COMPARISON OF THE EFFICACY OF PROGESTERONE AND NIFIDIPINE IN INHIBITING THREATENED PRETERM LABOR: A RANDOMIZED CONTROLLED STUDY

Protocol of Thesis

Submitted for Partial Fulfillment of the Master Degree
in Obstetrics and Gynecology

By

Alaa Sultan Mohammed

M.B.B.Ch, 2010
Ain Shams University
Resident of Obstetrics and Gynecology
Luxor International Hospital

Under The Supervision of

Dr. Noha Hamed Rabei

Assistant Professor of Obstetrics and Gynecology
Faculty of medicine - Ain shams university

Dr. Mohammed Osama Taha

Lecturer of Obstetrics and Gynecology
Faculty of Medicine - Ain shams University

Faculty of Medicine
Ain shams University
2014

Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality, and its prevention is an important healthcare priority **(The National academies press, 2007**). Threatened preterm Labor was defined as regular uterine contractions occurring at the frequency of at least one contraction in 10 minutes with no effacement and dilatation of the cervix between 20-37 weeks .The examination was taken for at least 30 minutes **(Chawanpaiboon, 2010)**. In 2005, 12.9 million births worldwide were preterm **(Beck et al, 2010).** Preterm Labor is the onset of regular uterine contractions associated with progressive cervical change between viability and 37 completed weeks of gestation. The incidence is between 5% and 10% in most developed nations. In the US, the incidence has increased from 9% to 12% in the past two decades**.** Preterm delivery can be associated with immediate and long-term neonatal complications. Long-term morbidity includes cerebral palsy, neurodevelopment delay and chronic lung disease. The lower the gestational age, the higher the risk of mortality and morbidity .The management of preterm Labor involves identification of high-risk women, prevention and treatment **(Jayanta et al, 2007).**

Progesterone is useful in allowing pregnancy to reach its physiologictem because at sufficient levels in the myometrium, it blocks the oxytocin effect of prostaglandin F2α and α-adrenergic stimulation and therefore, increases the α-adrenergic tocolytic response **(Fuchs et al, 1984).**Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. This is not true for certain artificial progestagens **(Keelan et al, 1997).** Progesterone has long been considered important agents in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of PTD **(Da Fonseca et al, 2003 - Noblot et al, 1991).** In study published in 2007, vaginal progesterone treatment reduced the rate of preterm birth among women who were at high risk for preterm labor because of short cervix **(Eduardo et al, 2007).**Progesterone has also been shown to delay parturition in animals **(Whitely et al, 1990).**

Calcium-channel Blockers interfere with the calcium ions transfer through the myometrial cell membrane. They decrease intracellular free calcium concentration and induce myometrial relaxation **(Simhan et al, 2007).** Nifidipine was first reported in 1980 in an observational study to be an effective tocolytic agent with minimal side effects (**king et al, 2003**). Nifedipine is an efficient tocolytic agent, with an easy oral route of administration, few side effects and a low neonatal complications rate .However, it should be used with caution in patients with compromised cardiovascular

condition as they may be at risk of pulmonary oedema and cardiac failure ***(Smith et al, 2009).*** The efficacy of maintenance tocolytic therapy after successful arrest of preterm Labor remains controversial. This question is not limited to the use of specific drug as the data are similar for terbutaline, magnesium sulfate, and calcium channel blockers ***(Sanchez-Ramos et al, 1999).***

Aim of the Work

Research question:

In pregnant Women with Threatened preterm Labor, Does progesterone has efficacy as that of Nifidipine in treatment of Threatened preterm Labor?

Research Aim:

Comparing the efficacy of progesterone with that of Nifidipine in treatment of Threatened preterm Labor .

Research hypothesis:

In pregnant Women with Threatened preterm Labor, The efficacy of progesterone equal to that of nifedipine as a tocolytic drug in treatment of threatened preterm Labor .

Patients and Methods

Study design:

- **Type of the study:** A randomized controlled study .All patients will be enrolled in the study after obtaining a written consent.
- **Setting:** This study will be carried in the outpatient clinic of Ain shams maternity Hospital.

- **Statistical Methods:**

-Sample size justification:

Sample size:

Sample size will be calculated using **Epicalc 2000** software With the following inputs:

The minimal sample size was 150 and Data from ***(Chawanpaiboon S et al, 2009)***

- Type I error (α) =5% with confidence level 95%

- Study power 90 % (power of test) with type error II 10% (Beta)

- The significance level (α) at 0.05

Source of funding: No funding.

- **Inclusion criteria:**
    - ***Singleton pregnancy in cephalic presentation with gestational age between 28-36 weeks.***

- ***Uterine contractions at least one contraction in 10 minutes. The examination was taken for at least 30 minutes.***
- ***Intact membranes.***
- ***No cervical effacement.***
- ***No cervical dilatation.***

- **Exclusion criteria:**
  - ***Serious maternal illness.***
  - ***Cardiovascular diseases.***
  - ***Diabetes mellitus.***
  - ***Bronchial asthma.***
  - ***Pregnancy induced hypertension***
  - ***Severe anemia***
  - ***Multiple pregnancy and polyhydromnios***
  - ***Malpresentation***

- **Methods :**

The women will be subjected to the following:

1. Detailed history taking

2. Clinical examination:

(a) General examination: pulse, temperature, blood pressure, body weight and height, body mass index.

(b) Abdominal examination.

3. **Ultrasonography** to calculate gestational age, fetal growth, amniotic fluid and to exclude any congenital malformation.

4. **All routine investigations:** C.B.C., Rh, blood grouping, blood sugar, kidney functions tests, liver enzymes.

5. Complete urine analysis and culture & sensitivity.

6. Cusco examination under complete aseptic technique.

7. All pregnant women will be distributed randomized in to two groups:

- Group 1: pregnant females who will use natural Progesterone 400mg per day vaginally as a tocolytic agent.
- Group 2: pregnant females who will use nifedipine 20mg orally every 30 minutes for 3 times then maintenance with nifedipine SR 20mg every 12hours .

8. The primary outcome is the inhibition of Threatened preterm Labor.

9. Treatment will be continued to two weeks to inhibit contractions. The inhibition of Labor had been prolonged until end of 37 weeks of gestation.

10. Randomization Table

1	Nifedipine	31	Nifedipine	61	Nifedipine	91	Progesterone	121	Nifedipine
2	Progesterone	32	Progesterone	62	Progesterone	92	Progesterone	122	Progesterone
3	Progesterone	33	Nifedipine	63	Progesterone	93	Nifedipine	123	Progesterone
4	Nifedipine	34	Nifedipine	64	Nifedipine	94	Nifedipine	124	Progesterone
5	Nifedipine	35	Nifedipine	65	Nifedipine	95	Nifedipine	125	Progesterone
6	Nifedipine	36	Nifedipine	66	Progesterone	96	Nifedipine	126	Progesterone
7	Progesterone	37	Progesterone	67	Nifedipine	97	Progesterone	127	Nifedipine
8	Progesterone	38	Nifedipine	68	Progesterone	98	Nifedipine	128	Progesterone
9	Nifedipine	39	Progesterone	69	Progesterone	99	Nifedipine	129	Nifedipine
10	Nifedipine	40	Nifedipine	70	Nifedipine	100	Nifedipine	130	Nifedipine
11	Progesterone	41	Nifedipine	71	Progesterone	101	Nifedipine	131	Progesterone
12	Nifedipine	42	Progesterone	72	Nifedipine	102	Nifedipine	132	Progesterone
13	Progesterone	43	Progesterone	73	Progesterone	103	Nifedipine	133	Progesterone
14	Nifedipine	44	Progesterone	74	Progesterone	104	Progesterone	134	Nifedipine
15	Nifedipine	45	Nifedipine	75	Progesterone	105	Progesterone	135	Progesterone
16	Nifedipine	46	Nifedipine	76	Progesterone	106	Nifedipine	136	Nifedipine
17	Progesterone	47	Nifedipine	77	Progesterone	107	Nifedipine	137	Nifedipine
18	Nifedipine	48	Progesterone	78	Nifedipine	108	Nifedipine	138	Nifedipine
19	Nifedipine	49	Progesterone	79	Progesterone	109	Progesterone	139	Progesterone
20	Nifedipine	50	Nifedipine	80	Progesterone	110	Progesterone	140	Progesterone
21	Nifedipine	51	Nifedipine	81	Nifedipine	111	Progesterone	141	Progesterone
22	Nifedipine	52	Progesterone	82	Progesterone	112	Progesterone	142	Nifedipine
23	Progesterone	53	Progesterone	83	Progesterone	113	Progesterone	143	Nifedipine
24	Progesterone	54	Progesterone	84	Progesterone	114	Progesterone	144	Progesterone
25	Nifedipine	55	Nifedipine	85	Progesterone	115	Nifedipine	145	Nifedipine
26	Nifedipine	56	Nifedipine	86	Nifedipine	116	Progesterone	146	Nifedipine
27	Nifedipine	57	Progesterone	87	Progesterone	117	Nifedipine	147	Nifedipine
28	Progesterone	58	Progesterone	88	Progesterone	118	Progesterone	148	Nifedipine
29	Nifedipine	59	Progesterone	89	Nifedipine	119	Progesterone	149	Progesterone
30	Progesterone	60	Progesterone	90	Nifedipine	120	Nifedipine	150	Progesterone

Statistics

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, unpaired student t-test, Mann-Whitney test, linear correlation coefficient and chi-square tests by SPSS V17.

1. Mean = $\frac{\Sigma x}{n}$

Where Σ = sum & n = number of observations.

2. Standard Deviation [SD] :

$$SD = \sqrt{\frac{\Sigma \left| x - x \right|^{-2}}{n-1}}$$

3. Standard Error [SE]:

$$SE = \frac{SD}{\sqrt{n}}$$

Student t-test [Unpaired]:

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{SE_1\,2 + SE_2\,2}}$$

Where:

$\overline{X}_1$ = Mean of the first group .

$\overline{X}_2$ = Mean of the second group .

SE_1 = Standard error of the first group.

SE_2 = Standard error of the second group.

Unpaired Student T-test was used to compare between tow groups in quantitative data.

Mann-Whitney

A nonparametric equivalent to the t test. Tests whether two independent samples are from the same population. It is more powerful than the median test since it uses the ranks of the cases. Requires an ordinal level of measurement. U is the number of times a value in the first group precedes a value in the second group, when values are sorted in ascending order

Chi-square the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Fisher's exact test and Yates' corrected chi-square are computed for 2x2 tables.

Linear Correlation Coefficient [r]:

$$r = \frac{\Sigma \left(X - \overline{X}\right)\left(y - \overline{y}\right)}{\sqrt{\left\{\Sigma \left(X - \overline{x}\right)2 \right\}\left\{\Sigma \left(y - \overline{y}\right)2\right\}}}$$

Where :

X= Independent variable.

Y= Dependent variable.

Linear Correlation coefficient was used for detection of correlation between two quantitative variables in one group.

References

Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, van look PF, Bull world health organ(2010): The Worldwide incidence of preterm birth :a systematic review of maternal mortality and morbidity . 88: 31 – 38.

Chawanpaiboon S, Sutantawibul A, Pimol K, Sirisomboon R, Worapitaksanond S (2009): comparison of the efficacy of progesterone and Nifidipine in inhibiting threatened preterm Labor in siriraj Hospital ,Thai Journal of obstetrics and Gynecology, January 2009, vol. 17, pp. 23-29.

Chawanpaiboon S (2010): Clinical practice guidelines: management of preterm Labor. Department of Obstetrics Gynecology, Faculty of Medicine, Siriraj Hospital. Mahidol University.

Da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M (2003): Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo –controlled double- blind study. Am J obstet gynecol 2003; 188:419- 424 .

Eduardo B, Fonseca MD, Ebru celik MD et al (2007): Progesterone and the risk of preterm birth among women with a short cervix. N Engl I med 2007; 357: 462-469.

Fuchs AR, Fuchs F (1984): Endocrinology of human parturition. a review. Br J Obestet gynaecol 91: 948-967.

Jayanta Chatterjee, Joanna Gullam, Manu Vatish and Steve Thornton, (2007): The management of preterm Labor. Arch Dis.Child. Fetal Neonatal Ed.; 92; 88-93.

Keelan JA, Myatt L, Mitchell MD (1997): Endocrinology and paracrinology of parturition. In: Elder MG, lamont RF, Romero R, (Eds) preterm Labor. Churchill livingstone, Philadelphia pp : 457-491.

King JF,Flenady VJ, Papatsonis DNM, Dekker GA, Carbonne(2003) : Calcium channel blockers for inhibiting preterm Labor .Cochrane Database of systemic reviews 2003 ,Issue 1 . Art. No.:CD002255 .DOI:10.1002/14651858.CD002255.

Noblot G, Audra P, Dargent D et al. The use of micronized progesterone in the treatment of menace of preterm delivery (1991): Euro J obstet gynecol Reprod Biol 1991;40: 203-209.

Sanchez-Ramos L ,Kaunitz AM, Gaudier FL, Delke I , The efficacy of maintenance therapy after acute tocolysis (1999) : Meta-analysis. Am J obstet gynecol 1999; 181 :484-490 .

Simhan H.N. and Caritis S.N. (2007): "Prevention of preterm delivery," the New England Journal of medicine, vol.357, no.6, pp.477-487.

The National academies press: Washington D.C., (2007): Committee on Understanding Premature Birth and Assuring Health Outcomes, Broad on Health Sciences Policy .Preterm birth Causes ,Consequences, and Prevention, Behrman RE, Butler AS (eds) .Institute of Medicine of the National academies.

V. Smith, D. Devane, C.M.Begley, M. Clarke, and Higgins (2009): "A systematic review and quality assessment of systematic reviews of randomized trials of interventions for preventing and treating preterm birth" European Journal of Obstetrics and Gynecology and Reproductive Biology, vol. 142,pp.3-11.

Whitely JL, Hartman PE, Willcox DL, Bryant – Greenwood GD, Greenwood FC (1990): initiation of parturition and lactation in the sow : effects of delaying parturition with medroxyprogesterone acetate J Endocrinal 124: 475- 484.

مقارنة بين فعالية البروجسترون و النيفيدبين في تثبيط الآم الولادة المبكرة المنذرة : دراسه عشوائيه

رسالة

توطئة للحصول على درجه الماجستير في إمراض النساء والتوليد

مقدمه من

الطبيب/ علاء سلطان محمد

بكالوريوس الطب والجراحة

(جامعه عين شمس – ٢٠١٠)

طبيب نساء وتوليد بمستشفي الاقصر الدولي

تحت إشراف

أستاذ مساعد / نهى حامد ربيع

أستاذ مساعد أمراض النساء والتوليد

كليه الطب– جامعه عين شمس

د/ محمد أسامه طه

مدرس أمراض النساء والتوليد

كليه الطب– جامعه عين شمس

كليه الطب

جامعه عين شمس

٢٠١٤