The Relationship of Sepsis Occurrence and The Reduction of Platelet Count: A Research in PKU Muhammadiyah Yogyakarta Hospital for The Period of January to December 2010

Linda Rosita
Clinical Pathology, Faculty of Medicine UII
Jl. Kaliurang Km 14,5 Yogyakarta 55584, Indonesia

Arifudin Cipto Husodo
Clinical Pathology, Faculty of Medicine UII
Jl. Kaliurang Km 14,5 Yogyakarta 55584, Indonesia

Abstract
Sepsis is a complication of infection characterized by systemic inflammation, which eventually can cause damage to several organs. One of the systemic inflammatory response of the body is to increase the number of platelets in compensation against vascular leakage caused by the systemic inflammation that can eventually lead to the overall reduction in the number of platelets. The purpose of this study is to determine the relationship between the sepsis occurrence and the reduction of platelet count. The research method used in this study is cross sectional method, data taken for the period of January to December 2010. The study was conducted at PKU Muhammadiyah Hospital in Yogyakarta. The data obtained will be processed using SPSS 16 for windows with Chi-Square method analysis. In addition, this study also uses the value of the ratio of prevalence to statistically determine the relationship between the sepsis occurrence and the reduction of platelet count. The total patients severe infection with and without sepsis are 76 patients which are 38 sepsis patients and 38 non-sepsis patients. From the patients with sepsis, we got 11 people who experienced platelet reduction, while the other 27 patients have normal platelets. Acquired p value 0,02 and prevalence ratio <1 between the sepsis occurrence and the reduction of platelet count with the research power of 95%. The conclusion of the test statistics with Chi-Square and prevalence ratio value indicates that there is a statistically significant relationship between the sepsis occurrence and the reduction of platelet count with the research power of 95%.
Keywords: Sepsis Occurrence, Reduction of platelet count, platelet count

1. INTRODUCTION

Prevalence of infection desease which can lead to sepsis are on the top second mortality cause of hospitalized patients in several hospitals in Indonesia with the occurence of 1679 people and *case fatality* rate of 2,89% on 2008.[1]

The most common cause of the mortality on sepsis is the sepsis complication that dangers the homeostatis process on the body. sepsis Sepsis itself is the condition where we can find the patogen microorganism or toxin in the blood leading to the disfunction of certain organ which eventually cause the mortality for the late reaction on that condition.[2]

According to The International Sepsis Definition Conferences (ISDC, 2001) Sepsis is a continuous process that begins from infection, SIRS, sepsis, severe sepsis, septic shock, and organ dysfunction which ended up with death.[3]

The number of sepsis occurence in the developing country is quite high around 1,8-18 per 1.000 life birth with the death rate of 12-68%, while in the developed country the number of sepsis occurence is around 3 per 1000 life birth with the death rate of 10,3%. In Indonesia, that number is not yet recorded because of the lack of the research conducted. Data obtained from Cipto Mangunkusumo Jakarta Hospital for the period of Januari up to September 2005 shows the number of neonatorum sepsis occurence of 13,68% with the death rate of 14,18%. [4]

The mortality rate of sepsis in the Hospital Sardjito Jogjakarta reached 59.17% with longer treatment in hospital during the day and 6.96 as the most frequent cause of death was septic shock with the highest comorbidities in astrohepatologi.[5]

According to the World Health Organization (WHO) there are 5 million neonatal deaths every year with neonatal mortality rate (death within the first 28 days of life) was 34 per 1,000 live births, and 98% of these deaths are from developing countries. In particular neonatal mortality rate in Southeast Asia was 39 per 1,000 live births. In a WHO report quoted from the State of the World's mother in 2007 (data from 2000-2003) noted that 36% of neonatal deaths are caused by diseases infeksi.[4]

The high mortality rate of sepsis is likely a result of taking that step too late in determining the diagnosis or therapy is less precise. So that rapid early identification and appropriate governance has a big influence in reducing the incidence of mortality from sepsis.[2,5]

The use of methods of culturing microorganisms are still the gold standard in determining the diagnosis of sepsis with high specificity value but has the disadvantage that the sensitivity is quite low, so that early identification of sepsis using culture methods still can not be used because they have to wait until a few days to find out certainly the result of the examination of culture, of course this can worsen the condition of sepsis patients.[6]

Platelets are one of the components of the blood cells that play a major role in the process of blood hemostatic namely as primary hemostatic. Platelets itself in the systemic circulation has a life span ranging from 7 to 10 days. The life span of platelets is reduced in case of the use of platelet thrombosis increased as the state, infection, and magnification limpa.[7]

Platelets are not nucleated blood cells derived from the fragmentation of the cytoplasm of megakaryocytes found in bone marrow. Trombopoesis greatly influenced by trombopoentin produced by the liver and stimulates the production of megakaryocytes and platelets by increasing the differentiation of stem cells into megakaryocytes, increasing the number of megakaryocytes, and increase the number of nuclear division megakariosit.[8]

Normal number of platelets in the blood ranged from 140-400 x 109 / L; a lesser amount is found in neonates (100-300x109 / L) and in the population race tertentu.[7]

In the situation where there is sepsis bacteria that are pathogenic or toxin in the systemic circulation can affect the levels of platelets in the circulation, it relates to cellular products of microorganisms can cause proinflammatory mediators that can ultimately lead to danya inflammation in the vascular endothelium accompanied by hemorrhage result in the destruction of that endothelial.[2]

With the mechanism of the vascular bleeding will directly increase the use of platelets by the body so that the decreased platelet count is very likely to occur Disseminated Intravascular Coagulation (DIC) is a common complication in sepsis. The consumption of clotting factors and platelets will induce severe bleeding complications. PIM simultaneously will cause microvascular thrombosis and bleeding. In DIC patients, PAI-1 levels are high can be linked to a bad prognosis buruk.[9,10,11]

Damage due to multiple organ disorder is not caused by the infection but is caused by systemic inflammation that is modulated by cytokines as mediators. Opinion was also corroborated by other opinions that say that abnormalities in sepsis caused by multiple organ thrombosis and coagulation in the small blood vessels, causing a state of septic shock that often end up with death.[2,11,12]

With the magnitude of the incidence of sepsis in developed countries and in developing countries such as Indonesia, where in Indonesia found morbidity and mortality are high enough on each occurrence of sepsis.

Therefore it is necessary for the data to determine the range of possible checks that can be done. Particularly the platelet count prior examination has not been done in a variety of research on its role in sepsis, although the role of platelets as primary hemostatic already widely known.

2. RESEARCH METHOD

The design used in this research is analytical descriptive statistic with cross sectional approach, which means the data are taken in one period of time. The target population of this research are the patients with the infection diagnosis. The affordable population of this research are the patients with the infection diagnosis in PKU Muhammadiyah Hospital while the sample of this research are the patients fulfilling the inclusion and exclusion criteria based on the sepsis criteria of *The Society for Critical Care Medicine (SCCM)* which explains that it can be categorized as sepsis if it fulfills at least 2 of the following criteria: 1.) Fever (>38°C) or hypothermia (<36°C); 2.) Takipneu (Respiration >24x/minute); 3) Takikardia (Heart Rate >90x/minute); 4) Leukositosis (>12.000/ul) or leukopenia (4000/ul), or > 10% bar.[3]

The minimal sample of this research are 70. Data taken are based on the medical record data in PKU Muhammadiyah Yogyakarta Hospital for the period of Januari up to Desember 2010.

3. RESULT

From the data collected from the medical records of PKU Muhammadiyah Hospital in Yogyakarta, obtained the data that the incidence of infection with sepsis at PKU Muhammadiyah Hospital in Yogyakarta on January 1, 2010 until December 31, 2010 there were 76 cases. Of the number 76, 38 of them are sepsis patients who avoid exclusion criteria that have been defined previously and the remaining 38 were as control, so 76 the number of samples that can be used as a sample in this study because it already meet the limits predefined sample.

Table 1. Basic Characteristic of Patient

Category	Sepsis	Non Sepsis	Total
Platelet			
Increase or Normal	27	17	44
Decrease	11	21	32
Gender			
Man	22	21	43
Woman	16	17	33
			76
Age			
Neonates	23	4	27
Infant	9	14	23
Toddler	0	13	13
Child	1	0	1
Adult	2	6	8
Elderly	3	1	4
Outcome			
Better	31	27	58
Worse	1	0	1
Dead <48 hours	2	10	12
Dead >48 hours	4	1	5

Of the total 76 patients on infection, including 38 patients with sepsis and 38 of which became the control group did not have sepsis. Platelet counts of total 38 patients suffering from sepsis showed normal or increased in value by 27 (71.1%) patients and decreased platelet count there were 11 patients (28.9%).

The youngest age sepsis patients is 1 day, while the oldest is 76 years of age. The age group that suffered most of sepsis in neonates that this study was 23 patients (60.5%), followed groups of infants were 9 patients (23.7%), there is a child's age group 1 patients (2.6%), group adult age there are two patients (5.3%), and the elderly group 3 patients (7.9%).

For patients with sepsis in neonates obtained is the main cause of neonatal sepsis, with 5 patients who also experience additional symptoms such as congenital abnormalities. Of the 23 patients of the neonatal there were 3 patients who died of> 48 hours after the first treatment in the hospital.

The number of patients aged baby in this study, as many as 9 people (23.7%) with disease the most common cause of sepsis derived from gastrointestinal infections and respiratory tract. For the age of the toddler, it was not found as samples of sepsis patients in this study.

As for the age of the child found as many as one person (2.6%) with disease cause is an infection with Salmonella bacteria as evidenced by the presence of IgM (+) Salmonella in patient serum examination.

In patients aged adults found as many as two people (5.3%) with disease that is infectious with petsida intoxication and history of dental pain in a few weeks earlier that he died <48 hours after first entering the emergency room in hospital.

Furthermore, to obtain as much as 3 elderly persons (7.9%) with sepsis causes such as gastric perfusion with peritonitis and pneumonia. Of the three patients with peritonitis and pneumonia, there are two of these patients experienced death <48 hours after the first treatment in the hospital.

The genders found in the study sample with a diagnosis of sepsis were 22 male patients (57.9%) and 16 female patients (42.1%). While the number of leukocytes in patients with sepsis are found is increased leukocytes (leukocytosis) of the 26 patients (68.4%) and decreased leukocyte (lekositopenia) there were 12 patients (31.6%).

Outcome obtained from a total of 38 patients in this study were 31 patients (81.6%) of them experienced improvement after the first patient in RSU PKU Muhammadiyah. And other data showed that there was one patient should be referred (2.6%), 2 patients died within less than 48 hours (5.3%) and 4 patients died

within a period of more than 48 hours (10.5%).

Platelet count of 38 sepsis patients who showed normal values to increase to 27 people, where comorbidities that accompany the occurrence of sepsis is most often caused by neonatal sepsis as many as 19 patients. Where neonatal sepsis is also accompanied by 3 cases of congenital anomalies, namely abscess sub galeal, megacolon and hypospadias.

There is also a history of disorders of the digestive system as much as 3 cases the cause of sepsis in this study is acute diarrhea, peritonitis due to gastric perfusis and a long history of dental pain with inadequate treatment. And the last one contained 3 patients with sepsis originating causa cause of infection in the upper respiratory system.

While the decrease in platelets in sepsis reached 11 people with a diagnosis of neonatal sepsis in 1 case which was followed by jaundice degree of 1. In addition there are also two patients with neonatal sepsis were followed by congenital diseases such as pulmonary atresia with Down syndrome. Then the concomitant causes the latter is an infection due to a history of prolonged labor case number 1 of a total of 11 cases of sepsis with thrombocytopenia.

Table 2. The Relationship Between Platelet Count and Sepsis Occurence

Category	Sepsis N (%)	Non Sepsis N(%)	Total	P value
Platelets Decrease	11	21	32	
Platelets Increase	27	17	44	0,02
Total	38	38	76	CI 95% (1.05 - 2.38)

Statistical test proves that there is a relationship between the sepsis occurrence and the reduction of platelet count with 95% of power research.

On the use of calculation methods prevalence ratio that is by dividing the prevalence of the effect on the group with the prevalence of risk factors with effects on the group without risk factors. In this study showed the prevalence ratio values <1, while the value Confident Interval (CI) is (1:05 to 2:38) then the interpretation is statistically there is a relationship between the incidence of sepsis with a reduced number of trombosit.[13]

4. DISCUSSION

Of the total 76 patients, 38 patients (50%) of them with sepsis, and 38 (50%) of them did not have sepsis which is used as a control in this study. Of the total 38 patients with sepsis, 22 (57.9%) were male sex and 16 (42.1%) were female. The youngest age of the patients who experienced early neonatal sepsis is 1 day and age of the oldest sepsis patients was 76 years, with the average age of the whole is less than 1 month.

Sepsis in RSU PKU Muhammadiyah Yogyakarta is the leading cause of death can be classified low, with death rates are only 6 (2.28%) patients during the period January 1, 2010 until December 31, 2010 of the 38 total patients with sepsis. Where two of them died in less than <48 hours post came early to the hospital. As for the cure rate against sepsis reached 31 (81.6%) patients of the total patients with sepsis.Several previous studies have found that the incidence of sepsis is a health problem in many major hospitals in Central Java and Yogyakarta. This is addressed by Subroto and Loehoeri (2003) that in 2002 the mortality rate in patients with a diagnosis of sepsis in the Hospital Dr. Sardjito amounted to 56.83%. Budiarso (2000) who conducted the research at Hospital Dr. Kariadi also stated that sepsis has a mortality rate that is high enough.

It has long been known by researchers that sepsis is closely related to the disruption of blood clotting in the body. Several cases of sepsis that has entered the stage visible changes on the phases of the onset of bleeding tendencies. In this study the number of platelets obtained from 38 patients with sepsis who showed the value increased to 27 people (71.1%), and decreased platelet reached 11 people (28.9).[10]

Research conducted Suliarni (2002) also obtain such a result, the number of platelets in samples of sepsis patients had a mean value of a normal than normal as a control group. Hurtado et al. (2009) also finds the same result.[10,14]

This study found that the age group most affected is the age group of neonatal sepsis is; 23 patients (60.5%), followed infant age group of 9 patients (23.7%), the child's age group 1 patients (2.6%), adult age group 2 patients (5.3%), and age groups elderly group is 3 patients (7.9%). It is appropriate Budiarso research (2000) and Karnadiharja (1998) as well as several other studies that the incidence of sepsis occur most commonly at the age neonates.[15,16]

While in the womb, the fetus is relatively safe to contamination because shielded by various organs such as the placenta, amniotic membrane, chorion, and some anti-infective factors in the amniotic fluid. Nevertheless, the possibility of contamination can arise through various avenues, namely: 1) Infectious bacteria,

parasites or viruses that affects the mother may reach the fetus through the bloodstream to penetrate the placental barrier and enter the fetal circulation. This situation is found in the TORCH infections (Toxoplasma, Others, Rubella, Cytomegalovirus, Herpessimplek virus (HSV Type 1 & 2), Triponema pallidum or Listeria and others; 2) Procedures obstetric less attention to factors antisepsis eg when sampling fetal blood, materials villi chorion or amniocentesis; 3) Exposure to germs that come from the vagina will be instrumental in fetal infection. In this situation vaginal bacteria into the uterine cavity and infants can be contaminated with germs through the respiratory tract or gastrointestinal tract. The incidence of contamination on unborn babies will increase if the membranes have ruptured more than 18-24 hours.[9,17]

Gender males have a higher number of events than the women in the study, which totaled 22 patients (57.9%) and 16 patients with female sex (42.1%). Male gender dominates the large number of patients with sepsis in this study by a margin of 6 patients than female patients. Budiarso (2000) in his research also found that patients with male sex most often found in samples of research on sepsis.[15]

According to Subroto and Loehoeri (2003), found that the number of patients with sepsis most is the female sex. This is quite reasonable because patients with sepsis can occur in all types of sex, according to some other studies.[18,19]

The number of leukocytes in patients with sepsis were found to increase there were 26 patients (68.4%) while decreasing the number of leukocytes contained 12 patients (31.6%). From these results it appears that increased leukocytes (leukocytosis) occurs in the majority of the study sample. This is according to research conducted by Suliarni (2002), as well as that carried out by Subronto and Loehoeri (2003) regarding the increase in the number of leukocytes in the incidence of sepsis caused by the body's protective against infection by increasing the number of leukocytes as a mechanism of resistance to infection.[5,10]

Some comorbidities were found in patients with sepsis in this study include respiratory tract infections, gastrointestinal infections and perinatal infections. This is in line with several previous studies which also found the comorbidities in sepsis as mentioned above.[15,20]

Prevalence ratio in this study was found RP <1, while the value Confident Interval (CI) is (1:05 to 2:38) then the interpretation is that there is a relationship between the incidence of sepsis with decreased platelet count.

The relationship between the incidence of sepsis with decreased platelet count in these statistics may be highly correlated with the theory that the bleeding in patients with sepsis caused by induction of proinflammatory cytokines such as IL-2, TNF, and IL-1. Of the three cytokines IL-1 is only the mechanism identified. IL-1 is known to work as an immuno-regulator also has an effect on blood vascular endothelial cells.[9,10]

These cytokines can later induce the synthesis and surface expression of endothelial adhesion molecules including the E-selectin, intrcellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which increases the adhesion of neutrophils to vascular endhotelium , There was also a stimulation of membrane endhotelium cyclooxigenase activity that will generate prostaglandin known as vasodilators poten.[2,9]

Other than as a vasodilator prostaglandins that play a role in increasing blood flow and adhesion of neutrophils to vascular endhotelium can also increase inflammation with exudation spur of the antibody and complement, as well as the migration of phagocytic cells into infected tissue. The effects of TNF and IL-1 is also enhanced by the ability of the bacterial cell wall component LPS (lipopolysaccharide) to activate the alternative pathway of complement and Hagemen factor (factor XII) .[2,9,10]

Activation of the complement will eventually produce anaphylatoxin, C3a and C5a which increases the permeability of blood vessels by stimulating the release of histamine from mast cells and basophils blood tissue. C5a is also a potent chemotaxin and activator of neutrophils in the blood.[2,10]

Thrombin have a diverse effect on inflammation and helps maintain the balance between coagulation and fibrinolysis. Thrombin has a proinflammatory effect on endothelial cells, macrophages and monocytes to cause the release of TF, platelet activating factor and TNF-α. In addition, thrombin stimulates the chemoattractant for neutrophils and monocytes chemotaxis to facilitate and stimulate the release of mast cell degranulation bioamin to increase vascular permeability and cause leakage kapiler.[9]

With the mechanism of the vascular bleeding will directly increase the use of platelets by the body so that the decreased platelet count is very likely to occur. *Disseminated intravascular coagulation* (DIC) is the most common complication on the sepsis. The consumption of coagulation factor and platelet will induce the severe bleeding complication. PIM simultaneously will cause the microvascular platelet and bleeding. For the PIM patient, the high PAI-1 can be related to the bad prognosis. [9,10]

5. CONCLUSION

From the medical record data of sepsis cases which are hospitalized in PKM Muhammadiyah Yogyakarta Hospital for the period of January 1 up to December 31 2010, we can conclude that the bivariate analysis result shows statistically significant relationship between the sepsis occurence and platelet count with p value of 0,02

(p < 0,05). Beside the measurement of p value, we also obtained the result of prevalence ratio which is < 1, while the Confident Interval (CI) value is 95% (1.05 - 2.38). Therefore the intepretation is that there is a relationship between the sepsis occurence and platelet count.

6. SUGGESTION

It needs further research about the impact of sepsis toward the platelet count, considering sepsis has the high mortality level in Indonesia, moreover if the sepsis patient also has abnormal platelet count. The further research can be conducted with more sample and better research design such as cohort design.

7. REFERENCES

1. Kementerian Kesehatan Indonesia. *Pusat Data dan Surveilans Epidemiologi*. *2010. Profil Kesehatan Indonesia 2009.* Jakarta.
2. Guntur, H., 2006. *Buku Ajar Ilmu Penyakit Dalam Ed: 4 jilid 3*. Jakarta. Pusat Penerbitan Departemen Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia. Indonesia
3. SCCM/ESICM/ACCP/ATS/SIS,*International Sepsis Definitions Conference. Intensive Care Medicine,* 2001, Volume 29, Number 4 - SpringerLink.htm
4. Aminullah A *et al*., 2005. *Sepsis pada Bayi baru Lahir-Masalah dan Penatalaksanaannya.* Kumpulan Makalah Ilmiah pada Simposium Nasional Peritanologi & Pediatri Gawat Darurat, hal 45-57
5. Subroto, Y.W., Loehoeri, S., 2003. *Profil Pasien yang Di Diagnosis Sepsis di RSUD Dr. Sardjito Tahun 2002*. Departemen Ilmu Penyakit Dalam. FK UGM. Jogjakarta. Berkala Ilmu Kedokteran Vol 35, No 4.
6. Therminary A.S., Retayas W., Kardana M., Lila I.N., 2008. *Diagnostic Accuracy of Septic Markers for Neonatal Sepsis. Pediatrica* Indonesian; 2008;5: 48.299-305
7. Mehta A.B., Hoffbrand V. 2006. *Haematology at a Glance*. Huriwati (alih bahasa) Penerbit Erlangga. Jakarta.
8. Wirawan, Riadi., 2007. *Pemeriksaan Agregasi Trombosit dengan ADP pada Orang Dewasa Normal*. Maj Kedokteran Indonesia, Volum: 57, Nomor: 7, Juli 2007
9. Goldstein B, Giroir B, Randolph A. *Linking The Sepsis Triad of Inflammation, Coagulation and Suppressed Fibrinolysis to Infants*. Pediatr Crit Care Med 2005; 6(1): 2-8 Short MA. Adv Neonat Care 2004; 5:258-73
10. Suliarni. 2002. *Aktivitas Faktor VII Pada Sepsis.* Bagian Patologi Klinik. Universitas Sumatra Utara. Medan
11. Bone R.C, Grodzin C.J, Balk R.A, *Sepsis: A New Hypothesis of Pathogenesis of the Disease Proces*. Chest. 1997. 112 : 235-43
12. Cohen J., *Sepsis Syndrome*. Journal of Med Int. Infection. 1996. 31-34
13. Dahlan, M.S., 2005. *Besar Sampel dalam Penelitian Kedokteran dan Kesehatan (Seri 2)*. Arkans. Jakarta
14. Hurtado FJ., Buroni M., Tenzi J. Sepsis: Clinical approach, evidence-based at the bedside. In: Gallo A, et al, editors. Intensive and Critical Care Medicine. Springer-Verlag Italia, 2009; p.299-309.
15. Budiarso, H. 2000. *Rasio Imatur/Total Neutrofil Pada Sediaan Apusan Darah Tepi Sebagai Petanda Dini Sepsis Bakterial Pada Anak*. FK UNDIP. Semarang.
16. Karnadiharja PP. 1998. *Usia, tingginya suhu dan jumlah leukosit sebagai prediksi Bakteremia pada Anak 1-24 bulan*. Thesis. FK UNPAD. Bandung
17. Motara F., Ballot DE, Perovic O., *Epidemiology of neonatal sepsis at Johannesburg Hospita*l. South Afr J Epidemiol Infect 2005; Vol 20 (3)
18. Adyana E., Utama S., Somia A., Parwati P., 2009. *Systemic Inflamatory Response Syndrome (SIRS)* .Departemen Ilmu Penyakit Dalam, Fakultas Kedokteran Universitas Udayan, Denpasar: Indonesia
19. Chan Y.L, Tseng C.P, Tsay P.K,Shy-Shin Chang, Chiu T.F, Chen J.C, 2004, *Procalcitonin as a marker of bacterial infection in the emergency department: an observational study* Critical Care February 2004. Vol 8 No 1.
20.Xavier Xl. 1995. *Application of new definition for evaluate outcome of pediatric patient with severe systemic infection*. Pediatric Infection Dis Journal. 1995; 14 (7): 557-60.
21.Martinhot A., 1996. *Definition*, *risk factor and outcome of sepsis in children*. In Tiboel (eds) Intensive care of childhood, the challenge of the future. Berlin. Spinger Verlag. 1996. 230-53