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Correlation between the Serum Level of Interleukin-2 in Hemodialysis Patients and Severity of Renal Pruritus

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ABSTRACT

Renal pruritus (RP) is a condition or symptom that is often found in end-stage chronic kidney disease (CKD) undergoing hemodialysis (HD). The etiology of RP is multifactorial, one of it due to inflammation mediated by interleukin 2 (IL-2). Study on the correlation between serum level of IL-2 and the severity of RP is still limited. This study will analyze the correlation between serum level of IL-2 in patients undergoing HD and the severity of RP. Our method is cross sectional design at Hemodialysis Installation of Dr. Mohammad Hoesin Hospital. Serum level of IL-2 examined by ELISA, the severity of RP assessed by a 5 dimensional pruritus scale. Inclusion criteria in this study included HD patients with RP ≥ 9, age ≥ 18 years and willing to sign informed consent. The results from 28 male (59.6%) and 19 female (40.4%) are the mean serum level of IL-2 (pg/ml) is 0.424 ± 0.077. The mean RP severity score is 18.98 ± 2.74. A strong positive correlation between serum level of IL-2 and the severity of RP (r = 0.750, p = 0,000). Our conclusion is the increase of serum level IL-2 in line with severity of RP.

1. Introduction

RP, formerly known as uremic pruritus, is the most common symptom found in patients with advanced CKD, especially in HD patients.[1] The clinical features of RP are not typical, sometimes without skin disorders. Some cases of RP have secondary lesions, such as lichenification, excoriation, and hyperpigmentation.[2] Most RP patients experience generalized pruritus, but can also be localized symmetrically.[1,3] RP predilection are the arm especially at the location of the arteriovenous fistula and the back.[4] Pruritus occurs almost every day and gets heavier, especially after HD.[3,5]

HD is a non-pharmacologic therapy in CKD patients. Pruritus complaints after HD are thought to be related to factors called HD biocompatibility. Biocompatibility of materials used in HD is an important factor. Biocompatibility of HD membranes can cause incompatibility processes so that inflammatory reactions occur.[6] Inflammatory reactions during HD resemble pseudo anaphylactic or complement activation related pseudoallergy (CARPA).[7] Activation of complement produces cytokines including IL-2. IL-2 is a cytokine produced by $CD4^+$ cells after activation by antigens. In RP patients there is an increase in T-helper 1 (Th-1) cells which triggers microinflammation. Overactivation of $CD4^+$ causes overproduction of pro-inflammatory cytokines IL-2. This situation strengthens the alleged inflammatory process in RP. IL-2 is a strong mediator of pruritus.[8] The results of study on the role of IL-2 in HD patients experiencing RP are quite varied and still limited. The purpose of this study was to determine the correlation between serum level of IL-2 in HD patients and the

severity of RP.

2. Methods

The study was conducted at the Hemodialysis Installation of Mohammad Hoesin Hospital Palembang, period 1 November - 31 December 2019. Samples were taken by consecutive sampling method. A total of 47 HD patients experiencing RP fulfilled the inclusion and exclusion criteria. Inclusion criteria included HD patients with severity of RP ≥ 9 assessed by the 5 dimensional pruritus scale method, age ≥ 18 years and willing to participate in the study by signing informed consent. Exclusion criteria are systemic diseases that cause pruritus, such as uncontrolled of diabetes mellitus (DM), hepatobilliary, cancer and human immunodeficiency virus (HIV) infections; using topical or oral drugs to treat pruritus two weeks before the study; and other skin diseases such as dermatitis, urticaria, mycosis, psoriasis or chronic lichen simplex.

IL-2 examination using quantitative sandwich enzyme immunoassay technique. The patient's blood is drawn as much as 5cc then centrifuged 3000 rpm for 20 minutes to obtain the serum, then an IL-2 examination is performed.

Statistical analysis uses statistical program for social sciences version 22.0 (SPSS Inc., Chicago). Correlation between variables was tested by Spearman test, a significant value if $p < 0.05$. The protocol of study has been approved by ethic committee Medical Faculty of Sriwijaya University. The certificate number is 531/kepkrsmhfkunsri/2019.

3. Results

The total subjects were 47 people consisting of 28 male and 19 female. The sociodemographic characteristic can be seen in table 1.

HD duration can be seen in Table 2. Most HD duration is 6-12 months in 33 subjects (70.2%).

In Table 3 the mean RP severity score was 18.98 ± 2.74 (range 12 to 22), with severity of severe RP found in 37 subjects (78.7%)

Table 4 shows that 55,3% (n=26) of study subjects did not have clinical manifestations

The correlation between serum level of IL-2 and the severity of RP is shown in Table 5 and Graphic 1.

The correlation between serum level of IL-2 and the severity of RP was assessed by the Spearman test. A significant positive correlation was obtained between serum level of IL-2 and severity of RP ($r = 0.750$; $p = 0,000$). This proves that increasing serum level of IL-2 will increase severity of RP (Graphic 1).

Table 1 Sosiodemographic Characteristics

Sosiodemographic characteristics	**N**	**%**
Age (yo, mean ± SD)	51.51 ± 12.11	
Age (yo)		
• 17 - 25	2	4.3
• 26 – 35	2	4.3
• 36 – 45	9	19.1
• 46 – 55	14	29.8
• 56 – 65	14	29.8
• ≥ 66	6	12.8
Sex		
• Male	28	59.6
• Female	19	40.4

Table 2. Correlation between duration of hemodialysis and the severity of RP

Characteristics	Severity			p
	Moderate	Severe	Very severe	
Duration of HD (month)				
6 – 12	4 (12.1)	26 (78.8)	3 (9.1)	0.787[a]
> 12	1 (7.1)	11 (78.6)	2 (14.3)	

[a] *Kruskal Wallis*

Table 3. Score and severity of RP

Variable	N	%
Score (mean ± SD)	18.98 ± 2.74 (12 -22)	
Severity/score of renal pruritus		
• Moderate	5	10.6
• Severe	37	78.7
• Very severe	5	10.6

Table 4. Correlation between skin manifestations and the severity of RP

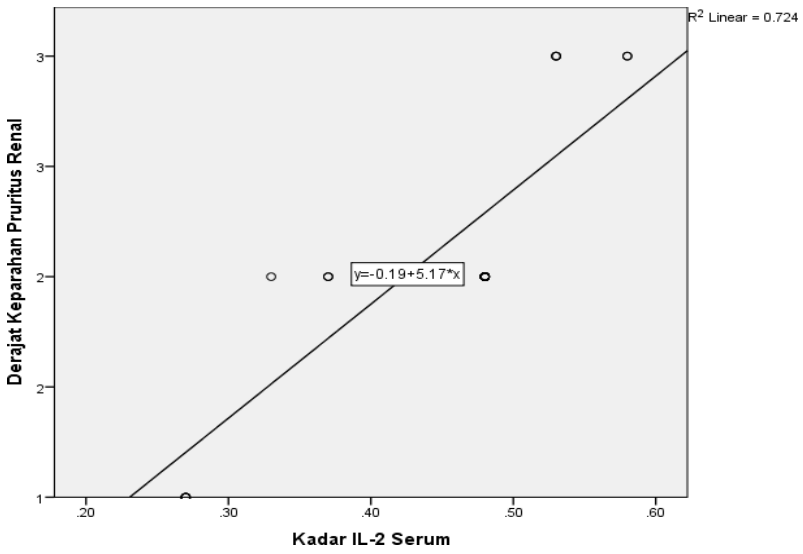
Characteristics	Severity			P
	Moderate	Severe	Very severe	
Skin manifestation				
None	1 (20.0)	24 (64.9)	1 (20.0)	0.074[a]
• Xerosis	2 (40.0)	6 (16.2)	2 (60.0)	
• Prurigo nodularis	0 (0.0)	2 (5.4)	1 (20.0)	
• Excoriation	0 (0.0)	2 (5.4)	0 (0.0)	
• Hiperpigmentation	2 (40.0)	3 (8.1)	0 (0.0)	

[a] *Kruskal Wallis*

Table 5. Correlation between serum level of IL-2 and the severity of RP

Severity	Serum level of IL-2 (pg/ml)			p
	X ± (SD)	Median	Min – Max	
Moderate : 12 - 17	0.270 ± 0.000	0.270	0.27 – 0.27	0.000*
Severe : 18 - 21	0.428 ± 0.044	0.400	0.33 – 0.48	
Very severe : ≥ 22	0.550 ± 0.027	0.530	0.53 – 0.58	

[*] *Kruskal Wallis*



Graphic 1. Correlation between serum level of IL-2 and severity of RP

4. Discussion

RP is the most common problem in the 90% range in patients undergoing HD. Various hypotheses related to the etiopathogenesis of RP.[2,9,10]

In this study, no significant correlation was found between age and the severity of RP (p = 0.791). Min et al. (2016) found no significant correlation between age and RP (p = 0.412).[11] Wu et al. (2018) also reported no significant correlation between age and RP (p = 0.46).[12] Age factor is one of the factors associated with increased risk of CKD. The older the age, the risk of CKD increases due to a decrease in the number of nephron cells and glomerulosclerosis.[13]

In this study there was no significant correlation between sex and the severity of RP (p = 0.364). Kavurmaci et al. (2015) reported no significant correlation between sex with the severity of RP (p> 0.05).[14] Different results by Kimata et al. (2014) reported that there was a significant correlation between male and RP (p <0.0001).[15]

In this study there was no correlation between HD duration and the severity of RP (p = 0.787). Hayani et al. (2016) also reported that HD duration was not associated with the severity of RP.[16] Different results by Hu et al. (2018) reported a significant correlation between HD duration and RP.[17] Adequate hemodialysis was associated with improvement of RP. According to Oliviera et al. (2017), another factor to improve RP is Kt/V. This value is the calculation of urea clearance based on the distribution volume of urea.[18] These factors are interrelated in determining the improvement of RP.[19] In addition, different method to measure the severity will cause different results. A better method for assessing the severity of RP is multidimensional methods such as 5 dimensional pruritus scale and several other methods.[5]

Most of the study subjects were 26 people (55.3%) did not have skin manifestations, and in this study found no significant correlation between skin manifestations and the severity of RP (p = 0.074). Chorazyczewska et al. (2016) reported xerosis significantly associated with RP (p = 0.002).[20] The skin of HD patients with RP, often showing no changes, it can even look like a patient without RP.[21] Skin manifestations that occur in RP patients are caused by a scratching cycle that causes skin manifestations such as prurigo nodularis, lichenification and secondary lesions in the form of excoriation and hyperpigmentation.[22]

Hemodialysis is a process to clean urea, creatinine and excessive fluid from the blood using membrane filters.[23] One of the causes of RP in HD patients is due to incompatibility between blood and HD membranes

during HD process. Types of synthetic HD membranes include polyethersulphone, polysulphone, polyamide and polymethylmethacrylate.[24,25] The HD membrane used in this study is polyethersulphone which is a synthetic high flux membrane. It has a higher permeability to clean toxins with low molecular weight. Polyethersulphone is hydrophobic, so it can absorb toxins, filter more cytokines and complement activators thereby reducing inflammation.[26] However, Weishaar et al. (2015), still found 31 people experiencing RP despite using a polyethersulphone membrane.[25] RP is thought to occur due to incompatibilities that cause activation of the complement via the lectin and alternative pathways. Activation of complement produces cytokines including IL-2. In RP patients there is an increase in Th-1 cells which triggers microinflammation. Overactivation of $CD4^+$ causes overproduction of pro-inflammatory cytokines IL-2. This situation strengthens the alleged inflammatory process in RP. IL-2 can affect the physiological function of nerve cells and modulate several neurotransmitters in the CNS. IL-2 can also induce or increase the perception of pruritus.[8]

Synthesis of IL-2 during HD occurs after the process of protein adsorption on the HD membrane. These proteins include ficolin 2 and properdin contained in the blood can activates complement via the lectin and alternative pathway respectively. The lectin pathway produces complement 3a (C3a) and C3b, the alternative produces C3a and C5a.[27] These complement will bind to their respective receptors and cause leukocyte activation then induces the release of proinflammatory cytokines, such as IL-1, IL-6 and TNF-α which stimulate lymphocytes for IL-2 synthesis.[27,28] In conjunction with C3a and C5a activation, a complementary homeostasis process occurs by CD46 will bind to the receptors on the surface of $CD4^+$ cells resulting in Th1 proliferation and polarization to produce IL-2.[7,29,30]

IL-2 bind to receptor tyrosine kinase (RTK) causes phospholipase C (PLC) to activate thereby activating protein kinase C (PKC).[31] PKC activates transient receptor potential channel vanilloid 1 (TRPV1) and transient receptor potential channel ankyrin 1 (TRPA1).[32,33] After that, there is an increase in intracellular calcium concentration which forms an electrical signal in nerve fibers. The signal is transmitted from afferent C terminal nerve fibers to neurons in the dorsal root ganglion and then spreads to the cerebral cortex resulting in pruritus.[34,35]

In this study, there was a strong correlation between serum level of IL-2 and severity of RP ($r = 0.750$; $p = 0{,}000$). The results of the study are consistent with Fallahzadeh et al. (2011), which reported a significant correlation between serum level of IL-2 and the severity of RP ($p < 0.0001$).[8] An increase of IL-2 would increase the amount of signal transmission to the cortex of neurons, resulting in increase of pruritus.[8,35]

5. Conclusion

Increase of **s**erum level IL-2 in line with severity of RP.

6. Conflict of interest

None

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