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RESEARCH

The Differences Between The Mean Levels of Maternal Serum IL-6 Based on The Success of The Administration of Tocolytic in Preterm Labor

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Abstract

Preterm labor needs to be prevented, one of the prevention methods is by tocolytic administration which could prevent labor thus providing a chance for lung maturation. Preterm Pregnancy is associated with increased concentrations of cytokines such as Interleukin (IL). The increasing concentration of maternal serum IL-6 can be used to predict preterm labor. This research uses the design Cross-Sectional Comparative to determine differences in means of maternal serum levels of IL-6 based on the success of the administration of a tocolytic agent on preterm labor. This study was performed on pregnant women who come to the obstetric emergency room of DR. MA. Hanafiah Batusangkar Hospital within August-November 2015. The total number which was included in statistical analysis was 34 pregnant women which were divided into 2 groups, 17 people in the group of patients who failed in tocolytic agent administration, and 17 people in the group who success in managed with a tocolytic agent. Statistical analysis was performed to analyze the validity using the T-test. There are significant differences in the average rate of maternal serum IL-6 in patients who failed to treat with a tocolytic agent and successful to treat with a tocolytic agent. Seen from the p-value 0.000. Levels of maternal serum IL-6 in patients who failed to treat with a tocolytic agent were higher than successful to treat with a tocolytic agent.

Keywords: *IL-6, Tocolytic, Preterm labor*

INTRODUCTION

Preterm delivery is a major cause of neonatal mortality and is associated with neonatal morbidity in both the short and long term. Preterm delivery is the term used for babies born at less than 37 weeks of gestation. [1,2]

Preterm delivery is associated with many maternal factors but the etiology has not been determined. Intrauterine infection plays an important role. Many attempts to prevent preterm labor have been made but none have been proven to be effective. Most interventions are carried out when signs of labor have appeared. Therefore, the intervention is more aimed at reducing neonatal morbidity and mortality.[2,3]

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The rate of preterm deliveries in Europe is approximately 5–7%. In the United States, the rate of preterm deliveries is 11%. In RSUP Dr. M Djamil Padang during 2002, the incidence rate of preterm labor was 17.83% (340 cases, both abdominal and vaginal birth) from 1906 deliveries that year. Of these, 56 cases (2.94%) were imminent preterm labor, with a perinatal mortality rate of 4.98%. Hospital Medical Record RS. M. Djamil Padang, in 2014, there were 132 cases of preterm labor from 1885 deliveries (7%). [3,4]

Preterm delivery has a large impact on short- and long-term morbidity. The level of morbidity can be reduced by preventing preterm labor, such as early and accurate prediction, intervention to eliminate risk factors, and delay the occurrence of labor. So this encourages us to do further research. Compared with babies born at term, preterm babies, especially those born with gestational age <32 weeks, have a 70 times higher risk of death, because they have difficulty adapting to life outside the womb due to immaturity of their organ systems such as lungs, heart, kidneys, liver and digestive system. The earlier the preterm birth, the greater the risk of morbidity and mortality. Considering that it is the main cause of neonatal morbidity and mortality, it is necessary to prevent preterm labor, one way is to administer tocolytics which can prevent the continuation of the labor process which is beneficial at least give a chance for lung maturation. [3,5,6,7]

Spontaneous delivery is associated with the activation of inflammatory reactions in pregnancy. Cytokines cause the recruitment of inflammatory cells into the choriodecidual membrane and are thought to be a contributing factor in the occurrence of preterm labor. In previous studies, it was stated that preterm pregnancy was associated with an increase in the concentration of cytokines such as Interleukin (IL), one of which was IL-6. In particular, elevated IL-6 concentrations appear to be a marker for preterm labor. These cytokines can stimulate the amnion and decidua to produce prostaglandins. [8,9]

These observations prompted us to investigate the participation of IL-6 in preterm labor. IL-6 is known as other cytokines as a major mediator in response to infection and tissue injury. Previous studies have found that the release of IL-6 will stimulate uterine tissue to form prostaglandins which will trigger parturition and cause preterm labor. [7,11,12] If there is a large amount of IL-6 release, the uterus will be more stimulated to contract, and possibly the success of tocolytics will be smaller.[7,11] No studies have been conducted to assess differences in mean maternal serum IL-6 levels based on the success of tocolytic administration in imminent preterm labor.

METHOD

This study used a cross-sectional comparative design to determine the differences in mean maternal serum IL-6 levels based on the success of tocolytic administration in preterm labor. This research was conducted at SMF Obstetrics and Gynecology, Faculty of Medicine, Andalas University, Padang-General Hospital DR. MA. Hanafiah Batusangkar. Starting from

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March 1st, 2015 to December 1st, 2015. The target population of this study was all patients treated with preterm labor at RSUD DR. MA. Hanafiah Batusangkar. The sample of this study were patients who met the inclusion criteria and did not have the exclusion criteria. Referring to the type of research 9, 17 successful tocolytic samples were obtained, and 17 failed sample tocolytics. Sampling was carried out by consecutive sampling The sample was considered successful tocolytic if within 2x24 hours after drug administration there was no delivery in a patient with an onset of labor between 24 complete weeks of gestation to 34 complete weeks (33 weeks 6 days) of gestational age which proved appropriate with HPHT and ultrasound and the presence of contractions. The inclusion criteria in this study were imminent preterm labor gestational age 24 weeks to 34 weeks (full) in RSUD DR. MA. Hanafiah Batusangkar, Primigravida, single pregnancy, normotension, and Willing to participate in research. While the exclusion criteria in this study were suffering from cardio-pulmonary, vascular, and metabolic diseases: excluded with a history of heart, lung, liver, kidney disease, diabetes mellitus, and hypertension, preeclampsia/eclampsia, IUFD, IUGR, antepartum hemorrhage, history of infection. in the mother, and other contraindications for the continuation of the pregnancy or there are indications for termination of the pregnancy. The mean difference test used the t-test with a significance limit of $p < 0.05$.

RESULTS

Of the 34 samples that met the inclusion and exclusion criteria of the study, 17 people in the tocolytic group failed and 17 were successful in tocolytic. The characteristics of the study sample based on age, body mass index, are as shown in table 1.

Table 1. Characteristics of the Research Sample

Characteristics	Group Fail Tocolytics (Mean ± SD)	Tocolytic Success (Mean ± SD)	p
Mother's Age	26.7 ± 5.7	27.5 ± 3.2	0.071
BMI	20.3 ± 2.4	22.2 ± 2.4	0.609
Gestational Age	32.12 ± 3.07	30.94 ± 3.07	0.195
Leukocytes	19.9 ± 3.8	10.2 ± 2.4	0,000

From table 1 it can be seen that the mean value of the study sample was 27.08 ± 4.6 years. Based on the characteristics of the age of the respondents in Table 1, it is found that the mean value of the age group of patients with imminent preterm labor who succeeded in tocolytics was higher than the mean value in the group of imminent preterm labor patients who failed tocolytic was 27.47 ± 3.2: 26.7 ± 5, 7. Statistically, this difference was not significant, as seen from the p-value = 0.636.

The average body mass index (BMI) of the study sample was 21.23 ± 2.90 kg / m2. Based on the BMI characteristics in table 1 of each group, the mean value of BMI in the group of

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patients with imminent preterm labor who succeeded in tocolytic was higher than the mean value in the group of imminent preterm labor patients who failed tocolytics was obtained (22.2 ± 3.1: 20, 3 ± 2,4). Statistically, this difference was not significant, as seen from the p-value = 0.609.

The mean gestational age in the tocolytic successful group was 30.94 ± 3.07 and the tocolytic failure group was 32.12 ± 1.26 This indicates that the difference in gestational age in patients who succeeded in tocolytics was equivalent to those who failed tocolytics, this is seen from the p-value of 0.159 (p> 0.05).

The sample means leukocyte count in this study was 15.097 ± 5.850 (103 / mm3). Based on the characteristics of serum leukocyte levels in table 1, the mean value of serum leukocyte levels in the group of patients with imminent preterm labor who failed tocolytic was higher than the mean value in the group of preterm imminent preterm labor who were successful tocolytic, obtained 19.9 ± 3.8 (103 / mm3): 10.2 ± 2.4 (103 / mm3). Statistically, this difference is significant, it can be seen from the value of p = 0.000.

Table 2. Differences in Mean Maternal Serum IL-6 Levels in Tocolytic Successful and Tocolytic Failure

	Tocolytic Success n = 16	Tocolytic Failure n = 17	p
Mean	56,294	1,732	0,000
SD	37,169	1,483	

Based on table 2, it is found that the mean maternal serum IL-6 levels in imminent preterm labor tocolytic failure was higher than the mean maternal serum IL-6 levels in successful imminent preterm labor, namely 1.732 ± 1.483pg / ml. The results of statistical analysis showed a significant difference between the mean levels of IL-6 in patients with imminent preterm labor who succeeded in tocolytics and in patients with imminent preterm labor who failed tocolytics. This can be seen from the p-value of 0.000. This suggests that maternal serum IL-6 levels in patients with imminent preterm labor who failed tocolytic were higher than those who succeeded in tocolytics.

In this study, the lowest IL-6 level in imminent preterm labor patients who failed tocolytic was 6.181 pg / mL, and the highest IL-6 level in imminent preterm labor patients who failed tocolytic was 556.735 pg / mL. Meanwhile, the lowest IL-6 level in the tocolytic successful preterm labor was 0.021 pg / mL and the highest IL-6 level in the tocolytic group was 5.800 pg / mL. At extreme IL-6 levels with a value of 556,735, data excluded were performed to help normalize the data. So that in this study only tests were carried out on 16 samples imminent preterm labor of the tocolytic failure group and 17 samples in the tocolytic success group after passing the data cleaning process.

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DISCUSSION

From 34 samples, 17 samples of preterm labor were successful tocolytic and 17 samples of imminent preterm labor failed tocolytic. In this study, the characteristic data were grouped based on the patient's age, gestational age, and leukocyte levels with the results of the mean age distribution in the group that succeeded in tocolytics were 27.47 ± 3.24 years and the group that failed tocolytics was 26.71 ± 5.74 years. This shows that the age difference between patients who succeed in tocolytics and those who fail tocolytics is equivalent, this can be seen from the p-value of 0.636 (p> 0.05). In line with Sina's 2014 study, the average age of patients with preterm labor was also 27.67 ± 7.26 years.

The mean gestational age in the tocolytic successful group was 30.94 ± 3.07 and the tocolytic failure group was 32.12 ± 1.26 This indicates that the difference in gestational age in patients who succeeded in tocolytics was equivalent to those who failed tocolytics, p. This can be seen from the p-value of 0.159 (p> 0.05). This indicates that there is no relationship between gestational age and the success of tocolytic administration.

The average number of leukocytes in the sample in this study was 15.097 ± 5.850 (103 / mm3). Based on the characteristics of serum leukocyte levels in table 1, it was found that the mean value of serum leukocyte levels in the group of patients with imminent preterm labor who failed tocolytic was higher than the mean value in the group of imminent preterm labor patients who were successful tocolytic was obtained (10.2 ± 2,4: 19, 9 ± 3.8 (103 / mm3)). Statistically, this difference is significant, it can be seen from the p-value of 0.000. In pregnancy, the number of leukocytes did increase to 14,800 in the second trimester. In connection with the inflammatory response mechanism that occurs at the onset of labor, leukocyte cells, especially neutrophil cells and certain monocyte cells, are found. Peltier in 2003, mentioned an increase leukocytes in the myometrium are mainly due chemokines MCP-1 and IL-6 which will also attracts macrophages and neutrophils. [12]

In this study, the lowest IL-6 levels in imminent preterm labor patients who failed tocolytic were 6.181 pg / mL, and the highest IL-6 levels in imminent preterm labor patients who failed tocolytic were 556.735 pg / mL. Meanwhile, the lowest IL-6 level in the tocolytic successful preterm labor was 0.021 pg / mL and the highest IL-6 level in the tocolytic group was 5.800 pg / mL. To get good mean and standard deviation value in this research, data cleaning was done. Patients with IL-6 levels of 556,735 pg / mL were excluded to eliminate data outside the norm so that it helped normalize the data distribution.

After the t-test was carried out on samples of patients with imminent preterm labor who were successful tocolytic and patients with imminent preterm labor who failed tocolytic, it showed that there was a significant difference in the mean maternal serum IL-6 levels in preterm preterm delivery with tocolytic failure was higher, namely 56,294 ± 37,169 pg/ml compared with the mean maternal serum IL-6 level in tocolytic successful imminent preterm labor, namely 1.732 ± 1.483pg / ml. The results of statistical analysis showed a significant

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difference between the mean levels of IL-6 in patients with imminent preterm labor who succeeded in tocolytics and in patients with imminent preterm labor who failed tocolytics. This can be seen from the p-value of 0.000.

IL-6 is part of the inflammatory pathway and is produced by endometrial stromal cells, decidual cells, and macrophages in response to interleukin-1 and tumor necrosis factor. IL-6 stimulates prostaglandin production, which predisposes to preterm labor. The increase in IL-6 production will increase the production of prostaglandins which will trigger an increase in Metalloprotease which in turn causes cervical thinning and Chorioamnion weakening and rupture, as well as myometrial contraction so that preterm labor occurs. Lockwood et al in a previous study also assessed the association between elevated IL-6 levels in patients with preterm delivery. There was an increase in IL-6 concentrations between 24 to 36 weeks of gestation wherein preterm delivery the IL-6 levels increased 3-4 times. [3,12,13]

This study is following Shahshahan Z et al, 2014 who identified maternal serum cytokine IL-6 in predicting preterm labor. In this study, there was a striking association with elevated IL-6 levels in women with preterm labor.

High levels of IL-6 are influenced by several things, including Uteroplacental Vascular Insufficiency, Maternal Stress, Exaggerated Inflammatory Responses such as inflammatory reactions triggered by infection, Decidual Hemorrhage, for example in Solutio Placenta which activates thrombin to form Matrix Metalloproteinase (MMP) produced by a fetal membrane, decidual and cervix thus stimulating changes in the cervix, preterm premature rupture of membranes and uterine contractions. The last factor that affects the increase of Interleukin-6 is the presence of multiple gestations and hydramnios.

CONCLUSION

There is a significant difference in the level of IL-6 serum maternal patients with imminent preterm labor who fail tocolytic and tocolytic success, IL-6 levels in imminent preterm labor who fail tocolytic are higher than imminent preterm labor who succeed tocolytic, where maternity progress will continue at High IL-6.

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