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Original Research Article

A comparative study of efficacy and side effects of nifedipine with nifedipine along with dydrogesterone in management of preterm labor

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ABSTRACT

Background: Preterm labor remains one of the major cause of neonatal morbidity and mortality**.** Different tocolytics have been studied for prolongation of pregnancy, role of progesterone in increasing latency period remains controversial. Aim of the study was to compare efficacy of nifedipine with nifedipine along with dydrogesterone as a tocolytic agent in case of preterm labor and find its impact on maternal and neonatal outcome.
Methods: This study was conducted in 100 women who presented with symptoms of preterm labor, patients were then randomized to nifedipine plus dydrogesterone therapy or nifedipine treatment. Group I received Nifedipine plus dydrogesterone 10 mg and group II received only nifedipine.
Results: There was significant difference in latency period between group I and group II polongation beyond 1 week was observed in 58% in group I and 32% in group II. There is significant difference in APGAR score at 1 minute and 5 minute between patients of group I and group II. In group I, 57.4% neonates have APGAR >7 whereas in group II 31.9% neonates have APGAR >7 at 1 minute. In Group I, 89.4 % neonates have APGAR >7 whereas in group II 68.1% neonates have APGAR >7 at 5 minutes. The mean birth weight in group I was 1.86 with SD 0.35 whereas in group II it was 1.72 with SD 0.34 which is statistically significant. However, no significant difference was found between admission in neonatal intensive care unit or neonatal complications and adverse effects between 2 groups.
Conclusions: This study found dydrogesterone along with nifedipine is more effective as tocolytic in comparison to nifedipine alone.

Keywords: Dydrogesterone, Nifedipine, Preterm labor, Progesterone, Tocolytic

INTRODUCTION

Preterm labor, defined as the onset of labor between 24 and 37 completed weeks of gestation and is the most significant clinical challenge for obstetricians, globally.

Preterm birth remains one of the major causes of perinatal mortality and long-term morbidity. More than 70% of the total perinatal mortality can be attributed to preterm birth.

The major neonatal morbidity includes respiratory distress syndrome, intraventricular hemorrhage. Patent ductus arteriosus, sepsis, necrotizing, enterocolitis, periventricular leukomalacia and retinopathy of prematurity.[1] Preterm infants are found to be more at risk for neurodevelopmental handicaps like cerebral palsy, hearing loss, and blindness. There may be presence of wide spectrum of intellectual impairments.[2] The non-neurologic long term sequelae can be chronic pulmonary disease or the compromise in overall growth of the preterm baby.[3]

The goal of tocolytic therapy is to reduce neonatal morbidity and mortality by delaying birth so that corticosteroid can be administered and patient can be transfer to a tertiary care centre.[4,5] Hence, inhibition of preterm labor is of special importance in the practice of obstetrics and gynecology. Royal College Of Obstetrician and Gynecologists (RCOG) states that tocolysis should be considered if a delay of labor for a few days will allow completion of a course of corticosteroids or facilitate in utero transfer.[6]

Different tocolytic agents has been used to inhibit preterm uterine contractions to postpone delivery namely betamimetics, magnesium sulphate (MgSO4), prostaglandin synthetase inhibitors, nitric oxide donors and calcium channel blockers.

To prevent preterm birth many trials have been conducted. Progesterone is one of the most promising agents to prevent preterm labor. Different trials have been conducted to prove efficacy of progesterone in preterm birth. American College of Obstetricians and Gynecologists (ACOG) 2012 recommended supplementation of prophylactic progesterone in women with a history of preterm birth and with a short cervical to prevent preterm birth. However, the role of progesterone supplementation is still a topic of debate for use in singleton woman with preterm labor but without history of preterm birth. After successful tocolysis, progesterone was given for maintenance tocolysis in some research and it was found that it significantly prolonged the latency period, while other studies did not. However, studies conducted in vitro have investigated the use of various progesterone and showed that only dydrogesterone rapidly and directly inhibit myometrial contraction and this inhibitory effect was dose dependent.[7]

METHODS

This randomized controlled trial was conducted in the Department of Obstetrics and Gynecology at U.I.S.E.M.H., Kanpur, Uttar Pradesh, India. Written consent was obtained from all the participants after explaining it to them in the language they best understand.

Women presenting with preterm labor were admitted and those fulfilling the inclusion were randomized to tocolysis in one of the two groups. The Group-I was of nifedipine with oral dydrogesterone and Group-II was nifedipine.

The women were randomly subjected to either of the treatment protocol using computer generated random number table.

Gestational age determination was done by the date of last menstrual period (LMP) with a reliable menstrual history, an early urine pregnancy test and/or an ultrasound prior to 20 weeks of gestation. Demographic profile, detailed history with complete general physical examination including per abdominal examination per vaginal and per speculum examination was done to assess cervical dilatation and to exclude any rupture of membranes. Subjects were monitored for maternal and fetal wellbeing during the admission. All women were screened for urinary tract infections (UTI)/bacterial vaginosis with a mid-stream clean catch sample and a high vaginal swab respectively and antibiotic treatment was instituted where it was necessary patients in both groups received injection dexamethasone 6 mg intramuscular 4 dosage 12 hours apart for fetal lung maturity.

Tocolysis was initiated with an oral loading dose of nifedipine 20mg. If contractions persisted after 60 minutes, a similar dose was repeated. If labor was suppressed after the first or second dose, a maintenance dose of 10mg orally every 8 hours was given and continued until 48 hours. In Group I, Tab nifedipine adjunctive dydrogesterone tablet 10mg given 12 hourly and in Group II only Tab nifedipine was given.

Blood pressure, heart rate and fetal heart monitored every 15 minutes in 1st hour then every 30 minutes in 2nd hour and then every 4 hourly. Any side effects like nausea, flushing, headache, hypotension, fetal and maternal tachycardia were noted. Treatment was considered successful if contractions stopped and no recurrence of contractions occurred within 48 hours of stopping treatment.

The study was conducted over period of 1 year (January 2021-January 2022) and the collected data was transformed into variables, coded and entered in Microsoft Excel. Data was analyzed and statistically evaluated using SPSS-PC-25 version.

Quantitative data was expressed in mean±standard deviation or median with interquartile range and depends on normality difference between mean of two groups were compared by unpaired t test or Mann Whiney U test. Qualitative data were expressed in frequency and percentage and statistical differences between the proportions were tested by chi square test or Fisher's exact test. p value less than 0.05 was considered statistically significant.

Inclusion criteria

Inclusion criteria were women between 28 to 36weeks of gestational age based on menstrual dates or earliest USG. Preterm labor i.e. at least four painful contractions in 20 minutes, effacement of cervix <50%, cervical dilatation of >1cm but not >4cm singleton pregnancy, case with intact membranes, presence of live fetus.

Exclusion criteria

Exclusion criteria were any maternal or fetal complications e. g. antepartum hemorrhage, antepartum eclampsia, chorioamnionitis, hypotension <100/60 mmHg/shock, known case of cardiac disease non-

reassuring heart rate pattern ,fetal growth restriction, multiple gestation (twins, triples etc.), hydramnios, intrauterine fetal demise, lethal fetal anomalies, cervical dilation >4 cms, treatment with other tocolytics within 24 hours.

RESULTS

A total of 100 patients were enrolled in study 50 patients were randomized in each group. The mean age (±) SD in both groups was 23.60±2.15 and 23.76±2.52 respectively. Majority of patients were unbooked in both groups 80% and 84% respectively in groups I and group II. Majority of the patients were from rural areas in both groups and were housewife who were illiterate or had done only primary education. The mean BMI was 22.40±1.99 and 22.77±2.49 respectively in group I and group II. Only 10% patients have experienced preterm labor in previous pregnancy and 2% has experienced recurrent pregnancy loss in group I while 12% patients experienced preterm labor in previous pregnancy and 4% experienced recurrent pregnancy loss in group II .Mean gestation age at time of admission was 33.4±1.2 and 33.6±1.1 respectively and median cervical dilatation was 3cm in both groups (Table 1).

Table 1: Sociodemographic factors of participants and obstetric history.

Variables		Group I (%)	Group II (%)
Age		23.60±2.15	23.76±2.52
Antenatal visits	Booked	10 (20)	8 (16)
	Unbooked	40 (80)	42 (84)
Area of residence	Rural	36 (72)	35 (70)
	Urban	14 (28)	13 (26)
Education	Illiterate	8 (16)	9 (18)
	Primary	22 (44)	24 (48)
	Secondary	10 (20)	9 (18)
	Graduate /PG	10 (20)	8 (16)
Occupation	Working	3 (6)	3 (6)
	Housewife	43 (86)	46 (92)
	Student	4 (8)	1 (2)
Past h/o preterm labor	Yes	5 (10)	6 (12)
	No	45 (90)	44 (88)
Past h/o recurrent pregnancy loss	Yes	1 (2)	2 (4)
	No	49 (98)	48 (96)
BMI (Mean)		22.40±1.99	22.77±2.49
Gestation age at admission (mean)		33.6 weeks±1.1	33.4 weeks±1.2
Median of cervical dilatation		3cms	3cms
Gravidity	Primigravida	21 (42)	20 (40)
	Multigravida	29 (58)	30 (60)

Table 2: Maternal outcome.

		Group I (%)	Group II (%)	P value	Chi square value
Latency period	2-7 days	16 (32)	25 (50)	0.03	6.87
	>7 days	29 (58)	16 (32)		
Mode of delivery	Vaginal	40 (80)	41 (82)	1	0.06
	Caesarean	10 (20)	9 (18)		

Table 2 shows maternal outcome. There was no gross difference in mode of delivery in both groups 80% and 82% of cases delivered vaginally in group I and group II respectively. Only 20% in group I and 18% in group II underwent caesarean only due to obstetrical indications. There was significant difference in latency period with p value 0.03 (<0.05). Prolongation beyond 1 week was observed in 58% in group I and 32% in group II. Latency period was <2 days in 10% patients in group I and 18% in group II and 32% patients has latency period between 2-7 days in group I and 50% patients in group II (Table 2).

Table 3 shows neonatal outcome. In this study, the APGAR scores were better in nifedipine and adjunctive dydrogesterone group. There is significant difference in APGAR scorer at 1 minute. Among Group I, 57.4% neonates have APGAR >7 whereas in group II. 31.9% neonates have APGAR >7 p value 0.03 (<0.05). Among Group I, 89.4% neonates have APGAR >7 whereas in group II 68.1% neonates have APGAR >7 at 5 minutes p value 0.03 (<0.05). There was no significant difference in neonatal complications in both the groups there were 3 still birth in each group, Neonatal Intensive Care Unit

admissions were comparable 56% neonates in group I and 58% in group II were admitted in Neonatal Intensive Care Unit (NICU). In group I 16% neonates and in group II 26% newborns developed respiratory distress syndrome (RDS), which is statistically insignificant, p value 0.21. However only 14% in group I and 26% in group II develop RDS and required mechanical ventilation. In group I, 42% neonates and in group II 32% neonates, admitted in NICU were on room air p value 0.47 which is statistically insignificant. However 4% babies in each group developed septicemia. 8% babies expired in group I and 10% in group II, p value 1 which is insignificant (Table 3).

Table 3: Neonatal outcome.

		Group I (%)	Group II (%)	P value	Chi square value
APGAR at 1 minute	0-3	6 (2.1)	3 (6.4)	0.03	6.51
	4-6	43 (86)	29 (61.7)		
	7-10	1(2)	1 (2)		
APGAR at 5minute	0-3	0	1 (2.1)	0.03	6.61
	4-6	5 (10.6)	14 (29.8)		
	7-10	42 (89.4)	32 (68.1)		
Mean birth weight		1.86±0.35	1.72±0.34	0.04	5.86
Admission in NICU		28 (56)	29 (58)	1.0	0.83
RDS		8 (16)	13 (26)	0.21	1.50
SEPSIS		2 (4)	2 (4)	1.0	-
Ventillition		7 (14)	13 (26)	0.67	0.05
Still birth		3 (6)	3 (6)	-	-

Table 4: Adverse effects.

Adverse effect	Group I (n=50)		Group II (n=50)		p value
Headache	14	28%	18	36%	0.58
Nausea	1	2%	1	2%	-
Vomiting	1	2%	2	4%	1.0
Hypotension	1	2%	3	6%	0.36
Hot flushes	4	8%	3	6%	0.67
Maternal tachycardia	4	8%	9	18%	0.23
Dizziness	3	6%	2	4%	0.24
Palpitations	2	4%	2	6%	-

There was no maternal mortality. The most common side effect observed among patients in both group was headache 28% in group I and 36% in group II. There is no significant difference between side effects of both groups (Table 4).

DISCUSSION

In the present study, the latency period was significantly more in group I as compared to group II with P value 0.03 (<0.05). These results were similar to the study conducted by Choudhary et al who used oral micronized progesterone and Areia et al who used vaginal progesterone and found that progesterone had significantly prolonged the latency period.[8,9] This finding in present study was different from study conducted by Areeruk et al who evaluated micronized progesterone for the use of maintenance tocolysis.[10] Present study contradicted with study conducted by Thongcham et al who did not found any significant difference in mean latency period between dydrogesterone group and placebo group.[11] This contradiction in results from present study could be due to difference in the route and type of progesterone supplementation.

Regarding APGAR score results unlike results were depicted by Areia et al, Areeruk et al and Nobolt et al who found no significant difference between APGAR scores in study and control group.[9,10,12] The difference in the result may be due to the fact that majority of them included threatened preterm labor which get arrested after intervention .

Results regarding improvement in mean birth weight were similar to study conducted by Areia et al and Borna et al.[9,13] Whereas results were found contrary to studies conducted by Areeruk et al, Thongchan et al and Noblot et al.[10-12]

Regarding NICU admissions and neonatal complications similar results were obtained in study conducted by Thongcham et al, Areia et al and Areeruk et al.[9-11]

The limitation of study was small sample size. Further, multicentric trials with larger sample size needs to be conducted to substantiate results.

CONCLUSION

Overall, the dydrogesterone along with nifedipine is more effective in arresting preterm labor and maintaining tocolysis than nifedipine alone. Also, latency period was found to be statistically increased in the dydrogesterone along with nifedipine group which lead to better birth weight and better APGAR scores.

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