Effects of Erdosteine Administration in Serum C-Reactive Protein Level in Stable Chronic Obstructive Pulmonary Disease Patients

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Background. Systemic inflammation contributes to the development of intrapulmonary and extra pulmonary disorders, and as an independent risk factor for exacerbation of chronic obstructive pulmonary disease (COPD) has proven. The use of corticosteroids as anti-inflammatory agents has limitation for their undesirable side effects and different efficacy among the patients. Erdosteine, a mucolytic agent widely used in COPD, has been proven to be able to inhibit several mediators such as reactive oxygen species (ROS) and eicosanoids, which are involved in oxidative stress and inflammation.
Objective. This study aimed to discover the effects of erdosteine administration in serum C - reactive protein (CRP) level in stable COPD patients.
Methods. The research was a randomized controlled trial, which compared add-on therapy used erdosteine 300 mg bid versus placebo, for 10 days, combined with COPD standard treatments. The patients was recruited at RSKP Respira Yogyakarta outpatient clinics. Diagnoses were confirmed used spirometry based on GOLD criteria. Evaluation of CRP levels was hold before treatment and on the eleventh day, used highly sensitive quantitative immunometric assay.
Result. Thirty-eight legible COPD patients recruited and randomly assigned to either erdosteine group or placebo group. One patient in erdosteine group was drop out because of exacerbation and one patient from each group were lost to follow up. There are 35 subjects (97.1% men, age range 40-77 years, median FEV1 0.83 (0.50-10.08) L, hs-CRP 0.84 (0.18-18) mg/L) who completed the study, 19 subjects in erdosteine and 16 subjects in placebo group. Baseline characteristics were similar between two groups. There were no significant decreases in median hs-CRP level in erdosteine vs. placebo group at day 11 (-0.10 (-16.16-+4.31) *vs.* 0.005 (-11.7-+11.03) mg/L; p 0.275). In COPD GOLD 3 sub-population, hs-CRP serum level decline was greater in erdosteine group compared to placebo (-0.56 (-16.16-+0.44) *vs.* 0.11 (-11.7- +11.03) mg/L; p 0.03) this might be related to greater oxidative stress in severe COPD that makes antioxidative effects of erdosteine reduce CRP more significantly in severe COPD.
Conclusion. Effects of erdosteine supplements, 300 mg bid for 10 days, could decrease hs-CRP level in erdosteine insignificantly compared to placebo.

Keywords*: table COPD, C-reactive protein, erdosteine, FEV1, GOLD*

Latar Belakang. Peradangan sistemik berkontribusi terhadap perkembangan gangguan paru intrapulmoner dan ekstra, dan sebagai faktor risiko independen untuk eksaserbasi penyakit paru obstruktif kronik (PPOK) telah terbukti. Penggunaan kortikosteroid sebagai agen antiinflamasi memiliki keterbatasan untuk efek samping yang tidak diinginkan dan kemanjuran yang berbeda di antara pasien. Erdosteine, agen mukolitik

yang banyak digunakan pada PPOK, telah terbukti dapat menghambat beberapa mediator seperti spesies oksigen reaktif (ROS) dan eikosanoid, yang terlibat dalam stres oksidatif dan pembengkakan.
Tujuan. Penelitian ini bertujuan untuk mengetahui efek pemberian erdostein pada tingkat protein C-reaktif (CRP) serum pada pasien COPD yang stabil.
Metode. Penelitian ini merupakan uji coba terkontrol secara acak, yang membandingkan terapi tambahan menggunakan tawaran erdosteine 300 mg versus plasebo, selama 10 hari, dikombinasikan dengan perlakuan standar COPD. Pasien direkrut di klinik rawat jalan RSKP Respira Yogyakarta. Diagnosis ditegakkan menggunakan spirometri berdasarkan kriteria GOLD. Evaluasi tingkat CRP ditahan sebelum perawatan dan pada hari kesebelas, menggunakan tes imunometrik kuantitatif yang sangat sensitif.
Hasil. Tiga puluh delapan pasien COPD yang dapat dibaca direkrut dan ditugaskan secara acak pada kelompok erdostein atau kelompok plasebo. Satu pasien dalam kelompok erdostine dikeluarkan karena adanya eksaserbasi dan satu pasien dari setiap kelompok hilang untuk ditindaklanjuti. Ada 35 subjek (97,1% pria, rentang usia 40-77 tahun, median FEV1 0,83 (0,50-10,08) L, hs-CRP 0,84 (0,18-18) mg / L) yang menyelesaikan penelitian, 19 subjek dalam erdosteine dan 16 subyek dalam kelompok plasebo. Karakteristik dasar serupa di antara dua kelompok. Tidak ada penurunan yang signifikan pada tingkat median hs-CRP pada kelompok erdostein vs plasebo pada hari ke 11 (-0,10 (-16,16- + 4,31) vs 0,005 (-11,7- + 11,03) mg/L; p 0,275). Pada sub populasi COPD GOLD 3, penurunan kadar serum hs-CRP lebih besar pada kelompok erdosteine dibandingkan plasebo (-0,56 (-16,16- + 0,44) vs 0,11 (-11,7- + 0,03) mg/L; p 0,03) ini mungkin terkait dengan stres oksidatif yang lebih besar pada COPD berat yang membuat efek antioksidan dari erdosteine mengurangi CRP lebih signifikan pada COPD berat.
Kesimpulan. Efek suplemen erdosteine, 300 mg bid selama 10 hari, dapat menurunkan kadar hs-CRP pada erdosteine secara tidak signifikan dibandingkan dengan plasebo.

Kata kunci: *tabel COPD, protein C-reaktif, erdostein, FEV1, GOLD*

Introduction

A chronic obstructive pulmonary disease is a chronic and progressive inflammatory disease involving not only the lungs but also multiple organs and systems outside of the lung[1,2]. Systemic inflammation contributes to the pathogenesis ofpulmonary and extrapulmonary disorders of COPD[2].

Systemic inflammation is currently regarded as a hallmark of COPD and found to contribute to the pathogenesis of pulmonary and extrapulmonary disorders PPOK[2,4] Increased systemic inflammation is an independent risk factor for acute exacerbations of COPD[4]. Recurrent exacerbations lead to decreased quality of life, decreased therapeutic response, increased progression of disease, as well as increased mortality[5].

Dal Negro *et al*[7] found that erdosteine, a mucolytic agent, has the ability to inhibit multiple mediators such as reactive oxygen species (ROS), 8-isoprostane serum, IL-8 bronchial, and eicosanoids which are involved in oxidative stress and inflammatory process. Through its ability as an antioxidant and anti-inflammatory, erdosteine expected to improve systemic inflammation in stable COPD. Improvements are expected to slow the systemic inflammatory worsening lung function, preventing extra pulmonary disorders, improving quality of life, as well as prevent exacerbations[9, 10, 11].

Material and methods

This study is a double-blind randomized controlled trial. Subjects are stable COPD

patients in the pulmonary clinic of RSKP Respira Yogyakarta. Inclusion criteria for the study subjects were patients aged ≥ 18 years, stable COPD category 1, 2, 3, or 4, and are willing to fill out informed consent. Patients did not include the categories if they have allergic to erdosteine, or mucolytic erdosteine and other thiol groups (N-acetyl cysteine). In the last 3 days, using corticosteroids, liver disorders, kidney disorders, infection, suffering malignancy, diabetes mellitus, acute myocardial infarction, ischemic heart disease, hypertension, asthma, cor-pulmonale, Crohn's disease, a history of trauma or undergone surgery in the last one month, pregnancy, and lactation.

Subjects who met the inclusion and exclusion criteria randomize into two different groups, receiving 2x300 mg of erdosteine and placebo for 10 days. Evaluation of serum CRP levels was hold before treatment and day 11. Examination of serum CRP is done using immunometric assay method (Immulite 2000^{R}) with result range between 0.1 mg/L to 100 mg/L.

Data analysis

The results of the study were analyzed by a computer program. The difference of numerical data was analyzed using independent t-tes of Mann Whitney U test. The difference in proportions of categorical data was testing by Chi-Square t-test.

Results

Table 1 showed the basic characteristics of study subjects in each group. The median decrease in serum CRP levels erdosteine groups is not statistically greater than placebo (Table 2). The proportion of study subjects who experienced a decrease in serum CRP levels at erdosteine group larger than the placebo group, although not statistically significant (63.2% vs. 50%, p 0.215).

In this research, we performed sub analysis test to the group of subjects with and without systemic corticosteroids as well as research subjects with GOLD two and three. The median change in serum CRP levels of erdosteine and placebo groups in subjects with systemic corticosteroids was -1.03 (-16.16 – (-0.05)) vs. -0.48 (+0.44 -11.7-) (p 0.26), whereas in subjects without systemic corticosteroids was 0.05 (-13- + 4.31) vs. 0.12 (-0.93- + 11.03) (p 0.285).

In the group of COPD GOLD 2, there was no significant change in serum CRP levels between erdosteine and placebo (0.56 ± 2.36 mg / L vs. -1.24 ± 1.83, p 0.085). In the group of COPD GOLD 3, we obtained a greater median decrease in erdosteine group than in the placebo group (Table 4).

Side effects that emerged during the study is shown in Table 6.

Discussion

Systemic inflammation is a major marker of COPD and is thought to be a liaison of the missing link between airway dysfunction with various systemic complications in COPD[4,12]. Erdosteine is a mucolytic agent that has the pleitropic effects, namely antibacterial, antioxidant, and anti-inflammation[13]. Through this ability, it is expected that erdosteine may decrease systemic low-grade inflammation that occurs in patients with stable COPD. Source of systemic inflammation in COPD was not yet fully know and was not

Table 1 Baseline Characteristics

Variable	Erdosteine (n =19)		Placebo (n =16)		p-value
	Number (%)	Mean ± SD Median (min-max)	Number (%)	Mean ± SD Median (min-max)	
Sex					
Male	19 (100)		16 (93.7)		0.09*
Age (year)		68 (40-77)		65 (48-73)	0.26**
Body weight (kg)		51.05 ± 9.77		50.06 ± 5.90	0.36***
Height (cm)		159.63 ± 6.35		157.63 ± 6.45	0.18***
BMI (kg/m^2)		19.93 ± 2.94		20.1 ± 2.03	0.40***
Smoking status					0.49*
Never smoker	0 (0)		2 (12.5)		
Ex-smoker	18 (94.7)		12 (75)		
Inactive smoker	0 (0)		0 (0)		
Active smoker	1 (5.3)		2 (12.5)		
Pack-years					0.50*
0-20	7 (36.8)		7 (43.8)		
21-40	11 (57.9)		7 (43.8)		
41-60	0 (0)		0 (0)		
≥ 61	1 (5.3)		2 (12.5)		
GOLD severity					0.23*
GOLD 1	0 (0)		0 (0)		
GOLD 2	8 (42.1)		5 (31.3)		
GOLD 3	10 (52.6)		11 (68.8)		
GOLD 4	1 (5.3)		0 (0)		
Patient group					0.40*
A	3 (15.8)		4 (25)		
B	5 (26.3)		1 (6.1)		
C	7 (36.8)		8 (50)		
D	4 (21.1)		3 (18.8)		
Routine therapy					0.50*
None	3 (15.8)		1 (6.3)		
Inhaler bronchodilator	0 (0)		2 (12.5)		
Oral bronchodilator Bronchodilator +ICS	10 (52.6) 0 (0)		6 (37.5) 0 (0)		
Bronchodilator + systemic corticosteroids	6 (31.6)		7 (43.8)		
FEV1 (Liter)		0.83 (0.50-1.74)		0.83(0.52-10.08)	0.40**
FVC (Liter)		1.49 ± 0.56		1.48 ± 0.31	0.47***
FEV/FVC		0.63 (0.44-0.94)		0.62 (0.33-0.69)	0.07**
FEV1 (% *predicted*)		0.45 ± 0.13		0.44 ± 0.12	0.35***
hs-CRP (mg/L)		1.14 (0.18-18)		0.77 (0.19-15.70)	0.32**
Statin		0 (0)		0 (0)	
ACE *inhibitor*		0 (0)		1 (6.3)	0.13*
ARB		0 (0)		0 (0)	
Beta blocker		0 (0)		0 (0)	
Vitamin E		0 (0)		0 (0)	
Arthritis		0 (0)		0 (0)	
Hypertension		4 (21.1)		5 (31.1)	0.38*

SD: standard deviation, BMI: body mass index, ICS: inhaled corticosteroids; ACE inhibitor: angiotensin- converting enzyme inhibitor. ARB: angiotensin receptor blocker, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, *: Pearson chi-square/Fisher's exact test/Kolmogorov Smirnov; **: Mann Whitney U test, *** Independent sample t-test

Table 2 Serum CRP levels Erdosteine and Placebo Group

Variable	Erdosteine (n=19)		Placebo (n=16)		p-value
	Median (min-max)	*Mean rank*	Median (min-max)	*Mean rank*	
hs-CRP serum (mg/L)					
day 0	1.14 (0.18-18)	18.74	0.77 (0.19-15.7)	17.13	0.321*
day 11	1.44 (0.10-6.44)	20.08	0.74 (0.1-11.84)	15.53	0.095*
delta	-0.10 (-16.16-+4.31)		0.005 (-11.7-+11.03)		0.275*

* Mann Whitney U-test

Table 3 Proportion of Subjects Experiencing Changes in Serum CRP levels in the placebo group and the erdosteine

	Serum CRP Level				p-value
	Decrease		Increase		
	n	%	n	%	
Erdosteine	12	63.2	7	36.8	0.215*
Placebo	8	50	8	50	
Total	20	57.2	15	42.8	

* Pearson chi-square

Table 4 Serum CRP Level in Subpopulation COPD GOLD 3

Variable	Erdosteine (n=10)		Placebo (n=11)		p-value
	Median (min-max)	*mean rank*	Median (min-max)	*mean rank*	
hs-CRP (mg/L)					
day 0	2.75 (0.26-18)	13.3	0.73(0.19-15.7)	8.91	0.052*
day 11	1.14 (0.25-6.44)	11.55	0.99 (0.15-11.84	10.50	0.349*
delta	-0.56 (-16.16-+0.44)		0.11 (-11.7- 11.03)		0.03*

* Mann Whitney U-test

Table 5 Proportion of Subjects Experiencing Changes in Serum CRP Levels in Subpopulation COPD GOLD 3

	Serum CRP Level				p-value
	Decrease		Increase		
	n	%	n	%	
Erdosteine	7	70	3	30	0.095*
Placebo	4	36.4	7	63.6	
Total	11	52.4	10	90.9	

* Fisher's exact test

Table 6 Side Effects of Erdosteine

Variable	Erdosteine	Placebo
Central nervous system	-	1
Gastrointestinal	2	1
Respiration	-	-
Skin	-	-
Others	-	-
Total	2/19 (10%)	2/16 (6%)

suspect to be multifactorial. Cigarette smoke damage to lung tissue. Lung hyperinflation, tissue hypoxia, changes in skeletal muscle and bone marrow, aging, oxidative stress, as well as autoimmune factors thought to contribute to systemic inflammation in COPD[14]. Erdosteine allegedly can improve the inflammatory process

indirectly through the detoxification of free radicals, increased levels of intracellular antioxidant, controlling the activation of NF-κB, as well as decreased production of eicosanoid[15]. Even with erdosteine treatment COPD inflammatory pathways other than the alleged oxidative stress is ongoing.

This is probably one of the causes of the decline of serum hs-CRP levels were not significant in this study.

In both study groups we did not find significant differences in confounding factors such as gender, age, smoking status, degree of GOLD, hypertension, arthritis, use of drugs such as statins, COX-2 inhibitors, inhibitors of the renin-angiotensin-aldosterone system such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), beta blockers, corticosteroids, and hormonal contraceptives.

Ten percent of COPD patients with normal BMI have increased relative and absolute fat mass. Adipose tissue is proven to generate several adipokines involved in the process inflammation[4]. In this study, we did not measure fat mass and fat-free mass. Therefore, the possible influence of the pro-inflammatory adipokines fat mass cannot be excluded.

Antioxidants contained in the daily diet such as vitamin C, vitamin E, beta-carotene, as well as natural products containing flavonoids or polyphenols, ginkgo biloba, polyunsaturated fatty acids or omega-3 fatty acids may play a role in the management of oxidative stress which is triggered by a cigarette and on COPD patients[15]. Antioxidant supplements in daily diet and exposure to pollutants in the workplace or in neighborhood were confounding factors that were not analyzed in this study

Sub-analysis test between groups of subjects with and without systemic corticosteroid therapy in erdosteine and placebo groups showed no significant differences in serum hs-CRP levels. Therefore, the confounding role of systemic corticosteroids may be excluded. On the other hand, it showed the possibility of steroid resistance in study subjects.

Kluchova et al[16] and Kirkham & Rahman[17] found the relationship between the various products of lipid peroxidation, protein nitration, and the antioxidant activity of glutathione peroxidase with COPD severity as assessed by FEV1. In subjects with COPD GOLD 3 (severe) allegedly occur greater oxidative stresses that Erdosteine antioxidant effect was more pronounced resulting in a greater decrease in serum CRP levels.

Based on the understanding of the relationship of oxidative stress with the severity of COPD, a decrease in serum CRP levels can be seen in COPD GOLD 4. However, this can't be assessed in this study because there is only one study subject with COPD GOLD 4.

These study limitations are several confounding factors cannot be controlled or not analyzed such as increase at mass, diet, and exposure to pollutants in the workplace environment or the working environment.

Diagnosis of several confounding comorbidities were not done accurately as echocardiography to rule out pulmonary hypertension or cor pulmonale and treadmill test to rule out ischemic heart disease. The number of study subjects had not meet the minimum sample size calculation, only 35 subjects completed the study. Moreover, sub-analysis test was not possible at all levels of COPD severity as research subjects is not divided evenly.

Conclusion

Erdosteine 300 mg bid for 10 days in patients with stable COPD decrease median serum CRP levels greater than placebo, but it was not statistically significant.

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