www.jmscr.igmpublication.org

Impact Factor 3.79
ISSN (e)-2347-176x

Journal Of Medical Science And Clinical Research
IGM Publication
An Official Publication Of IGM Publication

To Evaluate the Effect of 17 Alpha Hydroxyprogesterone Caproate (17OHPC) As a Maintenance Tocolytic in Preterm Labor

Authors

Asma Nigar[1], Seema Hakim [2], Zehra Mohsin [3]

[1]Assistant Professor, Department of Obstetrics and Gynecology, Integral Institute of Medical Sciences and Research, Dasauli, Kursi Road Lucknow.-226026
[2]Professor, Department of Obstetrics and Gynecology, Jawaharlal Nehru Medical College, Aligarh India
[3]Associate Professor, Department of Obstetrics and Gynecology, Jawaharlal Nehru Medical College Aligarh ,India
Email- *drasmanigar@gmail.com, drseemahakim@reddifmail.com*

ABSTRACT

Aims & Objective- *To evaluate the efficacy of of 17 alpha hyroxyprogesterone caproate after acute tocolysis with nifedipine in preventing preterm delivery.*

Material & Methods- *It was a prospective clinical trial that was carried out on 100 pregnant females between 28- 34 weeks of gestation diagnosed with preterm labor pains All patients in pretrm labor were given nifedipine for acute tocolysis and antenatal corticosteroid was given to all patient for lung maturity. After tocolysis undelivered patients were randomly allocated to progesterone(n=50) and control group(n=50).Patients in Progesterone were given 17 alpha hyroxyprogesterone caproate, 250 mg, weekly and continued till 36 weeks of gestation or delivery, which ever occurred earlier. Control group were given nifedipine as a maintanencetocolysis as and when required. Results were analysed in terms of gestational age at delivery and neonatal outcome in both groups.*

Results-*Mean gestational age at delivery was 35.2±2.3 weeks in progesterone group and 35.4±2.6 weeks in control group.It was statistically similar in two groups. Neonatal outcome was also found to be statistically similar in both groups.*

key words- *preterm labor, 17 alpha hydroxyprogesteronecaproate(17OHPC), nifedipine*

INTRODUCTION

Preterm labor and preterm births are the major cause of mortality and morbidity, and are huge burden on the cost of health care prominence. Birth before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks[1]- Despite intensive research efforts over the past 3 decades incidence of preterm birth has increased up to 20 percent[2]. Among them, 40- 50 percent preterm births are due to spontaneous preterm labor.

The pathogenesis of preterm labor is not well understood and it is often not clear wether preterm labor represents early idiopathic activation of the normal labor process or results from pathologic[3].Exact mechanism of action of progesterone is unclear, it is assumed to maintain uterine quiescence through inhibition of mymetrial oxytocin response[4]. Progesterone has been used as a therapeutic agent for preterm labor since 1960[5].The elevated intrauterine concentration of progesterone in early pregnancy may promote pregnancy maintanence [6]. Progesterone plays an important role inpregnancy progression [7]

17 aiphahydroxyprogesterone caproate (17OHPC) is a synthetic progestin, is made artificially by converting natural progesterone into a synthetic progestin by esterification of 17OHP with caproic acid. Current evidence supports the use of 17OHPC therapy in beginning in the second trimester of gestation and continued weekly till 36 weeks of gestation, in women with history of previous one or more preterm births [8].

Women who experience episodes of spontaneous preterm labor, but who remain undelivered after acute tocolysis are at risk of subsequent episodes of preterm labor and may require hospitalisation and preterm delivery. Randomized controlled trials have found that over all recurrence rates after treatment of spontaneous labor were 21 percent [9].

The present study was designed to evaluate the effectiveness of 17 alpha hyroxyprogesterone caproate as a maintanence tocolytic in delaying delivery in women preterm labor pains which were arrested by acute tocolysis .comparison was done between 17 alpha hyroxyprogesterone caproate and nifedipine.

MATERIAL AND METHODS

This was a randomized prospective case control study. After obtaining approval from ethical committee and written informed consent, 100 patients were included in the study

Inclusion criteria-

Patients between 28- 34 weeks of gestation with preterm labor pains Cervical dilatation 1-4 cm, Live fetus Intact membranes.

Exclusion criteria-

Cervical dilatation >4cm, Ruptured membranes, Intrauterine death, Fetal anomalies , Uterine anomalies, Short cervix, cervical circlage, Contraindication to tocolysis, Coexisting medical disease like hypertension, seizures, thromboembolic disorder, heparin therapy ,age <18 yrs.

On admission to the ward diagnosis was established .nifedipine 30 mg stat was given to all patients, followed by 10 mg, 8 hrly to arrest acute episode.

Simultaneously antenatal corticosteroid was given for lung maturity. After arrest of labor undelivered 50 patients were randomly allocated to progesterone and were given weekly intramuscular injection of 17 alpha hyroxyprogesterone caproate which was continued till 36 weeks of pregnancy or delivery which ever occurred earlier. All injections were given by trained nurses who were blinded about the type of drug. 50 patients who were kept on nifedipine were treated as control groups.

Demographic data like age, parity, social class, height, weight were asked by each patient, Both the groups were monitored by Maternal pulse rate, BP ,FHS and clinical assessment of uterine activity and cervical dilatation. Side effects of drugs were noted. Response was assessed by symptomatic relief, arrest of cervical changes and continuation of pregnancy. Outcome of the pregnancy was assessed by Primary outcome- delivery >37 weeks, delivery<37weeks, delivery<35weeks, delivery<32 weeks, Secondary outcome was -neonatal outcome- Live/stillbirth, Birth weight, septicemia, Respiratory distress syndrome, hyper bilirubenemia, necrotisingenterocolitis, ventilatorysupport, Intraventricular Haemorrhage.

Statistical analysis was done by applying t –test and chi-square test .To find out significance, p-value <0.05 and t value >2 was considered significant for evaluating the result.

RESULT

The demographic profile of the study population is shown in [table 1] .Mean age was 25.5±3.7years in progesterone group and 26.2±3.1years in control group (t =.7), which was similar. Likewise both groups were similar regarding parity, weight, height, BMI, social class. At the time of admission, condition of cervix as assessed by bishops score, which was similar in the two groups .No significant difference was observed in the previous preterm deliveries which is considered to be a major risk factor for preterm delivery.

At the time of admission mean gestational age was 31.8±1.6 weeks in progesterone group and 32.3 ±1.3 weeks in control group which was statistically similar.[table 2]

Gestational age at the time of delivery was 35.2±2.3 weeks in progesterone group verses 35.4 ± 2.6 weeks in control group. On analysis is no significant difference was found (p value=1).[table 3].

Table 4 shows prolongation of pregnancy in the two group's .Mean days prolonged were 24.5±11.9 days in progesterone group and were 25.2 ±12.6 days in control group. It was similar in both groups.

Table (5) Neonatal outcome shows that mean birth weight was 2.4±0.7kg in progesterone group and 2.4 ±0.6kg in control groups. Other complication of prematurity like RDS (24 % and 20 %), septicaemia (12 % and 4 %), hyper bilirubenemia, (40% and 36 %), Intraventricular haemorrhage (6 % and 4%), Necrtotising Enterocolitis (4 %in both), and ventilator support (4% and 6 %)were observed in progesterone and control group respectively. Neonatal morbidities were found to be more in progesterone group, although this difference was not found to be significant.

Neonatal deaths as shown in [table 6] was 12% .in progesterone group and 8% in control group that was not significant (p value= 0.654).

The most common side effect of 17 alpha hyroxyprogesterone caproate were pain (40%) ,injection site swelling (13%), urticaria (5%) , pruritis (0%) and nausea(0%).[table7]

In the control group who were treated with nifedipine only, tachycardia was seen in58% patients and was troublesome. Other side effects noted were hypotension (22%), hot flushes (11%), headache (16%) nausea (4%), chest pain (2%) [table 8]

Table-1

characteristic	progesterone (n=50)	control (n=50)	P value
Age	25.5 ±3.7	26.2±3.1	NS
Height	151 ± 4.8	150.8±4.7	NS
Weight	51.4±4.2	50.3±3.7	NS
Bmi	22.3±2	22±.4	NS
Social class	5.2±4.9	5±4.3	NS
parity	1.5±1.3	1.4±1.2	NS
Cervical length	2.1±.4	2±.3	NS
Bishop score	4±.8	3.9±1	NS

NS- Not significant

Table 2 Gestational age at the time of admission

Gestational age (in weeks)	Progesterone(n=50)	control (n=50)	P value
<31	28 %	20 %	NS
31-34	64 %	72%	NS
34-36	8 %	8 %	NS
Mean ±sd	31.8±1.6	32.3±1.3	NS

P value=0.5 not significant

Table 3 Gestational age at the time of delivery

Gestational age in weeks	Progesterone (n=50)	Control (n=50)	P value
<31 weeks	4 %	8%	NS
31- 34	24 %	16%	NS
34-36	28 %	24%	NS
36-39	44%	52 %	NS
Mean± SD	35.2±2.3	35.4±2.6	NS

P value =1

Table4Mean Days Prolonged (mdp) in progesterone &control group

Days gain	Progesterone N=50	controls N=50	P value
	mdp (Days)	mdp (Days)	
1-15	6.6±5.1	10.2 ±4.9	(0.338) NS
15-30	23±5.1	22.1±3.1	(0.704) NS
31-45	43.8±1.8	44.1±3.1	(0.611) NS
Mean ± SD	24.5±11.9	25.2±12.6	(0.338) NS

Table 5 Neonatal outcome

Characteristic	progesterone (n=50)	Control (n=50)	P value
Birth wt	2.4±.7	2.4±0.6	(1) NS
septicemia	12%	4%	(0.469) NS
RDS	24%	20 %	(0.469) NS
Ventilatory support	4 %	6 %	(0.442) NS
hyperbilirubenemia	40 %	36 %	(0.5) NS
IVH	6%	4%	(0.5) NS
NEC	4%	4%	(0.5) NS

Table 6 Neonatal death

Outcome	progesterone (n=50)	Control (n=50)
Alive	88%	92%
Death	12%	8%

P value =0.654, Not significant

Table 7 Side effects of 17 alpha hyroxyprogesteronecaproate

S.No.	Side effects	%
1	Pain	40
2	Injection site swelling	13
3	Urticaria	5
4	pruritis	5
5	nausea	0
6	Injection site nodule	0

Table 8 Side effects of control

S.No.	Side effects	%
1	Tachycardia	58
2	hypotension	22
3	Nausea	4
4	Chest pain	11
5	Hot flushes	16
6	headache	2

DISCUSSION

The incidence of spontaneous preterm births has increased and its management remains suboptimal .while considerable debate remains as to whether long term maintenance tocolysis is appropriate after an episode of spontaneous preterm labor. Several drugs have been used for maintenance tocolysis but they differ in terms of safety and efficacy.

Women who experience episodes of spontaneous pretermlabor, but ho remain undelivered after tocolysis are at risk of subsequent episodes of spontaneous preterm labor and may require hospitalisation and preterm delivery. Randomised controlled trials have found that overall recurrence rate after treatment of preterm labor was 17 %[10].

Although there is no consensus as to wether long term tocolysis is appropriate after an episode of spontaneous preterm labor, many practitioners support its use.

A recent survey by the society for maternal and fetal medicine found that 41 % of respondents would use maintanence tocolysis with arrested preterm labor at 31±2 weeks of gestation [11].

The present study was done to evaluate the effectiveness of 17 alpha hydroxyprogesterone caproate (17OHPC) as a maintanence tocolytic in those patients who remain undelivered after acute tocolysis and as a maintanence tocolytic. 17alpha hydroxyprogesteronecaproate injections were given weekly to progesterone group and nifedipine was given to control group as and when required.

Exact mechanism of action 17alpha hydroxyprogesterone caproate therapy in preventing preterm labor and delivery is not known . Various trials in past have suggested that progesterone therapy has no significant effectiveness when used to halt labor or as an adjunct to the use of other drugs to stop labor.

Kaupila et al (1980) [12] compared 17alphahydroxyorogesterone caproatewith ritodrine

in threatened premature labor and concluded that prolongation of pregnancy was statistically similar between two groups.

Borna et al reported that gestational age at delivery was 36.7 weeks in progesterone group and 34.5 weeks in control group , although this difference was not found to be significant (p value=.041). Neonatal morbidities in terms of NICU admission, respiratory distress, etc were similar in both groups.[13]

Recently a randomized controlled trial found that 17hydroxyprogesterone caproate given weekly to the patients in whom preterm labor was successfully arrested after tocolytic treatment, did not prolong pregnancy successfully [14]

Latest study as reported by Tan et al ,used 17hydroxyprogesterone caproate , single dose of 250 mg ,intramuscularly as an adjunct to nifedipin etocolysis in preterm labor and concluded that single dose of 17alphahydroxyprogesterone caproate in combination with nifedipine tocolysis for threatened preterm labor did not delay delivery[15]

In our study recurrence rate of preterm birth before 34weeks after successful tocolysis was found to be 26% . The mean gestational age at the time of admission was 31.8 $\pm$ 1.6 weeks in progesterone group and 32.3 $\pm$1.3 weeks in control group , difference was not found to be significant (p value=0.5). This is the group of women who are most benefitted by the supportive tocolytic therapy. Mean gestational age at delivery was 35.4 $\pm$2.3 weeks in progesterone group and 35.4 $\pm$2.6 weeks in control group , it was not significantly different between the two groups.

Neonatal morbidity and mortality were not significantly different in progesterone and control groups.

CONCLUSION

In our study it was found that mean gestational age at delivery and prolongation of pregnancy was similar in 17 OHPC (17alpha hydroxyprogesterone caprote) and nifedipine treated patients. Neonatal outcome was also similar in both groups. .How ever nifedipine was associated with more side effects compared which weekly administration of 17 alpha hyroxyprogesterone caproate was associated with no side effects other than pain &local irritation .So we can conclude that patients with preterm labor , arrested by tocolytics can be given 17alphahydroxy progesterone caproate as a maintanence tocolytic as a suitable alternative to nifedipine .But to warrant the use of 17alphahydroxyprogesterone caproate as a maintanence tocolytic routinely, large randomized controlled trials are needed.

REFERENCES

1. Marlow N, Wolke D, Bracewell MA et al.*Neurological and developmental disability at six yers of age after extremely pre term birth*.N Engl J Med2005 ;352:9-19.
2. National centre of health statistics. Birth final data for 2002 accredfeb7 ,2005
3. Robert L, *the management of preterm labor*. Obstet Gynecol-2002 ;100:1020-1037

4. Boagarki M, Silvia WJ - *Direct inhibitory effect of progesterone in oxytocin induced secretion of prostaglandin F2 from bovine endometrial tissue*. Biol; 67: 184, 2002
5. Levine L. Habitual Abortion. *A controlled clinical study of progestational therapy*. West J Surg Obste tGynecol 1964;72:30-36 .
6. Berek & novacs gynecology. 15th Ed Lippincott Williams &Wilkins a Wolters Kluvers Business. 2012;1206-1207
7. Astle S, slater DM, Thornton S. *The binvolvement of progesterone in the onset of human labor*. Eur J Obstet Gynecol Reprod Biol 2003;108: 177-181
8. 17OHPC for the prevention of preterm delivery-*Meis P J, society for maternal and fetal medicine*, Obstet Gynecol. 2005may; 105(5 pt1):1128-35.
9. *The world wide atosiban verses beta agonist study group. effectiveness and safety of atsiban versesbeta adrenergic agonist in the treatment of Preterm labor*. BJOG 2001;108:133-42
10. Motquin JM, Sherman D,Cohen H,Mohid P et al-*double blind randomised controlled trial of atosiban and ritodrine in the treatment of preterm labor* –a multicentric effectiveness and safety study. Am J Obstet Gynecol2000; 18:1191-9
11. Norwitz ER, Bahtiyar MO, Sibai BM, et al-*Defining standards of care in maternal fetal medicine*. Am J Obstet Gynecol 2004;191:1491-6
12. Kaupilla et al., *suppression of threatened premature labor by administration of cortisol and 17 alpha hydroxy progesterone caproate - A comparison with ritodrine*. Am J. Obstet gynecol. 1980, 138:404.
13. BornaS, Sahabi N .*Progesterone therapy for maintanencetocolytictherapy after preterm labor ;a randomised controlled trial*; Aust NZ J ObstetGynecol 2008
14. Rozenberg P, Chauveaud A, Dervelle P et al ..*Prevention of preterm delivery after successful tocolysis in preterm labor by 17alpha hydroxyprogesterone caproate; a randomised controlled trial* ..Am J Obstet Gynecol.2012;206: e 1-9
15. Tan PC, King AS, Vallikkannu N,Omar SZ et al –*effect of single dose of 17OHPC intramuscularly as an adjunct to tocolysis in preterm labor*. Arch Gynecol Obstetric 2012; march :285(3):585-90