Research Article

Betamethasone was more Effective than N-acetylcysteine for Lung Maturation

Betametason lebih Efektif dibandingkan N-acetylcystein untuk Pematangan Paru

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Abstract

Objective: To compare the effectivity of N-acetylcysteine with Betamethasone in fetal lung maturation.

Methods: This research was a double blind randomized clinical trials in women threatened by preterm delivery (28 to 34 weeks of gestation).

Results: There were 90 subjects randomly assigned to N-acetylcysteine group (n=30), betamethasone group (n=30), and the control group (who had not been given a tocolytic, n=30). Fetal lung maturation was assessed with the p. The values for lung maturation at random were 5 foams. After being tested with the Tapp, there were significant differences between the 3 groups of this study based on analysis of variance (ANOVA) (p = 0.001). The average foam on the N-acetylcysteine was 4.8 ± 1.3 while in the group Betamethasone, was 3.2 ± 1.0, and the average amount of foam in the control group was 5.5 ± 1.6. The end point of the Tapp were mature and immature, which in the N-acetylcysteine group there were 21 subjects (70.0%) with mature lung, Betamethasone groups 28 subjects (93.3%) with mature lungs, whereas in the control group, there were 15 subjects (50.0%) with mature lung.

Conclusion: Betamethasone was more effective than N-acetylcysteine for lung maturation in women threatened with preterm delivery.

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Keywords: betamethasone, fetal lung maturation, N-acetylcysteine

Abstrak

***Tujuan**: Membandingkan efektivitas pemberian N-acetylcystein dengan Betametason untuk pematangan paru janin.*

***Metode**: Penelitian ini merupakan penelitian uji klinis acak buta ganda pada wanita dengan ancaman persalinan preterm (usia 28 sampai 34 minggu).*

***Hasil**: Terdapat 90 subjek penelitian yang dipilih secara acak sederhana, pada kelompok N-acetylcystein (n=30), kelompok betametason (n=30), dan kelompok kontrol (yang tidak sempat diberi tokolitik, n=30). Penilaian kematangan paru janin dilakukan dengan uji Tapp. Batas nilai untuk maturasi paru secara acak adalah 5 busa. Setelah dilakukan uji Tapp, didapatkan perbedaan yang bermakna dari 3 kelompok penelitian ini berdasarkan analisis varian (Anova) (p=0,001), didapatkan rerata busa pada kelompok N-acetylcystein sebesar 4,8±1,3 sedangkan pada kelompok Betametason lebih sedikit dibandingkan kelompok N-acetylcystein yaitu 3,2±1,0, sementara rerata jumlah busa pada kelompok kontrol sebanyak 5,5±1,6. Hasil akhir uji Tapp adalah matur dan imatur, pada kelompok N-acetylcystein didapatkan 21 subjek (70,0%) dengan paru matur, kelompok Betametason sebanyak 28 subjek (93,3%) dengan paru matur serta merupakan kelompok yang paling banyak mengalami paru matur, sedangkan pada kelompok kontrol, didapatkan 15 subjek (50,0%) dengan paru matur.*

***Kesimpulan**: Betametason lebih efektif dibandingkan N-acetylcystein sebagai pematangan paru pada wanita dengan ancaman persalinan preterm.*

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***Kata kunci**: betametason, N-acetylcystein, pematangan paru janin*

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INTRODUCTION

Respiratory distress syndrome (RDS) is one of the main causes of infant death during the newborn period.[1-3] The incidence of respiratory distress syndrome (RDS) has been associated with maternal gestational age and birth weight of the newborn, which characterized by difficulty of breathing in infants, signed by the presence the two of four important symptoms: tachypneu (> 60 bpm), cyanosis, retraction of the ribs and sternum, and expiratory groaning.[4-6]

In an effort to reduce the incidence and the severity of RDS during threatening preterm delivery, the mother is administered with antenatal steroids or the prophylactic surfactant which can be given when resuscitate the newborn, or both. There have

been many studies conducted on the use of antenatal steroids with result in reducing of RDS by 50% as demonstrated by Liggins and Howie (1972) and by the NIH Consensus Development Panel (1994) with the conclusion that there is of no evidence of side effects of corticosteroid use in pregnancies with hypertension, gestational diabetes, multiple pregnancy, intrauterine growth restriction and fetal hydrops.[7-10]

The use of N-acetylcysteine to increase the levels of surfactant, was first conducted in 1980, in patients underwent lung surgery. They evaluated the surface tension of the specimen from lung biopsy. Based on this study, it is known that administration of i.m. 2 x 300 mg NAC significantly increased the activity of the superficial alveolar epithelial fluid by lowering the surface tension and increased the elasticity of lung tissues.[11] Administration of N-acetylcysteine in pregnant women who experienced acetaminophen intoxication, can be measured in umbilical blood, proving that N-acetylcysteine had the ability to pass through the placental barrier. N-acetylcysteine was also safe in pregnant and lactating women.[12]

METHODS

This research was a randomized double blind clinical trials in pregnant women threatened with preterm delivery (28 to 34 weeks) in RSMH Palembang. The study started in August 2010 and ended in February 2012. Inclusion criteria included women with 28-34 weeks of pregnancy threatened by preterm delivery, proven by an ultrasound examination and gave birth before 35 weeks of gestation, willing to join the study and signed the informed consent, and had never received medication for lung maturation in the past pregnancy. Patients who met the study criteria were then checked for physical examination, complete blood count, urinalysis and ultrasound examination. Then the data was recorded in the record of research and study registry book. Patients who were already in a state of labor were assigned to group 3 (control group) and been followed until the delivery. Patients who were given tocolytics, performed simply randomly with the aid of random table made by residents who had been trained previously to determine the group 1 (N-Acetylcysteine) and group 2 (Betamethasone). If side effects occur, the patient dropped out and treated according to the symptoms. The newborn birth weight, Apgar scores and the onset of RDS were observed during the treatment, indicated by clinical symptoms of dyspnoea (60x/min), cyanosis, grunting, and retractions, and then the severity of asphyxia was determined by Apgar scores (mild, moderate and severe asphyxia). The neonates will then underwent chest radiology examination. Patients received the tocolytic protocol, including Nifedipine 10mg per oral, which can be repeated 2-3 times/day, and continued every 8 hours until the contraction disappeared. Mothers who gave birth before 35 weeks of gestation, were tested with lung maturation test. One cc of Amniotic fluid sample was taken if the membrane ruptured >24 hours after the last drug administration. Assessment of fetal lung maturation performed with the Tapp test.

Data were collected in the form of research that has been prepared. Statistical processing of data was performed using SPSS 14 program, using Chi Square test, T-test and Anova test.

RESULTS

Of the 90 subjects, the group that received N-acetylcysteine 300 mg i.m. for 3 days (n = 30), betamethasone group 12 mg qd i.v. for 2 days (n = 30) and the control group (who had not given a tocolytic, n = 30), the age distribution of subjects are mostly in the age group of 20-35 years, with a body mass index of 18.5 to 25, housewife, graduated from high school, and the pregnancy was in the 33-34 weeks of gestation. According to the statistical analysis performed, which was chi-square and ANOVA, there was no significant difference in general characteristics of the three groups.

Assessment of fetal lung maturity was performed with the Tapp test. After testing the Tapp, the average number of foam in the group receiving N-acetylcysteine was 4.8 ± 1.3 and there was significant difference in the amount of foam before and after the Tapp test on the N-acetylcysteine group (p = 0.001). On Betamethasone group the average number of foam was less than the N-acetylcysteine group, which was 3.2 ± 1.0, even though there was also a significant difference in the number of foam before and after the Tapp test on Betamethasone group (p = 0.001). Meanwhile, the average number of foam in the control group after the test was as much as 5.5 ± 1.6, but there was no significant difference in the number of foam before and after the Tapp test in the control group (p = 0.077). The mean amount of foam of each re-

Table 1. General Characteristic of the subjects

Characteristic	N-acetylcysteine N %	Betamethasone N %	Control N %	p
Age (years)				0.552
< 20	2 (6.7)	0 (0.0)	3 (10.0)	
20-35	24 (80.0)	25 (83.3)	23 (76.7)	
> 35	4 (13.3)	5 (16.7)	4 (13.3)	
BMI				0.828
18.5-25	18 (60)	18 (60.0)	20 (66.7)	
> 25	12 (40)	12 (40.0)	10 (33.3)	
Occupation				0.444
Housewife	22 (73.3)	22 (73.3)	27 (90.0)	
Laborer	3 (10.0)	4 (13.3)	1 (3.3)	
Civil Servant	5 (16.7)	4 (13.3)	2 (6.7)	
Education				0.862
Junior high school	8 (26.7)	9 (30.0)	6 (20.0)	
Senior high school	20 (66.7)	18 (60.0)	22 (73.3)	
Bachelor	2 (6.7)	3 (10.0)	2 (6.7)	
Parity				0.543
1	18 (60.0)	14 (46.7)	18 (60.0)	
2	5 (16.7)	10 (33.3)	9 (30.0)	
3	5 (16.7)	5 (16.7)	3 (10.0)	
4	2 (6.7)	1 (3.3)	0 (0.0)	
Gestation				0.086
33-34 (w)	20 (66.7)	22 (73.3)	14 (46.7)	
< 33 (w)	10 (33.3)	8 (26.7)	16 (53.3)	

Chi- Square test

search group based on a complete test of the Tapp can be seen in Table 2.

Table 2. The average of foam in each group after the Tapp test

Group	Foam		*p*
	Before	After	
N-acetylcysteine	6.0±0.0	4.8±1.3	0.001
Betamethasone	6.0±0.0	3.2±1.0	0.001
Control	6.0±0.0	5.5±1.6	0.077

T-Pairs test

Then analysis of variance (ANOVA) was being performed to see the overall differences in the three study groups, statistical test results found a significant differences (p = 0.001) in the amount of foam in all three study groups. Analysis of variance (ANOVA) of the three groups was based on the Tapp test (Table 3).

Table 3. Variance analysis on the three groups based the Tapp test

Foam	Groups			p*
	N-acetyl cysteine	Betametha sone	Control	
Before	6.0±0.0	6.0±0.0	6.0±0.0	0.999
After	4.8±1.3	3.2±1.0	5.5±1.6	0.001

** ANOVA test*

The end result of the Tapp test was categorized into mature and immature. We found that there were 21 subjects (70.0%) in the N-acetylcysteine groups with mature lung and 28 subjects (93.3%) in the bethametasone group. Whereas in the control group, there were 15 subjects (50.0%) with mature lung, as listed in Table 4. Thus, it can be said that the administration of Betamethasone was more effective for lung maturation in women threatened with preterm delivery compared with N-Acetylcystein.

Table 4. Lung Maturation After Administration of N-Acetylcysteine Compared with Betamethasone in women threaten preterm delivery

Group	Test Tapp		N(=90)
	Mature (%)	Immature (%)	
N-acetylcysteine	21 (70.0)	9 (30.0)	30 (100.0)
Betamethasone	28 (93.3)	2 (7.7)	30 (100.0)
Control	15 (50.0)	15 (50.0)	30 (100.0)

DISCUSSIONS

Of the three groups there were no significant differences in general characteristic included age distribution of the subject which is mostly in the age group 20-35 years, with a body mass index of 18.5 to 25, housewife, graduated from high school, and had pregnancy of 33-34 weeks gestation, with p> 0.05. So that, it can be concluded that the subjects in this study was homogen and the final conclusions about the effectiveness of therapy among the three groups can be made.

Assessment of fetal lung maturation performed with the Tapp tests. Limit values for lung maturation at random was 5 foams. If there were no more than 5 foams on the ether layer, the lung is considered as a mature lung.[13-16] After performed the Tapp test, there was a significant differences from the 3 groups of this study which was based on analysis of variance (ANOVA) (p = 0.001), the average foam on the N-acetylcysteine was 4.8 ± 1.3, while in the group Betamethasone it was 3.2 ± 1.0, and in the control group was 5.5 ± 1.6. The end result of the Tapp test was categorized into mature and immature. There were 21 subjects (70.0%) in the N-acetylcysteine groups with mature lung and 28 subjects (93.3%) in the betamethasone group. Whereas in the control group, there were 15 subjects (50.0%) with mature lung. Based on the results of research Utami (2009) suggested the administration of a combination of N-acetylcysteine and Dexamethasone (77.3%) was proven to be more effective in lung maturation compared to the administration of only N-acetylcysteine (54.5%) or dexamethasone (36.4%).[17] In the meantime, Rahardjo study (2003) demonstrated that the 85.7% of patients receiving a combination of N-acetylcysteine and Dexamethasone achieved lung maturation, while only 57.2% of patients receiving a single dexamethasone administration achieved the same result.[18] The study on the role of N-acetylcysteine on lung was first described in the study by Mereto (1980) of 16 patients underwent thoracotomy surgery and also by Muller (2001), reporting the ability of NAC to protect against damage of surfactant metabolism by NO2.[11,19-21] Mechanism of action of NAC itself in the process of fetal lung maturation was as a precursor of glutathione, to prevent lipid peroxydation and inactivation of surfactant due to reactive oxygen compounds on the pneumosit type II.[22-26] This study showed that the use of corticosteroids, in this case betamethasone, more effective than the use of NAC in fetal lung maturation in women threatened with preterm delivery.

CONCLUSIONS

The effectivity of N-acetylcysteine for fetal lung maturation in women threatened with preterm delivery was 70.0%, meanwhile Betamethasone, it was 93.3%. It can be concluded that Betamethasone was more effective than N-acetylcysteine for lung maturation in women threatened with preterm delivery.

SUGGESTIONS

Betamethasone administration is recommended for fetal lung maturation in women threatened with preterm delivery. Further research is needed with a larger number of samples in order to obtain data that can support the role of N-acetylcysteine drug in lung maturation.

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