reported mild symptoms (24 patients, 19.8%) such as headache, facial flushing, nasal congestion, and

dyspepsia. These adverse actions were also reported at similar rates in the nifedipine-alone class (23 patients, 19.5%). All adverse actions were self-limited and managed conservatively. Both treatment classes reported no danger from intervention to either mother or fetus [17].

This study shows that there was statistically significant difference between the two studied classes in delivery 24hours after admission with less early deliveries among the nifedipine with sildenafil class. However, there was no statistically significant difference between the two studied classes in delivery 48hours after admission with less early deliveries among the nifedipine with sildenafil class. Also, there was statistically significant difference between the two studied classes in delivery 72 hours after admission with less early deliveries among the nifedipine with sildenafil class. This study shows that there was statistically significant difference between the two studied classes in cases remained undelivered till discharge with higher deliveries among the nifedipine only class. In a study by Maher et al., there was no statistically significant difference between both class as regard delivery within 24hours and 48 hours after admission. However, there was statistically significant difference between both class as regard delivery within 72 hours. The nifedipine–SC combined with associated with more patients still undelivered (81.8 versus 68.6%; P = 0.018) during hospitalization, fewer deliveries within one week of admission (9.1 versus 20.3%; P = 0.014), and prolonged latency (29.0 versus 7 days; P = 0.002) [17]. This study showed that there was no statistically significant deference between nifedipine and nifedipine with sildenafil groups regarding mode of delivery. This study shows that there was no statistically significant difference between the two studied classes as regard fetal heart rate, fetal outcome and the occurrence of neonatal infection. This study shows that there was statistically significant difference between the two studied classes in neonatal respiratory distress with more neonatal respiratory distress among the nifedipine with sildenafil class.This study shows that there was statistically significant difference between the two studied classes in neonatal respiratory distress with less neonatal respiratory distress among the nifedipine with sildenafil class. However, there was no statistically significant difference between the two studied classes in neonatal incubator admission. Also, there was no statistically significant difference between the two studied classes in neonatal birth weight.In a study by Maher et al., combination of SC was associated with fewer entering to NICU (31.4 versus 44.1%; P = 0.043), fewer deliveries between the very preterm (from 28 to <32 weeks, 20.7 versus 38.1%; P = 0.003) and augment neonatal birthweight (1900 versus 1500 g; P = 0.018) [17].The good dose of SC in threatened PTL has yet to be detected. The usual dosage is three times daily based on maximum median plasma concentrations arrived within 60 minutes and a half-life of 4 hours McDonough, [18], but higher doses may be required in pregnancy to arrive a therapeutic plasma concentration as a result of altered plasma volume and pH [5]. This trial chose the vaginal route for intake of SC because of its action and safety, with fewer adverse systemic actions Dmitrovic et al., [19], and to limit the concern according the feto-maternal unit. We chose the dose of SC used in our study from pharmacokinetic data reported in last two studies [3, 17]. According the safety of SC, although no deleterious actions were seen between babies after delivery, there was no long-term follow up. Animal studies determined no fetotoxic or teratogenic actions for the drug even when used in high doses Villanueva-Garcia et al., [20], and 3 years' follow up in human showed no action on the overall development of the babies Premalatha et al., [4]. Furthermore, as the drug would be taken in the third trimester, the risk of gross anomalies is past, and the benefits outweigh the risks [17].

CONCLUSIONS

this study offers hope that the combination of SC with nifedipine is more effective than nifedipine alone in preventing threatened PTL. other studies with different dosage regimens, probably multicenter, are required to confirm our results and gain a better understanding of the mechanism of action of this novel therapeutic intervention.

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