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Granulocyte Colony Stimulating Factor (G-CSF) Quantitative Analysis in Plasmodium Vivax-infected Malaria Patients Experiencing Thrombocytopenia

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Abstract

Background : P. Vivax has been refered as pathological factor underlying increasing prevalences of haematological abnormality including anemia and thrombocytopenia. Through the day, exact mechanism of thrombocytopenia in malaria infection has yet come to a conclusion, several hypothesis are still in considered, phagocytosis and platelets aggregation remain the major disscussion topics. G-CSF, cytocine with elevated serum quantity in P. Vivax infections, were responsible in increasing phagoctytosis and conducting direct effect on platelets aggregation using adequate ADP. Increasing number of ADP in malaria cases were correlated with erythrocyte haemolitic, leading to increasing platelets aggregation. Although numerous hypothesis has been compelled, only a-few research publication has been made corresponding to G-CSF serum level on malaria P. Vivax infection and its correlations to thrombocytopenic events. The study is intended to analyze the relations between G-CSF serum levels and parasite numbers towards platelets profile in infected malaria P. Vivax patients.
Methods : Study design using Prospective analysis. Thirty six patients with single infection of Malaria Vivax in Puskesmas Sukamaju (Primary Heath Care Centre) and Puskesmas Kota Karang were assessed for G-CSF plasma levels, platelet counts, and MPV. Data analysis were conducted using Spearman correlation methods with SPSS.
Results : Study results showing significant correlation between G-CSF serum levels towards Platelet conts (R = -0,397(p = 0,016)), without significant correlation between G-CSF and MPV value (p = 0,874)
Conclusion : G-CSF serum levels were related with thrombocytopenia, with no correlation towards MPV.

Keyword: G-CSF, *P. vivax*, Thrombocytopenia, MPV.

Background

Malaria still pose a major threat, becoming the leading causes in world health problems. In 2015, as estimated of 212 million cases of malaria occurred with 429 thousand death toll related to malaria.[1] Plasmodium vivax was one of the leading cause of malaria with wide sporadic distribution and major cause of malaria infection in Outer Sub Afrika Sahara region.[2]

P. Vivax were known as a disease disrupting red blodd cells and causing major haemathological abnormality, especially anemia and trombocytophenia with increasing prevalence.[3-8] P. vivax has been related in causing severe malaria, and in several cases were accompanied with thrombocytopenia.[9-11] Untill today, the role of thrombocyte in malaria pathogenesis and mechanism of thrombocytopenia in P. Vivax infection were yet to unfold a conclusion. Therefore, further analysis towards factors suspected to have a specific role developing thrombocytopenia in P. vivax malaria.

Several hypothesis has been eluded related to pathogenesis of thrombocytopenia in malaria, including coagulation disorder, spleen function, antibody mediated thrombocyte destruction, oxidative stress and platelets aggregation.[3] Trombocytopenia in P. vivax malaria proved in having a relation towards thrombocyte phagocytosis done by phagocyte.[12]

G-CSF are a type of cytocine with elevated serum levels on malaria infection and though to expressed a significant role in phagocytosis. G-CSF receptor were known and likely to be found in thrombocyte and exerting a direct effect. [13-15] Administration of G-CSF recombinant as main therapy proved inducing thrombocytopenia.[16] Nevertheless, yet only a few published data related to G-CSF level in P. vivax malaria patients and its relation toward G-CSF platelets profile (platelet counts and Mean Platelet Volme/MPV) in P. vivax malaria. Therefore, this study were conducted to assess any possible relation between G-CSF serum levels toward thrombocyte progile in P. vivax malaria patients, so it can be used as a basis to comprehend about thrombocytopenia in malaria vivax infection.

Methods

This study were conducted using a prospective analysis design and conducted on August until December 2017. Sampling were done in Puskesmas Sukamaju and Puskesmas Kota Karang, Bandar Lampung. Respondent in this study design were all patients infected with single malaria strain aged between 6 years or older, willing to be subject in this research, and fulfill inclusion criteria and does not fall under exclusion criteria., expressed on informed consent paper (for children respondent, were sign by parents or guardian). Positive confirmation of P. vivax were done using microscopic examination by 2 experts staff. Only Positive Confirmed subject by both of the experts, will then be continued to proceed to further research program. Respondent will then undergoing a vein blood, G-CSF serum and haematological assessment.

Blood sample acquired from the vein blood analysis will then undergoes haematological assessment in Clinical Pathology Laboratory, Blood transfusion service unit, Heatlh Laboratory of Lampung District using *automatic hematology analyzer* from ABX. Plasma sample for G-CSF assessment were stored under temperature of -20^{o}C until assessment comes in turn. G-CSF serum assessment were done in Biomolecular Laboratory, Medical Faculty of Sriwijaya using ELISA Assays (Sunlog Biotech).

Data Analysis conducted using spearman correlation test and regression analysis by SPSS and Microsoft excel (p= 0,05)

Result

Haematological Results

Average platelet conts of P. vivax malaria patients were evaluated under normal values (95,64±36,64 ribu/µL) with median of 88.500/ µL, showing different results from red blood cells and haemoglobin counts which considered within normal values (12,84 dan 4,6 g/dL).

Table 2. Haematological Results

Parameter	Mean	SD	Median	Minimal	Maksimal
Platelet Counts(10^3/µL)	95,64	36,64	88,5	16,00	171,00
MPV (fL)	7,46	0,67	7,45	6,20	8,90
RBC (10^6/ µL)	4,57	0,79	4,54	3,00	6,61
Hemoglobin (g/dL)	12,84	2,17	13,05	8,10	18,90
Haematocrit (%)	38,92	6,83	38,80	25,10	56,70

The frequency of haematological abnormal changes (anemia, thrombocytopenia) are elucidated in table 3.

Table. 3 Frequency of Haematological abnormal changes (n =36)

Parameter	Frequency	Percents (%)
Anemia		
• Man	13	56,50
• Woman	7	53,80
Total	20	55,56
thrombocytopenia	33	91,70

It is concluded from this results, thrombocytopenia being the most common changes experienced as 91.70% and followed by anemia 55,56%

G-CSF Plasma serum results and relations toward platelet counts and MPV

G-CSF Plasma serum in patients with P. Vivax malaria evaluated within 21,28 pg.mL (11,56-359,33 pg/mL) with mean value 49,18±79,78 pg/mL. spearman correlation analysis showed significant correlation between G-CSF Plasma serum levels towards platelet counts in P. vivax malaria patients (p=0,016, R= -0,397). Correlation coefisien of 0,397 concluded a negative relation between G-CSF Plasma serum level towards platelet counts, depicting elevated G-CSF plasma serum leading to decreased platelet counts. Spearman analysis between G-CSF and MPV showing no significant relations (p= 0,874)

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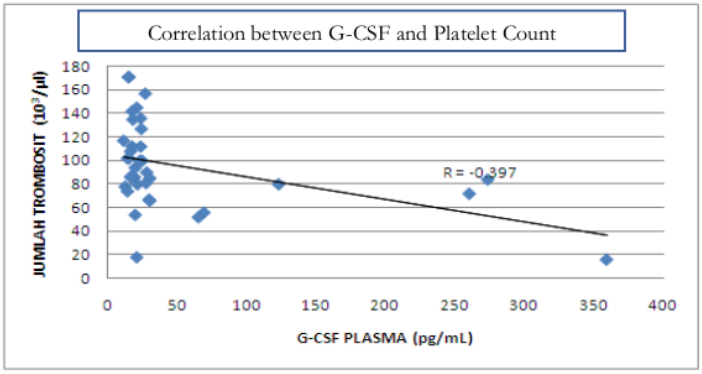

Picture 1. Correlation Chart between G-CSF and Platelet Counts.

Discussion

In this study, the majority of the respondents were male (63,9%), where most outdoor activities in night are done by men. Due to the outdoor preference of *Anopheles sundaicus* mosquito activities – which include biting – as the main vector for malaria in coastal Lampung area, males are more likely to be infected. The fact that majority of respondents are within the age group 26 – 45 year-olds (50%) – which are the productive population – shows that malaria might affect the productivity of the general population.

Malaria is a disease caused by protozoan infection of the red blood cells, and so causes haematological alterations.[3] In this study, thrombocytopenia occurred most often (91.60%) – the subjects had an average platelet count of 95.64±36.64, which is below the recommended normal range. A different result was demonstrated by Ferawati *et al*. where the average platelet count of Vivax malaria patients were normal, despite thrombocytopenia was found in few cases.[18] Thrombocytopenia has also been reported by Chetiwal *et al*. and Mangla *et al*. in which 85.29% and 80% patients of Vivax malaria had thrombocytopenia, respectively.[7,8] Most of the patients with low platelet count in this study had mild thrombocytopenia (93.9%) and only 2 cases (6.1%) were severe. This finding showed that a single infection by P. *vivax* might cause severe thrombocytopenia.

Although thrombocytopenia is the most common haematological alteration in this study, the mean platelet volume (the average volume of platelet corpuscles) remained unchanged. We found the average MPV 7.4 ± 0.67, which was within the normal range. This finding does not replicate the results of past studies, which showed an increase of MPV in Vivax and Falciparum malariae.[19,20] The value of MPV is influenced by platelet production. In thrombocytopenia, bone marrow reacts by increasing the rate at which platelet is produced in order to maintain a normal platelet count, therefore, immature

and larger platelet would be launched to the peripheral circulation. That way, MPV will increase, and in other words, MPV could be used as an indicator of marrow response towards thrombocytopenia.

Another haematological alteration we found was anaemia. In this study, anaemia was found in 55.56% of respondents. Similar results had been obtained in past studies, but in smaller rates.[7,8] The mechanisms of anaemia in malaria are as follows: the lysis of haemoglobin by parasites, the haemolysis of infected and non-infected erythrocytes (by schizogony or phagocytosis), vulnerability of erythroctes to deformation, decreased erythrocyte life-span, and decreased erythropoieseis.[22] Despite anaemia and thrombocytopenia were the most common haematological changes observed in this study, but the relation between the two and the severity of the disease itself could not be established.

The plasma G-CSF in this study was 21 pg/mL (11.56 – 359.33 pg/mL), this high level is interpreted as the increase of G-CSF in Vivax infection, compared to the average level in healthy persons, 4.3 pg/mL.[13] This result is consistent with past studies, in which there were increased plasma G-CSF in both Vivax and Falciparum infections.`[13,27]

Just like in bacterial infections, it is still unclear which cell produces G-CSF in *Plasmodium* infections.[27] Wahlgren *et al*. showed that in cell cultures, malaria-infected erythrocytes will induce the macrophages, monocytes, and endothelial cells to produce G-CSF.[28] G-CSF production is also induced by several inflammatory mediators as a response against parasitic infections and parasitic toxins like IL-1, TNF-α, and IF-γ.[29,30] G-CSF synthesis is regulated by transcriptional and post-transcriptional mechanisms. The G-CSF promotor contains NF-κB p65 and NF-IL6/C/EBPβ binding site. These two molecules are known as transcription factors and is involved in inflammatory and immune response pathways. It is also known that G-CSF production is controlled by IL-17, whose concentration is strongly influenced by neutrophilic turnover.[31]

In a *Plasmodium* infection, the role of neutrophils in controlling parasites in blood has been established. Greve *et al*. shows that neutrophils release reactive oxygen intermediates, which plays as the first-line defence system against *Plasmodium*.[32] When neutrophilic migration to the tissues is inhibited due to the depletion/lack of adhesive molecules; the macrophages and dendritic cells will produce IL-23, which stimulates the production of IL-17, thereby increases G-CSF production.[33]

In our study, plasma G-CSF levels had a wide range and standard deviation. It sat within 11.56 – 359.33 pg/mL, with the average level of 49.18 ± 79.78 pg/mL. This is due to the varying host response against *Plasmodium* infections, and is also affected by the type of parasite strains and the host themselves.[34] An animal model study in *Plasmodium yoelii* strain Py17X-infected mice showed that TGF-β was produced 5 days post-infection, however, strain Py17XL-infected mice produced TGF-β within 24 hours. This slow production of TGF-β in 24 hours caused the slow response of TNF-

α and IFN-γ, therefore slowing down parasite clearance.[35] This further proves that "strain" factor also plays in infection response and affects the difference in levels cytokines in patients infected with different strains. The same pattern is also present in cytokine production. There was heterogeneity in cytokine responses against Falciparum infection, in which three groups of subjects were given a bite by infective mosquitos, in a same dose and time, there were differences among the types and the levels of cytokines among the three groups.[36]

In the next step of our study, Spearman correlation analysis showed there was a significant correlation between plasma G-CSF levels and platelet count in Vivax malaria patients (p= 0.016). Correlational coefficient of -0.397 indicates a negative correlation between the two; in other words, an increase in G-CSF concentration is associated with a lower platelet count. It can be interpreted that, G-CSF induces thrombocytopenia, just as is happening with patients who receive therapeutic G-CSF. G-CSF mediates biological activities by binding to a specific receptor. G-CSF has no tyrosine kinase activity, but during ligand binding, the receptor will undergo a conformational change, which activates several signaling pathways such as JAK/STAT, P13/AKT, and MAP/ERK – they play roles in the proliferation, differentiation, and mobilisation of myeloid cells.[38] The cytoplasmic end of G-CSF receptor is divided into 3 regions. Boxes 1 and 2 plays ini the proliferation, while box 3 plays in the differentiation, of myeloid cells. Outside the box regions, there are 4 tyrosine residues in positions 704, 729, 744, and 764, which is phosphorylated quickly during ligand binding, and also participates in mediating G-CSF activities.

Besides in myeloid series cells, G-CSF receptors is also known to be expressed in platelets, in which there are an average of 40 G-CSF binding sites/cell with high affinity, equally high to the affinity of those in granulocytes. The bond between G-CSF and platelet via its receptor causes the increase in thrombocytic response towards adenosine diphosphate (ADP), consequently increases platelet aggreggation.[15] In malarial infection, haemolysis is followed with the release of ADP, and also contributes in increasing thrombocyte aggreggation.[3] The binding of G-CSF and its receptor in platelets – which induces aggreggation due to ADP – happens via the same mechanism of the radical oxygen species by neutrophils due to the binding of ligands with G-CSF receptors in those cells,[15] which is called the receptor-mediated triggering agent. In that case, the binding of G-CSF with its receptor in neutrophil does not directly cause the release of radical oxygen without chemotactic peptide.[40]

Apart from triggering platelet aggreggation, the fact that G-CSF is also a cytokine that increasaes the presence of phagocytic cells (monocytes/macrophages) and its phagocytosis function,[14] and thrombocytopenia in Vivax infection has been shown to be related with the phagocytosis of

thrombocytes; it can be inferred that the increase in G-CSF increases the phagocytosis of thrombocytes.[12]

Although in this study, G-CSF levels has been shown to be related to platelet levels, correlational analysis between the two did not exhibit significant correlation ($\nabla = 0.847$). This proves that in malarial infections, G-CSF is only associated with the destruction of platelets, but not directly with its production.

Conclusion

Elevated G-CSF serum levels in malaria vivax infection showing significant effect towards thrombocytopenia incidents, without any effect exerting forming stimulation. Nevertheless, G-CSF related thrombocytopenic-induction pathway in malaria vivax infection still required molecular levels study to further comprehend its role.

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