COMPARATIVE STUDY BETWEEN CALCIUM CHANNEL BLOCKER AND PROGESTERONE THERAPY IN PREVENTION OF RECURRENT PRETERM LABOR

By

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ABSTRACT

Background: Preterm labor (PTL) is the leading cause of perinatal and neonatal morbidity and mortality and strongly related to the developmental and neurological disabilities later in life.

Objective: To compare between calcium channel blocker and progesterone in the prevention of Preterm Labor in patients with history of recurrent spontaneous preterm labor.

Patients and Methods: A comparative clinical study was done at Al-Hussein Hospital on one hundred pregnant women with history of previous spontaneous preterm labors were selected in this study, and randomly arranged into two groups: calcium channel blocker group (A), and progesterone group (B).

Results: There was no statistically significant difference between all groups as regards age, parity and number of previous preterm labors, There was a statistically significant difference between the progesterone group and the calcium group as regards GA at delivery, with higher percentage of lower GA at delivery among the progesterone group (35.61 weeks) compared to the calcium group (37.11 weeks), There was a statistically significant difference between the progesterone group and the calcium group as regards mean values of birth weight with higher percentage of lower birth weight among the progesterone group (2.37 kg) compared to the calcium group (2.93 kg), There was a statistically significant difference between the progesterone group and the calcium group as regards mean values of five minutes APGAR Score with higher percentage of lower five minutes APGAR Score among the progesterone group (7.66) compared to the calcium group (8.57), There was no statistically significant difference between all groups as regards the mode of delivery. There was a statistically significant difference between the progesterone group and the calcium group as regards NICU admission with higher percentage of NICU admission among the progesterone group (40%) compared to the calcium group (17.1%), There was a statistically significant difference in different studied groups before and after progesterone administration as regards mean values of serum progesterone, There was a statistically significant difference in different studied groups before and after progesterone administration as regards mean values of serum calcium.

Conclusion: The use of calcium channel blocker and progesterone reduced the rate of preterm labor, prolonged gestational age at delivery, reduced the frequency of uterine contractions, and improved the symptoms of preterm labor in women with history of recurrent spontaneous preterm labors. Calcium channel blocker was more superior on progesterone as regards prevention of recurrent preterm labor.

Key words: Preterm labor - progesterone - calcium channel blocker.
INTRODUCTION

Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (before completing 37wks of gestation) (ACOG practice bulletin no. 127, 2012).

The incidence of this problem is rising and is reported to be 15% of pregnancies in the developed world. So, its prevention is considered a major challenge for obstetricians (Chen et al., 2019).

By gestational age, 5% of preterm labors occur at less than 28 weeks (extreme prematurity), 15% at 28-31 weeks (severe prematurity), 20% at 32-33 weeks (moderate prematurity), and 60-70% at 34-36 weeks (near term) (Lipi et al., 2013).

Survival of the preterm infant is directly related to gestational age at delivery. Survival increases from less than 50% before 24 weeks to more than 95% by 33 weeks' gestation and there is a corresponding inverse relationship between the risk of severe disability in survivors and gestational age at delivery (Chenet et al., 2019).

Complications from preterm birth are not limited to the neonatal period such as in retinopathy of prematurity, intraventricular hemorrhage, necrotizing enteric colitis, respiratory disorders and sepsis. They can also constitute sequelae such as abnormal neurophysiological development in early childhood and underachievement at school (Nayeri et al., 2018).

The early detection of pregnant women at high risk for preterm labor could be the best way to prevent preterm labor (Urquhart et al., 2017).

Most common interventions recommended to prevent preterm birth have been proved to have a little or no benefit. However, bed rest, once universally advocated, is now largely historical. Cerclage, antibiotics or tocolytics may be beneficial only in specific circumstances (Lucovnik et al., 2011).

Calcium channel blockers exert their tocolytic effect by preventing the influx of extracellular calcium ions into the myometrial cell. They are entirely non-specific for uterine as distinct from other smooth muscle cells, but have been demonstrated in vitro to have a potent relaxant effect on human myometrium (Gáspár et al., 2013). The most widely used and studied CCB is nifedipine, which along with nifedipine, belongs to the dihydropiridine group. Nifedipine was first reported in an observational study in 1980 to be an effective tocolytic agent with minimal side effects. Nifedipine can be given orally or by intravenous route, whereas nifedipine can only be administered orally (Conde-Agudelo et al., 2011).

Progesterone is useful in allowing pregnancy to reach its physiologic term. In animal studies, medroxyprogesterone treatment prevented labor and possessed anti-inflammatory activity in vivo. Moreover, progesterone antagonists given at term increase the rate of spontaneous labor (Norwitz et al., 2011).

Progesterone and 17α-hydroxyprogesterone acetate slow the process of cervical ripening, and this is the rationale for prophylactic long-term
progestin supplementation mostly studied so far. However, progesterone (but not 17α-hydroxyprogesterone acetate) also inhibits myometrial activity even after the cervix has already ripened. Moreover, these effects depend greatly on the vehicle used and the route of administration. Understanding different mechanisms of action, as well as the importance of progestin formulation, vehicle and route of administration is the key to finding the optimal progestin treatment for prevention of preterm birth (Lucovnik et al., 2011).

Progesterone administration was considered to be effective in the prevention of PTL in women at risk, especially women with history of previous spontaneous PTL (Dodd et al., 2010).

The aim of this study was to compare between calcium channel blocker and progesterone in the prevention of preterm labor in patients with history of recurrent spontaneous preterm labor.

**PATIENTS AND METHODS**

This comparative clinical study was carried out at Al-Hussein Hospital. One hundred pregnant women who have history of previous spontaneous preterm labors, singleton pregnancy, gestational Age of 20 to 24 weeks or past history of one or more spontaneous preterm labor. They were randomly arranged into two groups calcium channel blocker group (A) and progesterone group (B).

**Exclusion criteria:**

Patients with multi-fetal pregnancy, history of ante partum PROM, cervical incompetence or current cervical cerclage, known fetal anomaly, hypertension requiring medications, progesterone or heparin treatment in current pregnancy or history of thrombo-embolic disorders, known allergy to progesterone, known liver disease or established preterm labor.

**All women were subjected to:**

**A. At the first antenatal visit:**

Full History taking, were full personal, obstetric, menstrual and medical history was taken. Data were collected in a special form for each patient. Complete General and abdominal examination and Routine laboratory investigations (full labs). Estimation of gestational age; estimation was done based on the last menstrual period and ultrasonography up to 12 weeks or by two concordant scans between 12 and 24 weeks. Routine trans-abdominal ultrasound to assess the gestational age and to exclude fetal anomalies. Trans-vaginal ultrasound every four weeks to assess cervical length and funneling, prophylactic medical treatment.

All pregnant women in the study received prophylactic medical treatment for bacterial vaginosis and Chlamydial infection in the form of Azithromycin tablets (500 mg) orally once daily for 3 days, and Metronidazole tablets (250 mg) three times per day for 7 days. Medications were given just before starting progesterone therapy.

Treatment was started at 20-24 weeks gestation; (Group A) were given calcium channel blocker tablets twice daily, and (Group B) were given progesterone. Treatment was continued until completed 36 weeks gestation or until occurrence of PROM or delivery.

All women were advised about the benefit of the drug used and a written approval of the study was taken from each
woman. A schedule of next visits was given to each woman.

B. At the follow up visits:

All pregnant women were submitted to uterine contraction monitoring by an external tocodynamometer every other week for 60 minutes by an external monitor from 28 to 36 weeks of gestation while women in left lateral position. We determined the frequency of contractions. A positive test was considered when there were four or more contractions per hour before the 30th week of gestation, and from 30 weeks onward, 6 or more contractions per hour. All pregnant women were asked for symptoms of preterm labor like heaviness, cramps, abdominal colic, and sudden gush of fluid.

Statistical analysis:

Recorded data were analyzed using the statistical package for the social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Probability P-value <0.05 was considered significant. t-test was used to compare means and Chi-square test was used to compare frequencies.

RESULTS

There was no statistically significant difference between all groups as regards the age, parity and number of previous preterm labors. There was a statistically significant as regards GA at delivery with higher percentage of Lower GA at delivery among the progesterone group (35.61 weeks) compared to the calcium group (37.11 weeks). There was a statistically significant difference as regards mean values of birth weight with higher percentage of lower birth weight among the progesterone group (2.37 kg) compared to the calcium group (2.93 kg). There was a statistically significant difference between mean values of five minutes APGAR Score with higher percentage of lower five minutes APGAR Score among the progesterone group (7.66) compared to the calcium group (8.57). There was no statistically significant difference as regards the mode of delivery. There was statistically significant as regards NICU admission with higher percentage of NICU admission among the progesterone group (40%) compared to the calcium group (17.1%).

There was a statistically significant difference before and after progesterone administration as regard mean values of serum progesterone. There was a statistically significant difference before and after progesterone administration as regards mean values of serum calcium.
Table (1): Comparison between groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Progesterone group (n=50)</th>
<th>Calcium group (n=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td></td>
<td>28.65±4.82</td>
<td>29.14±4.15</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td>2.95±0.57</td>
<td>3.19±0.61</td>
<td>0.045</td>
</tr>
<tr>
<td>No. of PLT</td>
<td></td>
<td>2.55±0.52</td>
<td>2.53±0.52</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td>35.61±1.12</td>
<td>37.11±1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td></td>
<td>2.37±0.37</td>
<td>2.93±0.30</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Apgar score</td>
<td></td>
<td>7.66±0.75</td>
<td>8.57±1.14</td>
<td>0.001*</td>
</tr>
<tr>
<td>Delivery by CS</td>
<td></td>
<td>16 (32%)</td>
<td>19 (38%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td></td>
<td>34 (68%)</td>
<td>31 (62%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Not needing NICU</td>
<td></td>
<td>30 (60.0%)</td>
<td>41 (82%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Needing NICU</td>
<td></td>
<td>20 (40.0%)</td>
<td>9 (18%)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Serum progesterone</td>
<td></td>
<td>50.88±1.70</td>
<td>51.50±1.97</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Serum progesterone</td>
<td></td>
<td>95.70±1.57</td>
<td>103.00±2.02</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>before</td>
<td>13.74±0.32</td>
<td>13.91±0.37</td>
<td>&lt;0.02*</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>after</td>
<td>11.26±0.30</td>
<td>9.87±0.38</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Prematurity is the leading cause of neonatal death and handicap. Improvement in neonatal care have led to higher rates of survival among very preterm infants, but a major effect on the associated mortality and morbidity will be achieved only by better identification of women at higher risk for preterm labor and by development of an effective intervention to prevent this complication (Copen et al., 2017).

Progesterone is a steroid hormone that helps to maintain pregnancy. Removal of progesterone, or blockage of its receptors, reliably ends pregnancy at all gestational ages, and in many non-human species, falling levels precipitate natural labor (Lucovnik et al., 2011).

The vasodilator effect of progesterone on uterine circulation in the non-pregnant female and during the first trimester of pregnancy is well known, but little information is available about its effect on uterine and fetal circulations later in gestation. In one study performed by Barda et al. it showed that vaginal micronized progesterone used for the prevention of PTL was associated with a significant reduction in the fetal middle cerebral artery (MCA) pulsatility index (PI) but with no effect on uterine circulation (Vafaei et al., 2016).

Calcium channel blockers are used to control hypertension, but it had been found to have a role in decreasing uterine premature contractions. There have been reports of the lack of action of nifedipine in premature contractions. Uterine contractile activity is regulated by the increase in intracellular Ca2+ concentration in the myometrial cells (Gáspár et al., 2013).

The current study included 100 pregnant women selected on basis of previous one or more preterm labor, singleton pregnancy and pregnancy at gestational age less than 24 weeks and excluded ante-partum ROM, cervical incompetence, cerclage, congenital fetal malformations, hypertension requiring medications, progesterone or heparin...
therapy or history of thrombo-embolic disorders, known liver disease and progesterone allergy.

Gestational age was calculated on the basis of the last menstrual period, and ultra-sonographic examination. Medications started at 24 weeks of gestation and stopped at the end of 36 weeks of gestation and proceeded by prophylactic medical treatment for bacterial vaginosis.

There was no statistically significant difference between the two groups as regarding to age, parity, mode of delivery and number of previous preterm labors.

This agreed with the studies of Fonseca et al., (2014), Meis et al., (2015) and deFonseca et al., (2016).

In a meta-analysis of RCT by Farine et al., (2018), there is a good evidence to recommend the use of vaginal progesterone 200 mg daily in the prevention of PTL in women with short cervix <15 mm detected during TVS scanning at 22–26 weeks. In the prevention of recurrent PTL in women with previous PTL, vaginal progesterone 100 mg daily was advised, or IM 17 alpha hydroxyl progesterone 250 mg once weekly. As regards timing of starting progesterone for prevention of PTL, no apparent benefit of early start before 20 weeks and also the use of higher doses is not beneficial (Dodd et al., 2013).

This study compares calcium channel blocker with progesterone for the prevention of PTL, we found that both were effective in the prevention of threatened PTL, PTL < 37 weeks and PTL < 34 weeks in women at risk with higher efficacy in the calcium channel blocker group running in agreement with many previous studies (Vafaei et al., 2016).

On the other hand, one study by O’Brien et al., (2012) concluded that vaginal progesterone did not reduce the rate of early PTL, neonatal morbidity or mortality and this could be explained by performing their study on women with one risk factor (previous PTL) and considering the primary outcome PTL < 32 weeks, also, they used progesterone in a dose of 90 mg and in the form of vaginal gel.

Some studies found that although calcium channel blocker is effective in the prevention of PTL, it was not effective in reducing the rate of hospital admission for PTL (threatened PTL) (Meis et al., 2016).

In this study and in accordance with previous studies by Tita et al. (2015) and Farine et al. (2018) the mean birth weight and the mean GA at delivery were significantly higher in the calcium channel blocker treated group in comparison with the progesterone treated group.

Also, our results showed that the ratio of neonatal ICU admission to neonatal mortality reduced in both groups that had received calcium channel blocker in relation to the progesterone group.

On the other hand, two other studies reported that the ratio of neonatal admission to ICU was significantly lower in women who had received progesterone but without changes in the neonatal deaths (Cetingoz et al., 2011 and Tita et al., 2015).

The vasodilator effect of progesterone on fetal cerebral circulation may be supported by animal studies that showed that the brain is sensitive to progesterone
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During critical periods of development and maturation and presence of progesterone receptors in the brain, also progesterone reduces brain edema in animal models (Xu et al., 2014).

As regards serum progesterone level before and after progesterone administration, our study revealed that it was below the normal level at 24wks measuring approximately 50ng/ml compared to the average normal level at this gestational age 73ng/ml.

Six weeks after progesterone administration (at thirty weeks gestation), serum progesterone level was approaching the average normal level at this age (100ng/ml).

No data from RCTs and other studies indicate that progesterone use in the prevention of PTL was not safe, apart from a single retrospective study by Rebarber et al., (2014) who showed that the incidence of gestational diabetes mellitus was 12.9% in women treated by I.M 17 alpha hydroxyl progesterone (250 mg weekly) compared to 4.9% in control cases. In this study, safety could not be confirmed due to the small number of cases and further large series studies are advocated.

**CONCLUSION**

Prophylactic use of progesterone reduces the rate of preterm labor, prolongs gestational age at delivery, reduces the frequency of uterine contractions, and improves the symptoms of preterm labor in women with history of recurrent spontaneous preterm labors.

Calcium channel blockers have superior effect on inhibiting premature uterine contractions in comparison with progesterone administration and prolong gestation ages, lowering preterm births and liability into NICU admissions.

**REFERENCES**

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دراسة مقارنة بين العلاج باستخدام محصرات قنوات الكالسيوم والبروجستيرون في الوقاية من الولادة المبكرة المتكررة

رأفت محمد حسان، فريد إبراهيم حسن، مفيد فوزي محمد
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خلفية البحث: يعتبر المخاض المبكر هو السبب الرئيسي لإصابة بالاعتبات والوفيات خلال الفترة المحيطة بالولادة ولدى حدوث الولادة، ويرتبط بقوة بالإعاقات العصبية والعصبية في وقت لاحق من الحياة.

الهدف من البحث: المقارنة بين علاجات قنوات الكالسيوم والبروجستيرون في الوقاية من المخاض المبكر عند المرضى الذين لديهم تاريش من المخاض العفوي المتكرر.

المريضات وطريقة البحث: تم إجراء الدراسة الحالية كدراسة مقارنة إكلينيكية في مستشفى الحسين على مائة امرأة حامل لهيمن تاريش سابق من المخاض (الخراج) والعنوي السايك وتم تقسيمهم بشكل عشوائي إلى مجموعتين: مجموعة مانع قناة الكالسيوم (أ) ومجموعة البروجستيرون (ب).

نتائج البحث: لم يكن هناك فروق ذات دلالة إحصائية بين كل مجموعة فيما يتعلق بالعمر، وعدد مرات الولادة المكتملة وكذلك عدد مرات الولادة المبكرة السابقة، وكان هناك فروق ذات دلالة إحصائية بين مجموعة البروجستيرون ومجموعة محصرات قنوات الكالسيوم فيما يتعلق بعمر الجنين عند الولادة بنسبة أعلى من العمر الجنيني الأقل عند الولادة بين مجموعة البروجستيرون (34 أسبوعًا) مقارنة مع مجموعة محصرات قنوات الكالسيوم (36 أسبوعًا). كما كان هناك فروق ذات دلالة إحصائية بين مجموعة البروجستيرون ومجموعة محصرات قنوات الكالسيوم فيما يتعلق بالقيم المتوسطة من الوزن عند الولادة بنسبة أعلى من إنخفاض الوزن عند الولادة بين مجموعة البروجستيرون (2.32 كجم) مقارنة مع مجموعة محصرات قنوات الكالسيوم (2.87 كجم). وكان هناك فروق ذات دلالة إحصائية بين مجموعة البروجستيرون ومجموعة محصرات قنوات الكالسيوم فيما يتعلق بالقيم المتوسطة لمدة خمس دقائق مقياس أبجر بنسبة أعلى من إنخفاض...
خرمس دقائق مقياس ابجر ضمن مجموعة البروجستيرون (7.5) مقارنة مع مجموعة محصرات قنوات الكالسيوم (8.4). ولم يكن هناك فروق ذات دلالة إحصائية بين المجموعتين فيما يتعلق بطريقة الولادة.

وكان هناك فروق ذات دلالة إحصائية بين مجموعة البروجستيرون ومجموعة محصرات قنوات الكالسيوم فيما يتعلق بنسبة دخول الحضانة مع نسبة مئوية أعلى في مجموعة البروجستيرون (40%) مقارنة مع مجموعة محصرات قنوات الكالسيوم (11.4%).

الاستنتاج: يقلل استخدام مانع قناة الكالسيوم والبروجستيرون من معدل المخاض قبل الأول، ويطيل عمر الحمل عند الولادة، ويقلل من تكرار انقباضات الرحم، ويحسن أعراض المخاض قبل الأول، لدى النساء اللواتي لديهن تاريخ من المخاض العفوي المتكرر، ومائع قناة الكالسيوم أكثر تفوقا على البروجستيرون فيما يتعلق بالوقاية من المخاض المتكرر.