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A Comparative Study of Intramuscular 17 α-Hydroxyprogesterone Caproate and Oral Nifedipine in Management of Preterm Labor Pain

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Abstract: ***The aim of study was to compare efficacy and safety of intramuscular17 α hydroxy progesterone caproate and oral nifedipine in management of preterm labor. Study was conducted in 340 women divided in two groups after randomization. In group A (170 cases) single dose of injection 17 α hydroxyprogesteronecaproate (500mg) was given and in group B (170 cases) tablet oral nifedipine (30mg stat followed by 10 mg 8 hourly till 3 doses) was given. We conclude that both drugs have similar tocolytic effect, there was no statistically significant difference (p>0.005) in efficacy of these two drugs. But the prolongation of pregnancy was significantly longer (p<0.005) with 17OHPC and NICU stay was shorter (p <0.005) with 17OHPC.***

Keywords: 17 α hydroxy progesterone caproate (17OHPC), Nifedipine, Preterm labor, PROM (premature rupture of memberane)

1. Introduction

Preterm labor (PTL) is defined as onset of labor after the gestation of viability (WHO 22 weeks, India-28 weeks, UK-24 Weeks) and before 37 completed weeks (< 259 days) of pregnancy (WHO). In Preterm labor pain there is occurrence of regular and frequent uterine contractions and cervical changes (cervical length < 2.5 cm and cervical dilation >1cm) in women with intact membranes and gestational age < 37 weeks[1].Preterm birth is a common cause of neonatal morbidity and mortality. Perinatal morbidity and mortality are inversely related to gestational age, therefore delaying delivery may improve perinatal outcome. Various drugs have been used for tocolysis. Nifedipine is the first drug of choice for treatment of preterm labor. It is dihydropyridine type of calcium channel blocker and act by inhibiting smooth muscle contractions. Progesterone is a steroid hormone which plays a crucial role to maintain human pregnancy. Progesterone is important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction associated protein genes. The onset of labor at term and preterm is associated with a functional withdrawal of progesterone activity at the level of uterus.[2]This is the rationale behind the use of progesterone supplementation to prevent preterm labor and birth. In 2011 the US Food Drug and Administration (FDA) approved the use of progesterone supplementation, specifically 17 α-hydroxyprogesteronecaproate injections to reduce the risk of preterm birth.[3] In our present study we compared the effect of oral nifidipine 10mg (3 stat + 3 doses 8 hourly) and intramuscular 17 α hydroxyprogesteronecaproate 500mg (single dose) in preterm labor.

2. Material and Methods

- **Study Participants:** Primigravida with preterm labor between 28 to 34 weeks period of gestation attending ANC OPD in Department of Obstetrics & Gynaecology, SMS Medical College.
- **Study Place:** SMS Medical College, Jaipur.
- **Study Design:** Randomized control prospective study.
- **Study Type:** Hospital based comparative study.
- **Study Duration:** From June 2019 to august 2020.
- **Sample Size:** Total 340 women with preterm labor pain, 170 women for each group.

Selection Criteria:

- **Inclusion criteria:** Singleton primigravida women aged >18 years with preterm labor pain (cervical length ≤ 25mm and cervical dilation ≥1cm), Period of gestation 28 to 34 weeks, Willing to participate in the study (written informed consent).
- **Exclusion criteria**: Cervical dilation >3cm, Vaginal bleeding, PROM, Intrauterine fetal death, Uterine overdistension due to polyhydramnios or multiple gestations, Uterine anomalies, Systemic infection, Fever >38 degree C, Fetal distress, Intrauterine growth restriction, Blood pressure >160/100 and <100/60 mmHg; Medical disorders as liver disorder and heart disease.

2.1 Methodology

After applying inclusion and exclusion criteria total 340 cases were selected for the study.

Detailed history was taken regarding duration of gestation,

uterine contraction, and duration of pain, leaking, vaginal bleeding or discharge. Detailed general and physical examination was done. Per abdomen examination was done to note the fundal height, presentation, position, uterine contraction, foetal heart rate.

Routine blood and urine investigation were done.USG for foetal status, diameter of internal os, placental location, cervical length. Cervical length was measured between internal and external os and funneling is not included in length. It can be measured transvaginal or transabdominal but the transvaginal method is superior. In our study we used transabdominal method as it was acceptable by all women.

Randomization was done by coin method. All cases were divided into 2 groups-

Group A (170 cases): Inj. 17 α hydroxyprogesteronecaproate (500mg) single dose was given to this group.
Group B (170 cases): Tablet oral nifedipine (30mg stat followed by 10 mg 8 hourly till 3 doses) was given

Dexamethasone coverage was done for both groups with Inj. Dexamethasone 6mg 4 doses, 12 hour apart. Women were counselled to report for appearance of any side effect like nausea, dizziness, flushing, palpitation, allergy, oedema, pain or rash at injection site. Then cases were closely monitored for pulse rate, blood pressure, auscultation of heart and lung.

Cases were monitored by CTG for uterine contractions, noted after every 6, 12, 18, 24 hours and 48 hours and foetal heart rate was also monitored. Adequate contractions were considered when intensity was >40mmHg and 4 contractions were seen in 20 minutes tracing of CTG.

The value of uterine contractions in Montevideounits (MVU) is calculated by subtracting resting tone of uterus by its peak amplitude (recorded on CTG machine) then summing these intensities in a ten-minutes period. Those cases in whom contractions stopped within 24 hours of intervention were considered successful. All cases were followed till delivery to note interval between treatment and delivery, mode of delivery, foetal outcome in terms of Apgar score, birth weight and NICU stay. Statistical analysis was done.

3. Results and Analysis

Table 1: Demographic characteristics in two groups

S.No.	Variables (mean±SD)	Inj. 17α OHPC (n=170)	Oral Nifedipine (n=170)	P-value
1.	Maternal age (years)	21.71±1.76	21.81±1.68	0.531
2.	Gestational age at admission (weeks)	31.68±1.48	31.76±1.52	0.632
3.	BMI (kg/m^2)	21.41±1.10	21.47±1.30	0.443
4.	BISHOP score at admission	6.14±0.88	6.12±0.9	0.39
5.	Cervical length at admission(cm)	2.37±0.23	2.37±0.21	0.941
6.	Uterine Contraction (MVU) at admission	138.47±23.4	138.82±23.60	0.890

Table 2: Maternal and neonatal outcome of pregnancy in two groups (chi square and T test)

S. No.	Variables (mean±SD)	Inj. 17α OHPC	Oral Nifedipine	P-value
1.	Gestational age at delivery (weeks) (mean±SD)	34.67±2.2	34.31±2.13	0.128
2.	Gestational age (n%) Term- Preterm-	 24.7 75.3	 21.76 78.24	0.607
3.	Mode of delivery (n%) LSCS- Vaginal-	 29.42 70.58	 30.58 69.42	0.99
4.	Birth weight of newborn (Kg) (mean±SD)	2.42±0.31	2.36±0.33	0.07
5.	NICU admission (n%)	8.24	9.41	0.848
6.	NICU stay (days) (mean±SD)	5.71±3.24	18.5±11.26	0.001
7.	Apgar score at 5 min. (mean±SD)	6.92±0.31	6.88±0.40	0.293
8.	Interval between treatment and Delivery (days)	23.36±14.56	19.19±14.28	0.001

Table 3: Success of treatment in different study population

Success of treatment	Group-A		Group-B		p-value
	No	%	No	%	
<24 hours	29	17.05	31	18.23	0.887
>24 hours	141	82.95	139	81.77	
Total	170	100.00	170	100.00	

Chi-square=0.202, df= 1

Table 4: Prolongation of period of gestation in different study groups

Prolongation of delivery	Group-A		Group-B		p-value
	No	%	No	%	
<24 hours	29	17.05	31	18.23	0.99
24 hours-<48 hours	5	2.95	4	2.35	
48 hours - 7 days	17	10.00	22	12.94	
>7 days	119	70.00	113	66.47	
Total	170	100.00	170	100.00	

Table 5: Success rate in relation to cervical length

Cervical length (cm)	Group-A				Group-B				p-value
	<24 hr		>24 hr		<24 hr		>24 hr		
	No	%	No	%	No	%	No	%	
2.5	11	37.93	128	90.78	13	41.94	127	91.37	0.269
2	16	55.17	13	9.21	16	51.61	12	8.63	
1.5	2	6.89	0	0.00	2	6.45	0	0.00	
Total	29	10.00	141	100.00	31	100.0	139	100.0	

chi-square= 0.32 df=6

Table 6: Success rate in relation to uterine contraction

Uterine contraction (Montevedio units)	Group-A				Group-B				p-value
	<24 hr		>24 hr		<24 hr		>24 hr		
	No	%	No	%	No	%	No	%	
≥160	25	86.20	12	8.51	25	80.65	24	17.27	0.41
120-159	4	10.35	94	66.67	6	19.35	89	64.02	
<120	0	3.44	25	17.73	0	0.00	26	18.70	
Total	29	10.00	141	100.00	31	100.0	139	100.0	

Chi-square=0.98, df=6

Table 7: Success of treatment in relation to BISHOP score

Bishop score	Group-A				Group-B				p-value
	<24 hr		>24 hr		<24 hr		>24 hr		
	No	%	No	%	No	%	No	%	
<5	0	0.00	1	0.71	1	3.33	1	0.07	0.12
5-7	17	58.62	135	95.74	19	61.29	135	97.12	
>7	12	41.38	5	3.55	11	35.48	3	2.16	
Total	29	100.0	141	100.00	31	100.0	139	100.0	

chi-square=0.16, df=6

Total 340 women were randomized to receive either intramuscular inj. 17α hydroxyprogesteronecaproate (170 in group A) or oral nifedipine (170 in group B). Demographic characters were same in both groups. Women in both groups were statistically the same considering maternal age, residence, gestational age, BMI, Socioeconomic status, Bishop Score, cervical length and force of uterine contractions (Montevideo units) (Table:1)

Success of treatment that is prolongation of pregnancy by 24 hours was almost same in two groups. But slightly more in group A that is 82.95% and in group B 81.77% that is statistically not significant (table:3). These women further followed till delivery, Out of which 24.7% in group A and 21.76% in group B continued pregnancy till term. Mean gestational age at delivery for group A was 34.67 ± 2.2 and in group B the mean was 34.31 ± 2.13. Thus results were statistically same for both group. Mean birth weight was not significantly different in both groups. For group A it was 2.42±0.31 and for group B it was 2.36±0.33. NICU admission of newborn was 8.24% in group A and 9.41% in group B, slightly higher but statistically not significant. But NICU stay was significantly longer with oral nifedipine (18.5 ± 11.26 days) than 17 OHPC (5.71 ± 3.24). Thus neonatal outcome was better with inj. 17 OHPC. (Table 2)

Inj. 17OHPC significantly prolonged the period of gestation. In group A mean duration between intervention and delivery was 23.36 ± 14.56 days and in group B after giving oral nifedipine it was 19.19 ± 14.28 days.(p value 0.001).(table 2)
There was no significant difference between the two groups for the number of patients who delivered within 48 hours, within first week and after first week (table:4).

Success rate in relation to BISHOP score, cervical length was slightly higher for inj. 17OHPC than oral nifedipine. And with intense uterine contraction nifedipine was more effective. But statistically there was no difference in success rate of these 2 drugs in relation to BISHOP score, cervical length and uterine contractions at admission. (Table: 5, 6, 7)

Both the drug did not cause any major side effect. 5 women in group A and 6 ingroup B had minor complains as nausea, dizziness and transient hypotension with nifedipine and mild pain at injection site with progesterone.

4. Discussion

In this randomized clinical trial we compared the efficacy of inj. 17OHPC with oral nifedipine in the treatment of women with preterm labor pain. Both drugs successfully inhibited uterine contractions but inj. 17 α hydroxyprogesteronecaproate significantly prolonged the period of gestation, similar results were found in a study by Maryam Arif et al (2019)[4]. In an another study by Ladan Haghighi et al (2017)[5] to compare efficacy of intramuscular progesterone with oral nifedipine for treating threatened preterm labor has shown the success rate 83% and 82.7%, with progesterone and nifedipine respectively. Many other studies as by Rabei N. et al (2016), Xue-Mei Zhanga et al (2016) has compare the efficacy of progesterone and nifedipine and found the similar results as in our study.

These drugs can be used to treat preterm labor pain as these drugs significantly increase the duration of gestation at birth and and improve neonatal outcome by reducing NICU admission and NICU stay as these drugs give sufficient time for administration of steroids for fetal lung maturation and reduce neonatal morbidity and mortality caused by prematurity. Although there is no statistically significant difference in neonatal outcome with both drugs but the inj. 17 OHPC is associated with shorter NICU stay (5.71±3.24 days) than oral nifedipine (18.5±11.26 days) and this difference was statistically significant (p value 0.001). In a study that is carried out by LadanHaghighi et al (2017) Progesterone administration was associated with lower duration of NICU stay as compared with nifedipine. In an another study by Bushra Ashraf (2012)[6] has shown in her study the number of neonates admitted in neonatal intensive care unit and rate of Low birth weight were significantly less in group B (progesterone) than group A (nifedipine).

5. Conclusion

In this randomized controlled trial inj. 17 α hydroxyprogesteronecaproate 500 mg (single dose) and oral nifedipine (30 mg stat followed by 10 mg 8 hourly till 3 doses) proved to have similar tocolytic effect. But the prolongation of pregnancy was significantly longer with 17 OHPC and NICU stay was shorter with 17 OHPC.

Although difference of efficacy of these two drugs was statistically not significant but success rate was slightly higher with inj 17 α hydroxy progesterone caproate. And it significantly prolonged the pregnancy and significantly improved neonatal outcome.

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