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Compare the efficacy of Indomethacin and magnesium Sulphate in prevention of preterm labor

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A B S T R A C T

Premature labor is responsible for almost 75% of all neonatal deaths and cause 50% of childhood neurological complications. Postponing the treatment of preterm labor and delivery, increased infant survival and better quality of life and is reduce costs of care for premature infants. The aim of this study was to compare the effect of Indomethacin and magnesium sulfate to prevent preterm labor. In a clinical trial study that performed in Department of Obstetrics & Gynecology of Tabriz University of Medical Sciences on patient with preterm labor, the effects of Indomethacin and magnesium sulfate to prevent preterm labor, evaluated. Mean time interval between beginning of pain to patient labor in Indomethacin group was 83.01 ± 91.53 hour and mean time interval between beginning of pain to patient labor in Magnesium Sulfate group was 83.76 ± 127.42 hour that significant difference was not found in mean time interval between beginning between both groups ($P=0.968$). In our study, Magnesium Sulphate in 32% and 60% of patients was caused to delayed delivery of more than 24 and 48 hours and Indomethacin in 37% and 63% of Patients was caused to delayed delivery of delayed delivery was more than 24 and 48 hours. Mean of first minute Apgar of case group (Indomethacin) was significantly more than mean of first minute Apgar in Control group and significant difference was not found in Mean of first minute Apgar between case and control groups. 41 of neonates in Case group and 47 of neonates in control group were alive. Our study, Indomethacin was effective in reducing preterm labor and as, Magnesium Sulphate has beneficial effects. Also, no significant differences was found in terms of fetuses born at birth between the two groups ($P=0.294$).

Introduction

The beginnings of labor (delivery) pains, before 37 weeks, are considered as

premature labor which is one of the most common causes of the infant mortality (1).

30-35% of the preterm labor due to obstetric indications, 40-45% due to the spontaneous preterm labor and 30-35% occur after preterm rupture of membranes.

The reasons leading to preterm labor have several characteristics which often have interaction with each other, and also there are several factors contribute to their occurrence. These complexities make it difficult to efforts in order to prevent and treat this problem. This is especially obvious in the case of preterm rupture of membranes and spontaneous preterm labor which cause the 70-80% of preterm labors (1-2).

In the most cases, the preterm labor happens followed by the spontaneous labor. According to reports, previous preterm delivery is the strongest indicator of the risk. It is estimated that the incidence of preterm delivery increases up to 14.3% following the first labor and it would reach to 28% after the second birth (3).

Whereas it is difficult to early distinguish between real (true) and false labor before the effacement and observable dilation in the cervix so the utter attention to the uterine activity might be misleading. These contractions described as painful or painless, irregular non-rhythmic contractions could considerably interfere with the diagnosis of the real preterm labor. In women who experience the preterm labor, the uterus activities are attributed to the Braxton Hicks contractions in relatively rare cases. Whereas the uterine contractions might individually be misleading it might incorrectly diagnosis as a false labor. In addition to the painful or painless uterine contractions, it has been experimentally noticed that the symptoms such as pelvic pressure, severe cramps similar to menstrual cramps, watery vaginal discharge and back pain are associated with the imminent

preterm labor. Iams and colleagues (1994) found that the warning signs and symptoms of preterm labor such as uterine contractions occur only during the 24 hours prior to preterm labor (1).

The major cause of premature death is the respiratory distress syndrome, necrotizing enterocolitis (NEC), intracranial hemorrhage, seizures and septicemia (2). Since this problem involves a wide range of the fetal-neonatal disorders such as cardiac pulmonary abnormalities, nervous and gastrointestinal diseases so the importance of efforts to prevent the problem would be obvious (2).

Different therapeutic techniques have been evaluated to prevent the preterm labor. All of which are to delay preterm labor and reducing neonatal infection (3). Although the prevention of preterm labor has been difficult and unattainable goal; but the recent reports indicate that it could be achieved in some specific populations. The women with the risk of preterm labor and the women hospitalized with the labor preterm symptoms are considered as candidates for a number of medical interventions in order to improve the neonatal outcomes (2).

In the absence of fetal or maternal indications for immediate labor, the medical interventions would be applied in order to prevent preterm labor; nevertheless these interventions are not necessary in all cases and in the best case, some of these interventions lead to relative improvement and also the influence of others has not been established. It is believed that by delaying the time of delivery, further improvement is achieved due to fetal maturation. On the other hands, this delay provides enough time for complementary therapies which improve clinical neonatal outcomes. In 1998, the American College of Obstetrics and

Gynecologists recommended that in the cases where the uterine contractions are associated with the cervical dilation and effacement, the tocolytics therapy should be applied (1-2).

Tocolytics drugs include magnesium sulfate, Nifedipine, Ritodrine, NSAID, nitroglycerin and atosiban however there are different results listed in order to the efficiency of the above methods especially tocolytics drugs. The American College of Obstetricians and Gynecologists has concluded that tocolytics agents do not result in significant prolongation of pregnancy but they could postpone childbirth for at least 48 hours in some women.

The prostaglandin inhibitors have been significantly taken into consideration since prostaglandins are involved in large natural labor contractions. The antagonists would affect by inhibiting the production of prostaglandins or blocking their function in the target organs. The group of enzymes collectively called prostaglandin synthetase, are responsible for the conversion of free arachidonic acid to prostaglandins. Some medicines such as acetyl Salicylic acid and Indomethacin could block this system. Indomethacin is used to treat preterm labor in some studies and If it is taken up to 24-32 weeks of pregnancy and discontinued 72 hours prior to delivery, this drug wouldn't be harmful to the mother and fetus (4). In a study, it has been reported that Indomethacin is the only drug that could lead to labor delaying for more than 7 days (5).

By the possibility of the positive impacts of this drug in order to increase the labor delay and the usage of the Indomethacin, the followings are expected:

The significant decrease in maternal and neonatal complications caused by the preterm labor and its costs.

Considering the importance of this issue and consequences originating from preterm birth and the controversy that has been found in the effectiveness of the administered drugs especially Indomethacin, this study would be conducted to determine above impact on preterm labor and the aim of this study was to compare the effect of Indomethacin and magnesium sulfate on the prevention of preterm labor.

Materials and methods

In a clinical trial conducted on patients with preterm labor in the Department of Obstetrics and Gynecology, at Tabriz University of Medical Sciences, the impacts of Indomethacin and magnesium sulfate to stop preterm labor were evaluated and compared.

In this study, we have selected and enrolled the singleton pregnant women between 28 and 32 weeks of pregnancy who hospitalized with initial primary diagnosis of preterm labor. First of all, the consent was obtained from participants based on randomly placed in each of the two intervention groups. Patients were matched based on their maternal age and gestational age, parity and cervical dilatation rates, then the uterine contractions of the patient was examined by a gynecologist assistant for about 20 minutes following the fetal heart rate auscultation.

The inclusion criteria were as follows

At least two uterine contractions were happened for 30 seconds during 10 minutes, the cervical dilatation rate was less than 5-6 cm, the cervical effacement were observed as 60% -50% or less with the soft cervical consistency.

Exclusion criteria were as follows

PROM (premature rupture of membranes), vaginal bleeding, dilatation greater than 5

cm, fetal heart rate turbulence, known sensitivity to Indomethacin and tocolytics therapy, kidney failure and gastrointestinal bleeding. The patients were hydrated with normal saline solution after resting. Then the 12 mg of ampoule Betamethasone were intramuscularly injected and in the absence of preterm labor, a second dose of Betamethasone was repeated after 24 hours. The patients were randomly assigned in one of the two study groups. 4 g of magnesium sulfate 50% was intravenously injected to the control group during 20 minutes. Then 2 g of intravenous infusions was injected once in an hour and this process was continued until the reduction or cessation of uterine contractions. The Indomethacin suppository (50 mg) was initially administered and then it was repeated every six hours for 24 hours. The monitoring was performed by fetal heart rate auscultation every half hour. Also the NST was performed to monitoring the health of fetus 6 hours after the cessation of the uterine contractions. The basic fetal heart rate and fetal heart rate variability was assessed in the NST. Due to the potential risk of adverse outcomes such as oligohydramnios after taking Indomethacin, Ultrasound was performed in all patients 24 hours after cessation of the uterine contractions among the patients.

In this study the sampling was randomly performed. According to the error type 1 (0.05) and the error type 2 (0.2) and the power of test as 80%, the 75 cases were determined for each group.

This clinical trial was registered in IRCT.ir with the number of (IRCT2013062613777N1).

Results and Discussion

In this study the results of monitoring on the women with the preterm labor who

experienced the tocolytics therapy by use of the Indomethacin or magnesium sulfate, were compared with data obtained from the control group.

Demographic findings of patients are shown in table I. Among the cases and control group, the average intervals between the start of pains and the true labor were respectively 83.01 ± 91.53 and 83.76 ± 127.42 ($P=0.968$).

Among the studied group, the maternal uterine contractions were respectively inactive and active at the birth moment of 46 and 24 infants and among the control group, the maternal uterine contractions were respectively inactive and active at the birth moment of 50 and 20 infants ($P=0.466$). Corticosteroid dose was just completed in 46 infants of studied group and 47 infants of control group ($P=0.856$).

56 infants of studied group and 61 infants of control group were hospitalized in NICU after the birth. Thus there was no significant difference between two groups in terms of hospitalization in NICU ($P=0.254$). The infant hospitalization causes are shown in the Table II.

56 infants of studied group and 61 infants of control group were passed away. So there was no significant difference between two groups in terms of the mortality rate among the infants born ($P=0.294$).

The strong and subsequent initiation of uterine contractions with progressive cervical dilatation and effacement at 20-37 weeks of pregnancy is defined as preterm labor and its prevalence has been reported as 6-15% (5). Thus 25% of preterm labors occur after the premature rupture of membranes and 40-50% of them happen spontaneously (1).

Table.I Demographics finding of patients

	Group		P
	Case	Control	
Mother age	24.53 ± 5.83	24.89 ± 5.48	0.709
Gestational age	29.93 ± 1.40	29.77 ± 1.52	0.526
Baby count	1.91 ± 1.33	1.86 ± 1.24	0.793
Gravidity	0.63 ± 1.13	0.59 ± 1.06	0.817
Abortion count	0.29 ± 0.76	0.29 ± 0.73	-
1-minute Apgar score	2.99 ± 0.12	2.80 ± 0.40	<0.001
5-minute Apgar score	2.64 ± 0.48	2.63 ± 0.49	0.862

Table.II Causes of NICU admission of neonates

	Group		P
	Case	Control	
RDS	42	56	0.010
NEC	26	19	0.205
Sepsis	22	20	0.712
IVH	1	2	-

The preterm labor is responsible for almost 75% of all neonatal deaths and 50% of childhood neurological complications (5-6) and it also leads to the prolonged hospitalization and increased hospital charges (7). Preterm labor with the 6-10% prevalence is the most common cause of prenatal mortality (8). Although its causes are almost unknown, in 50% of cases it is multi-factorial (9-10).

Considering the importance of the subject and the increased prevalence of preterm labor in recent years, it is very critical to find a way to cure this disease. So the several studies provide different approaches in order to treat preterm labor based on its etiology (11).

There is a wide range of therapeutic methods to prevent the progression of preterm labor which are in order to postpone the disease occurrence and reducing neonatal infection (12).

In this study, we evaluated the effects of Indomethacin and magnesium sulfate to prevent preterm birth. Since the treatment of preterm labor and postpone it would increase the survival of newborns and could improve the quality of him/her life and also it would reduce the costs required for the care and cure of premature infants, so the tocolytics drugs such as magnesium sulfate and calcium channel blockers like Nifedipine are used to achieve this purpose (13).

Nowadays, tocolytics are widely consumed and they are considered as the first-line of treatment (14). However, no tocolytics drugs -with complete efficacy and without any side effects- have been introduced. Therefore the researches are still being continued in order to provide the safe drugs for this serious problem (15).

Magnesium sulfate and Terbutaline is used as the first line of treatment of the preterm labor and Nifedipine and Indomethacin are recommended in the cases which are more difficult and resistant to cure. Furthermore in some articles, they are presented as drugs which are preferred to the first line medicines (16). But it was not approved by the results of the other researches. It is noted that Indomethacin treatment is not effective for such problem so Further research is needed to confirm its impacts on preterm labor (17-18). Since there is no theoretical consensus regarding the administration of tocolytics so it should be empirically decided to choose a prepare treatment for this disease (19).

After finishing the necessary studies on the efficacy of Indomethacin, King and colleagues reported that this drug could further reduce the rate of preterm deliveries compared with placebo and magnesium sulfate (19-20). In our research, it has been also demonstrated that Indomethacin has beneficial effects on reducing preterm birth such as magnesium sulfate. There is no significant difference between the patients of two groups in terms of the physical conditions of the newborns and the infants at birth ($P=0.294$).

In a research conducted by Lewis and colleagues on the 44 pregnant women with symptoms of preterm delivery, the synthetic efficacy of (Indomethacin + Magnesium Sulphate) was compared with the Magnesium Sulphate in order to postpone the preterm labor and It was indicated that the preterm labor delay in the patients who have consumed a combination of tocolytics drugs and the cases who have taken just a Magnesium Sulphate were respectively as 368 hours and 71 hours (21).

In our study, the average intervals between the start of pains and the true labor were respectively 83.01 ± 91.53 and 83.76 ± 127.42 among the cases (Indomethacin) and control group So there was no significant difference in the average intervals between the onset of pains and the true labor among two groups($P=0.968$).

Whereas Indomethacin is a potent inhibitor of prostaglandin, so in some studies, it has been introduced as the most effective tocolytics drugs which has the most efficacy in order to the treatment of preterm labor (22). Potential effects of Indomethacin are superior to magnesium sulfate which is considered as a first line treatment; so it could inhibit the preterm labor more than 48 hours (17).

In Panther et al' research, it was indicated that the oral tocolytics Indomethacin could inhibit the preterm labor more than 48 hours in 81% of case while the placebo could stop this process more than 48 hours just in 56% of cases. This could be due to initial treatment with magnesium sulfate or Ritodrine and longer duration of Indomethacin (18). In our study, the delivery delay was more than 48 hours in 26 cases of the patient groups (Indomethacin) which was higher than the 22 cases of control group but this difference was not significant.

Magnesium sulfate which is the first line treatment of preterm labor is widely used in obstetric services. The analysis of Amon and colleagues indicated that intravenous magnesium sulfate could delay the delivery about 24 – 48 hours, in 74 and 60 % of women (23). In our research, the magnesium sulfate led to a delay in preterm labor more than 24-48 hours in 32-60% of cases.

In other study, the intravenous magnesium sulfate (initial dose: 6 grams, then 2 grams per hour) are less effective in delaying delivery compared with the oral Nicardipine (initial oral dose: 40 mg and then 20 mg per 2 hours, maximum to 80 mg) (22). According to Makunz et al' analyses, the neonatal complications are higher in the Indomethacin group which is due to the lack of control over the confounding variables (17). Despite this fact that Pantr and colleagues mentioned to the two Necrotizing enterocolitis caused by Indomethacin, but this difference was not statistically significant (18).

Conclusion

In our research, it has been also demonstrated that Indomethacin has beneficial effects on reducing preterm birth such as magnesium sulfate. There is no significant difference between the patients

of two groups in terms of the physical conditions of the newborns and the infants at birth and there was no significant difference between the average intervals of the pains onset and the true labor. In our study, the magnesium sulfate led to a delay in preterm labor more than 24-48 hours in 32-60% of cases and in contrast, the Indomethacin led to a delay in this progress more than 24-48 hours in 37-63% of cases.

The apgar rate of infants in the Indomethacin group was significantly higher than in controls at the first second. There was no significant difference between the infants of both Indomethacin and control groups in terms of the apgar rate at the fifth seconds. The infants' mortality rate and the hospitalization in NICU were similar in both methods.

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