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A Comparative Study between the Efficacy of 17-alpha-Hydroxy Progesterone Caproate Plus Salbutamol with Magnesium Sulfate in Treatment of Preterm Labor

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Abstract: This study was a comparison between salbutamol plus 17-αHP and magnesium sulfate for the prevention of PTL. One hundred and four of patients admitted for prevention of PTL were randomly assigned to two groups having 52 patients in each group. One group was given 5 mg salbutamol in 500 mL of 5% D/S, at a dose of 10 μ min^{-1} to a maximum of 45 μ min^{-1} until contraction ceased or side effects started, then we initiated soon, 250 mg of 17-αHP, it was administrated by weekly intramuscular injection and was continued until 36 weeks 6 days or delivery. Another group was given 10 g magnesium sulfate intramuscular then 5 g every four hours until contraction ceased or side effects started. Successful tocolysis achieved similar in each group. Mean uterine contraction ceasing time in group I was 5.4 h and in group II, 16.8 h. The delay in the delivery till 37 weeks of gestation in group II was lower and this differences is due to administration of in group I.Salbutamol and magnesium sulfate are equally effective regarding delay of delivery in first 48 h, but salbutamol plus 17-αHP prevents preterm labor if be continued 36 weeks 6 days.

Key words: Magnesium sulfate, preterm labor, progesterone, salbutamol, tocolysis

INTRODUCTION

Lack of reliable and effective ways to treatment Preterm Labor (PTL) together with prevent recurrence of uterine contractions has resulted with very slight alter in the occurrence of preterm birth throughout the last forty years (Bastek *et al*., 2008). Clinicians are often faced with the problem of managing an established PTL with a variety of drugs which may have a lack of uterospecificity, low efficiency or potentially severe side effects for the mother or the unborn baby (Meloni *et al*., 2009).

For example, tocolytics are frequently administered to women with symptoms of PTL to prolong gestational age for a short period of time, but the conclusive evidence that their use improves the quiescence of uterine as well as adverse neonatal was not satisfactory (Hamiltonm and Tower, 2010). Due to the powerful data description capability of the antenatal corticosteroids to reduce adverse neonatal outcomes, many clinicians agree that women at high risk of PTL should take a single course of antenatal corticosteroids (Mahony *et al*., 2010). However, there is limited evidence that repeat courses are helpful for patients staying undelivered 7 to 10 days after a single course (Mahony *et al*., 2010). Treatment of PTL may improve significantly if the method of administration is optimized.

It is noteworthy that a published randomized controlled trial was shown that if the pregnant women had a spontaneous preterm birth in a previous pregnancy, progesterone administered from 16 weeks forwards could efficient in reducing the risk of preterm delivery (Meis *et al*., 2003). In addition, it was shown that administering a tocolytic together with progesterone could more effective to treat preterm birth (Borna and Sahabi, 2008). However, the evidence that a tocolytic plus progesterone has potential to preserve the quiescence of uterine and also to reduce maternal side effects is inconclusive. Since the data in support of using repeat courses of magnesium sulfate (Hui *et al*., 2007) or salbutamol plus progesterone to treat PTL and also recurrence of uterine contractions is limited, we tried to assess the potential efficacy of these treatments method and which of them has more efficient to inhibit uterine contractions.

MATERIALS AND METHODS

A comparative randomized clinical trial was carried out in the obstetrics and gynecology ward of Razi and Imam Khomeini teaching hospitals in Ahvaz. This study was performed between April 2009 to April 2010 and targeted singleton pregnant women between 20 and 37 weeks of gestation who were admitted for uterine contractions.

The Ethics Committee of Jondishapour Ahvaz University of Medical Sciences approved this study.

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Preterm Labor (PTL) was recognized as the simultaneous occurrence of contractions (> four contractions in 20 min) and cervical changes, either shortening and softening or dilation, by physical examination.

Recurrence of PTL was defined as reappearance of uterine contractions through 48 h after initial successful inhabitation of the uterine contractions. Arrested PTL was defined as a 12 h contraction-free period after initial successful inhabitation of the uterine contractions. Inclusion criteria were singleton pregnancy, intact membranes, no cerclage, cervical dilation of more than 1 cm and the dating of pregnancy proved through first trimester ultrasound scanning.

Exclusion criteria included clinical symptoms of intra-amniotic infection or pyelonephritis, two or more fetuses in one amniotic sac, medical complications contraindicating tocolysis, chronic medical illness (e.g., therapeutically-treated hypertension or insulin-requiring diabetic patients) and sonographic confirmation of congenital anomalies inconsistent with life. The duration of gestation at the time of admission was determined according to a previously described algorithm on the basis of the last menstrual period and the results of ultrasonographic measurement of the fetus at the earliest ultrasound (Carey *et al*., 2000).

The simple urn method of randomization (Wei and Lachin, 1988) with stratification according to clinical center was used to create a randomization sequence for each center. The boxes of 17-αHPC plus salbutamol or magnesium sulfate were packaged for each center according to the randomization sequences. The women who participated in this study and the research colleague were not aware of the study group assignment. During the year after entering the study, women were initially hydrated with 500 mL of Ringer's lactate over a 30 min period.

Women as randomized were assigned to receive salbutamol by continuous infusion at a rate of 10 μg up to 45 μg min^{-1} (until uterine contractions were absent) followed intramuscular injection (250 mg 17-αHPC in 1 mL castor oil) and also continued weekly injections until the 36 weeks 6 days of gestation. The other group was given intramuscular injection magnesium sulphate, with an initial bolus of 10 g followed by continuous injection at a rate of 5 g per 4 h. After that, women came back for weekly injections through the end of the 36 weeks 6 days or until delivery. At each visit, all patients were examined systematically for side effects. The usual clinical care provided to women in the study was not otherwise perturbed. Additionally, all patients also were checked up weekly; if the patient complained of increased uterine activity, the physician did a digital exam.

The data were analyzed by the x^2 and Fisher exact tests. Normally distributed continuous data were assessed by the Student's t-test. Comparison Cervical effacement and cervical dilatation were made with Cochran-Mantel-Haenszel test. Latency period were tested by the Mann-Whitney U-test. For all other outcomes, a nominal p-value of $p<0.05$ was considered significant.

RESULTS AND DISCUSSION

Outcome data were available for 100% of the randomized women. One hundred four women were assigned randomly; Fifty-two women received salbutamol +17-αHPC and 52 women were given sulfate magnesium. None of the patients was lost to follow up (Fig. 1).

The two groups were similar with respect to maternal age, gestational age at admission, Bishop Score and PTD risk factors. Forty- eight patients were primary gravid and 56 were multigravida. Fifty of the patients were less than

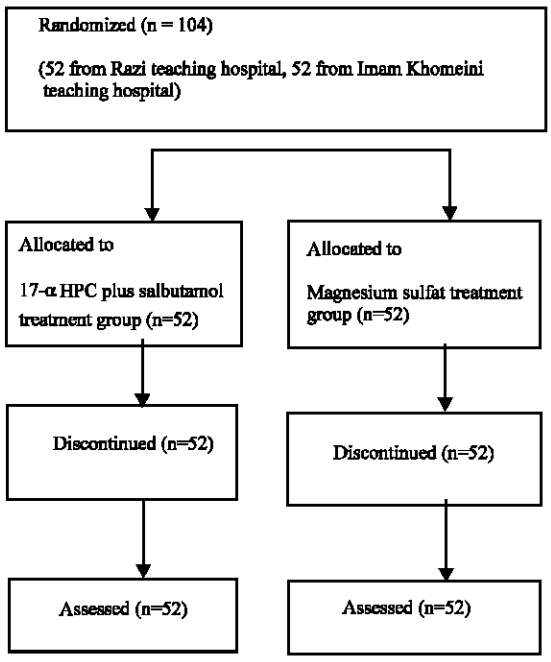

Fig. 1: Flow chart of participants during the clinical trial

Table 1: Maternal demographic and clinical characteristics at randomization characteristics

Maternal characteristic	No (%)
Maternal age<25years	50(48.1)
Week of gestation<34weaks	48(46.2)
Primary gravid	48(46.2)
Multi gravid	56(53.8)
Preterm birth history	8(7.7)
Prior PTL history	14(13.5)

Table 2: Cervical dilation and count of uterine contraction women who admitted to the department with symptoms and signs of PTL that were appropriate for the assessment

Cervical dilatation (cm)	No (%)	Uterine contraction (Counts)	No (%)
1	34(32.7)	4	76(73.1)
2	56(53.8)	5	19(18.3)
3	13(12.5)	6	4(3.8)
4	1(1)	8	5(8)

Table 3: Gestational age and cervical dilation in salbutamol+17-αHP group and sulfate magnesium group

Maternal characteristic	Salbutamol+17-αHP group (Mean±MSE)	Sulfate magnesium group (Mean±MSE)	p value
Week of gestation	32±3	31.9±3	0.84
Cervical dilatation (cm)	1.77±0.68	1.87±0.69	0.47

Table 4: Recurrent effacement in 60-80% and recurrent effacement in more than 80 % in salbutamol+17-αHP group and sulfate magnesium group

Maternal characteristic	Salbutamol+17-α HP No. (%) 60-80%	Salbutamol+17-α HP No. (%) >80%	Sulfate magnesium No (%) 60-80%	Sulfate magnesium No (%) >80%	p value
Effacement	23(56%)	29(44%)	16(69.3%)	36(30.7%)	0.16

Table 5: The side effect in salbutamol+17-αHP group and sulfate magnesium group

Maternal characteristic	Salbutamol+17-α HP. No (%) Yes	Salbutamol+17-α HP. No (%) No	Sulfate magnesium. No (%) Yes	Sulfate magnesium. No (%) No	p value
Side effect	19 (36.5%)	33 (63.5%)	0	52 (100%)	0.001

25 years old and the gestational age of forty-eight patients was less than 34 weeks.

Of 104 women who took part in the trial, 14 had a prior history of PTL during the present pregnancy and 8 had a preterm birth history (Table 1).

Of all of the patients studied, the cervical dilation of 34, 56, 13 and 1 patients was 1, 2, 3 and 4 cm, respectively and the cervical effacement of 39 women was at least 80% and others (65) was between 60 to 80% (Table 2).

Overall, rates of uterine contractions during admitted to the department were similar in both treatment groups and were 4, 5, 6 and 8 times for 76, 19, 4 and 5 patients, respectively (Table 2).

The uterine contractions of 82 women were stopped during the initial medication and the others (22) were delivered due to unceasing contractions.

There was not significant difference in the gestational age between the two groups. The Cervical dilation (1.77±0.67 vs. 1.87±0.69) and also the cervical effacement were not significantly different between the two groups (Table 3).

No significant differences were found in the recurrent effacement of uterine cervix of the patients that were given salbutamo l+17-αHPC in Comparison to women were treated by sulfate magnesium (Table 4).

Table 6: The variety of side effects in salbutamol+17-αHP group and sulfate magnesium group

Maternal characteristic	Salbutamol+17-α HP No. (%)	Sulfate magnesium No. (%)
Head ache	6(11.5%)	0
Vomiting	5(9.6%)	0
Dizziness	4(7.7%)	0
Head ache and Vomiting	4(7.7%)	0
Without side effect	33(63.5%)	0

Table 7: The mean successful cessation of uterine contractions women who admitted to the ward with symptoms of PTL in salbutamol+17-αHP group and sulfate magnesium group

Maternal characteristic	Salbutamol+17-α HP No. (%) (mean hour±MSE)	Sulfate magnesium No. (%) (mean hour±MSE)	p value
Discontraction	44(5.4±1.9)	38(16.8±2.9)	0.001

Table 8: The canceled delivery of women who admitted to the ward with symptoms of PTL in salbutamol+17-αHP group and sulfate magnesium group

Canceled birth	Salbutamol+17-α HP. No (%)	Sulfate magnesium. No (%)	p value
Up to 48 h	7(13.5%)	14(26.9%)	0.001
From 48 h up to one week	1(1.9%)	8(15.4%)	0.001
From 1th week up to before 37th week	3(5.8%)	10(19.2%)	0.001
Up to after 37th week	41(78.8%)	20(38.5%)	0.001

Nineteen of the patients in the salbutamol+17-αHPC group were compliant and reported side effect that were linked apparently to the treatment. In contrast, none of the women of the sulfate magnesium group reported adverse events that were linked apparently to the treatment (Table 5).

From nineteen women who had side effects, 6 were experienced head ache, 5 had vomiting, 4 felt dizziness and 4 had head ache and vomiting together (Table 6).

The mean successful cessation of uterine contractions during initial medication was not significant in the salbutamol+17-αHPC group in Comparison to the sulfate magnesium group. However, the duration time to inhibit contractions were faster in the salbutamol+17-αHPC (5.41±1.9 h) in versus to the sulfate magnesium group (16.79±2.9 h) ($p<0.001$). It would be noted that the maximum time to inhibit uterine contractions in the salbutamol+17-αHPC group was 10 h after giving medication, while in the sulfate magnesium group was 48 h after giving drug (Table 7).

In overall, the Salbutamol+17-αHPC group in versus to the sulfate magnesium group had a longer mean latency period until delivery day. This observed difference for delivered within 48 h, one week , from one week up to before 36th week and after 37th week were (13.5 vs. 26.9%), (1.9 vs. 15.4%), (5.8 vs. 19.2%) and (78.8 vs. 38.5%), respectively (Table 8).

DISCUSSION

The present study showed that both salbutamol and magnesium sulfate are equally effective to inhibit, uterine contractions. However, if the gestational age is longer than 36 weeks, the salbutamol plus 17-αHP works better than the magnesium sulfate to prolong Pregnancies. The effectiveness of beta agonist medications to stop preterm delivery within 48 h after giving drug was extensively reported (Macones *et al*., 1995; Worldwide Atosiban versus Beta-agonists Study Group, 2001; Zygmunt *et al*., 2003).

The present research also has shown that the salbutamol +17-αHPC and the magnesium sulfate have the same potential to stop uterine contractions through 48 h. Nevertheless, salbutamol +17-αHPC therapy can terminate contractions faster than magnesium sulfate treatment method. In spite of this finding, a cochrane review has concluded that the magnesium sulphate is ineffective in postponing or preventing preterm delivery. Also its use is associated with an increased mortality in the newborn (Crowther *et al*., 2002; Lorzadeh *et al*., 2007).

On other hand, the salbutamol is the commonly used beta sympathomimetic drug that acts through c-GMP to cease uterine contractions. However, its use is usually associated with serious and clinically critical maternal side effects (i.e., pulmonary edema, myocardial ischemia, arrhythmia and death) (Chua *et al*., 1997).

In addition, it was found that the 17-αHPC and the salbutamol were similarly effective in treating preterm labor. However, the 17-αHPC was better tolerated than the salbutamol. Therefore, when the 17-αHPC is given together with the salbotamol to treat preterm delivery, the dose of salbutamol must be decreased proportionally that may help to decrease side effects.

However, in the present examine the side effects were correspondingly observed again among the women assigned to salbutamol+17-αHPC therapy and overwhelmingly associated with head ache, vomiting and dizziness. Even though, these side effects were not more dangerous than those aforementioned that more women due to intolerable of them had discontinued salbutamol treatment.

In the present comparative randomized clinical trial, the rate of preterm birth in the salbutamol+17-αHPC group was lower than the magnesium sulfate group.

Management of preterm labor is restricted to the use of tocolytics, which inhibit uterine contractility but do not reverse the delivery process. Recently, it has been shown that among women who had spontaneously delivered before 37 weeks, 17-αHPC administration helped carry their pregnancies longer than 37 weeks. As well as, the prophylactic administration of 17-αHPC in mid-pregnancy to women who had a PTL history, may halve the rate of recurrence (Dodd *et al*., 2006; Da Fonseca *et al*., 2003; Da Fonseca *et al*., 2009; Fonseca *et al*., 2007; Garfield *et al*., 1980; Garfield *et al*., 1998) have been recommended that progestins regulate delivery through genomic actions by regulation of various proteins that are consideration to be involved in controlling myometrial contractility. Garfield *et al*. (1980) in a study also claimed that sufficient progesterone level in myometrium is able to neutralize prostaglandin stimulatory activity as well as oxytocin properties that augment the activity of ß-agonists. So continuing treatment by 17-αHPC after successful treatment of preterm labor, may maintenance the quiescence of uterine.

In the present experiment, the salbutamol+17-αHPC caused shortening of the uterus cervix. However, it was not significant as compared with the magnesium sulfate therapy. In agreement with the current study Facchinetti *et al*. (2007) also reported that administration of 17-αHPC can useful to inhibit preterm delivery of pregnant women by shortening of the uterus cervix . In contrast, Durnwald *et al*. (2009) did not reveal that 17-αHP had effect on cervical length in the women who has potential to preterm labor. Therefore, it seems that further research is necessary to identify the precise capacity of 17-αHPC to prevent recurrent PTL and whether this progestin has effects on the cervix to inhibit cervical ripening.

Although, the present study had a number of restrictions. First, it was not double blind. Sample size and power to detect clinically essential outcomes were small. The trial was not designed with sufficient power to address important infant's outcomes. Nevertheless, it was shown that the magnesium sulfate as well as the salbutamol+17-αHPC, as prescribed in this trial, have well capacity to cessation of uterine contractions through 48 h.

Indeed, the salbutamol+17-αHPC could be considered to be a candidate to regulate uterine contractility and cervical function and as a result, the onset and progress of delivery. Treatment with the salbutamol+17-αHPC appears to be safe for the mother and may be for her fetus with fewer side effects that more frequently reported in the women receiving only salbutamol therapy.

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Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (by a revised Urmia University of Medical Sciences that approved by WMA).

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