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Original Article

Associated Factors Of Post Thrombotic Syndrome In Patients With Deep Vein Thrombosis

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Background: Post-thrombotic syndrome (PTS) is a chronic complication of deep vein thrombosis (DVT) which results in decreased quality of life and high health-care costs. Age, gender, obesity, type 2 diabetes mellitus, ipsilateral DVT, history of surgery, use of anticoagulants, and history of malignancy are risk factors that associated with the occurrence of PTS.
Method: This case-control study was conducted in 2019 at Sanglah Hospital, Denpasar. The presence or absence of risk factors of patients who met the inclusion criteria would then be obtained from medical records. Univariate, bivariate and multivariate analyzes were performed using SPSS.
Results: From 48 patients, 60.5% of the subjects were ≤60 years old and 56.3% were female. In the bivariate analysis it was found that not using anticoagulants (OR: 7.28; 95% CI = 2.03-26.10; p = 0.00), obesity (OR: 26.4; 95% CI = 5.54- 125.7; p = 0.00) and history of surgery (OR: 4.94; 95% CI = 0.92-26.41; p = 0.04) were risk factors associated with the incidence of PTS. Meanwhile, in the multivariate analysis, it was found that obesity status was the most dominant factor in which obese patients had a 31.91-fold higher risk of experiencing PTS (95% CI: 4,623-220.3; p = 0.00).
Conclusion: Obesity, not using anticoagulants and history of surgery were factors that were independently associated with the occurrence of PTS in patients with DVT.

Keyword: Anticoagulant, deep vein thrombosis, history of surgery, obesity, post-thrombotic syndrome
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INTRODUCTION

Post-thrombotic syndrome (PTS) is the chronic complication of deep vein thrombosis (DVT) in lower extremity with symptoms of pain, edema and ulceration. The prevalence of PTS in patients with DVT is around 20 – 50%, while the incidence of DVT is one per 1000 persons a year. Approximately 5 – 10% patients with PTS develop severe PTS which manifest as foot ulcer. (Brunicardi *et al.,* 2006; Kahn *et al.,* 2016; Tick *et al*., 2008) Static ulceration is a severe clinical manifestation of PTS and associated with reduced quality of life due to patient's limited ability to do daily activities. This is supported by a study who showed that PTS caused the loss of approximately 2 million effective work days per year in the US. Other than that, PTS is also associated with high medical cost due to the need of long term management in patients with PTS (Strijkers et al, 2011).

As the main chronic complication of DVT, PTS incidence tends to increase (around 20 – 50%) despite optimal anticoagulant therapy. Generally, the underlying mechanism of PTS is high venous pressure as a result of persistent venous obstruction or venous reflux. Santori et al in 2014 mentioned that age, gender and duration of anticoagulant therapy is not risk factors of PTS (Thick et al,. 2009).

Few comorbids that are associated with PTS in patients with DVT including dyslipidemia, DM type II, and malignancy. Dyslipidemia as a risk factor of PTS is hypothesized as reduced adiponectin level can cause increased NO and leptin level in blood, which will eventually result in thrombotic event. However, studies that discuss the relationship between dyslipidemia and PTS are still limited, as in study conducted by Mrozinska *et al*, thus further studies are needed to identify the relationship between dyslipidemia and PTS (Mrozinska et al, 2018). Apart from being associated with various comorbids, the incidence of PTS is also associated with the clinical characteristics of venous insufficiency experienced by patients. The clinical characteristics referred to in this regard are the location of proximal venous insufficiency, history of ipsilateral DVT, and history of surgery (Thick et al, 2009).

Based on the descriptions above, it can be concluded that further research on the risk factors for PTS is still needed because various studies still show inconsistent results regarding the relationship between risk factor and the incidence of PTS. The results of this study is expected to describe the relationship between various risk factors and the

incidence of PTS to identify factors that are significantly related to the occurrence of PTS at the Sanglah General Hospital.

METHOD

This study is an analytical case control study to identify risk factors that are associated with the occurrence of PTS in DVT patients from January to December of 2019. Total sample was 49 patients.

The inclusion criteria in this study were patients aged over 17 years who went to Sanglah Hospital with diagnosis of DVT within period of January 2019 to December 2019. The exclusion criteria in this study were patients who refused to participate, did not return for control to Sanglah General Hospital or died.

Each subject who met the inclusion criteria would be recorded for their identity, history, BMI, physical examination, history of anticoagulant usage, type 2 diabetes mellitus, malignancy, surgery and location of DVT recurrence obtained from the patient's medical record.

All data obtained were then analyzed using SPSS version 21 software for windows.

RESULT

Characteristic of Study Participants

In this study, it was found that 60.5% of the study subjects were ≤ 60 years old and 56.3% were female. Most of the patients had no history of type 2 diabetes mellitus (73%), history of malignancy (94%), history of surgery (79.2%) and experienced DVT with PTS (52.1%). 56.3% of patients were obese and 58.3% of patients had ipsilateral DVT recurrences.

Table 1. Characteristic of Study Participants

Variable	n = 48
Age (%)	
> 60 years old	19(39,5%)
≤ 60 years old	29(60,5%)
Gender (%)	
Male	21(43,7%)
Female	27(56,3%)
Type 2 Diabetes Mellitus (%)	
Yes	13(27,0%)
No	35(73,0%)
History of Malignancy (%)	
Yes	3(6%)
No	45(94%)
Use of anticoagulants (%)	
Yes	24(50%)
No	24(50%)
Obesity (%)	
Yes	27(56,3%)
No	21(43,7%)
History of Surgery (%)	
Yes	10(20,8%)
No	38(79,2%)
Location of DVT recurrence(%)	
Ipsilateral	28 (58,3%)
Contralateral	20 (41,7%)
Outcome (%)	
Unfavorable (DVT with PTS)	25(52,1%)
Favorable (DVT without PTS)	23(47,9%)

Factors that are associated with PTS

From the bivariate analysis result, the variables that had significant relationship with the occurrence of PTS in DVT patients were not using anticoagulants, obesity, and a history of surgery with p-value of 0.001, 0.001, and 0.04 (p value <0.05) respectively and obtained OR values for each of these variables were 7.28 (95% CI 2.034-26.10), 26.4 (95% CI 5.542-125.7), 4.94 (95% CI 0.924-26.41).

Table 2. Bivariate Analysis Result

Variable	OR	CI 95%	p-value
Age			
> 60 years old	1,04	0,326-3,302	1,00
≤ 60 years old			
Gender			
Male	0,49	0,154-1,575	0,36
Female			
Type 2 Diabetes Mellitus			
Yes	0,72	0,201-2,589	0,86
No			
History of Malignancy			
Yes	1,91	0,162-22,63	1,00
No			
Use of anticoagulant			
Yes	7,28	2,034-26,10	0,00*
No			
Obesity			
Yes	26,4	5,542-125,7	0,00*
No			
History of Surgery			
Yes	4,94	0,924-26,41	0,04*
No			
Location of DVT recurrence			
Ipsilateral	7,28	2,034-26,10	1,00
Contralateral			

*variable with p value of p < 0,05

Meanwhile, in the multivariate analysis, the result showed that obesity status was the most dominant factor with a p value of 0.000 (<0.05) and an OR value of 31.91 (95% CI: 4.623-220.3). In addition, not using anticoagulants was also statistically significant with a p value of 0.025 and an OR value of 7.851 (95% CI: 1.290-47.80). While the operation history did not show significant results (p value = 0.114).

Table 3. Multivariate Analysis Result

Variable	**OR**	**CI 95%**	**P-value**
Obesity	31,91	4,623-220,3	0,000*
No history of anticoagulant usage	7,851	1,290-47,80	0,025*
History of surgery	6,099	0,648-57,37	0,114

*variable with p value of p < 0,05

DISCUSSION

This study involved 48 respondents, of which 25 respondents (52.1%) had PTS and 23 other respondents (47.9%) had no PTS. In this study, 8 independent variables were evaluated for their relationship to the incidence of PTS in DVT patients.

After conducting a bivariate analysis using the Chi-Square test, it was found that the factors of anticoagulant use and obesity nutritional status had significant effect on the incidence of PTS in DVT patients. The status of patients who do not use anticoagulant therapy together with the nutritional status of obesity and a history of surgery can increase the risk of developing PTS in patients with DVT. After performing multivariate analysis using logistic regression, it was found that obesity was the most dominant risk factor for outcome in patients with DVT. In this study, there was no relationship between age and the incidence of PTS in patients with DVT. This result is in accordance with study by Yamaki et al. in 2011, which showed that age did not have a significant effect on the incidence of PTS. Although in the study it was stated that increasing age was directly proportional to the incidence of DVT, it was not the case for PTS. This is because old age is associated with the presence of factor V Leiden or the prothrombin gene mutase which can reduce the risk of developing PTS. Another study conducted by Schulman et al, 2006 proved that old age is an independent factor along with circulatory disorders that is closely related to the incidence of PTS in patients with DVT.

In this study, there was no significant relationship between gender and the incidence of PTS in patients with DVT. This result is the same as a study conducted by Yamaki et al. 2011. The relationship between gender and the incidence of PTS may be influenced by the hormone estrogen, but the underlying mechanism still cannot be explained

Result from this study showed that there was no association between diabetes mellitus and the incidence of PTS in patients with DVT. These results are not in accordance with the research conducted by Yang et al., 2015 where the study found a significant relationship between DM and the incidence of PTS. This is because patients with hyperglycemia and uncontrolled blood sugar are closely related to poor prognosis and have the potential to experience persistent thrombosis due to inflammatory process, increased prothrombotic factors, and will cause an imbalance between thrombosis and fibrinolysis. The study showed that DVT patients with diabetes mellitus and hyperglycemia will have two to six times the risk of experiencing PTS. This study obtained different results because of the inclusion of DVT or PTS patients with controlled blood sugar

There was no association between history of malignancy and the incidence of PTS in patients with DVT found in this study. This is possible because there is a significant difference in the number of groups with a history of malignancy and those without. These results are consistent with a study conducted by Huang, 2017 which showed that history of surgery, trauma, and cancer are not significant factors affecting the incidence of PTS. In contrast to the research conducted by Yang et al in 2015, it was found that malignancy is a major risk factor for recurrence of DVT which will then develop into PTS with HR value of 2.10 (CI 95% 1.73-3.05) and a p-value of <0.001. This is because in patients with history of malignancy, inflammatory and procoagulant factors will increase, the development of complications and side effects of treatment, as well as the number of procedures that must be performed contribute to the occurrence of DVT which will eventually develop into PTS due to the disorder or damage to the endothelium.

In this study, there was no association between ipsilateral DVT and the incidence of PTS in patients with DVT. Research conducted by Prandoni et al, 2002 showed that recurrence of DVT in contralateral locations further increases the risk of pulmonary embolism and PTS due to the presence of residual thrombus associated with procoagulant diathesis. The incidence of recurrent DVT, especially in the ipsilateral region, is closely related to skin and blood vessel damage.

This study found a significant relationship between obesity and PTS in patients with DVT. This is the same as research conducted by Baldwin et al, 2013 and Tick et al, 2010. This is because obesity will reduce the body's exercise capacity and increase venous pressure. Obesity is associated with chronic inflammation which will increase pro-inflammatory cytokines such as IL-6 and TNFα as well as acute phase proteins such as CRP. The direct effect of pro-inflammatory cytokines will cause the formation of thrombus by inducing oxidants and causing endothelial dysfunction. In addition, obesity can also reduce venous pressure chronically which lead to disruption of venous flow, especially in the lower extremity.

Not using anticoagulants is also a factor that influences the incidence of PTS in patients with DVT. This is in accordance with the research conducted by Cheung et al. in 2016, in which giving anticoagulants can be useful to reduce the risk of PTS. This is closely related to the pathogenesis of PTS itself, including the presence of chronic venous obstruction, venous valve damage, and microcirculation disorders which subsequently will lead to venous hypertension. The occurrence of coagulation caused by pro-inflammatory factors and other cytokines will cause clotting to form and eventually result in the occurrence of PTS, so anticoagulants are needed to prevent these complications. In another study conducted by Hull et al., 2009 which compared the use of heparin and warfarin as an anticoagulant in preventing PTS in post-DVT patients, it is shown that the use of heparin as an anticoagulant has a better outcome because it can maintain its stability, has protective effect on vascular endothelium and acts as an anti-inflammatory and anti-angiogenic. Recent studies also show that the use of the anticoagulant rivaroxaban has the most effective result because it inhibits the formation of new thrombin and suppresses the activation of thrombin activatable fibrinolysis inhibitor (TAFI) (Ursoy et al, 2008).

History of surgery also has significant effect on the incidence of PTS in patients with DVT. This is supported by the study of Ginsberg, et al. 2000 showing that patients with history of surgery are closely associated with the occurrence of proximal DVT. In this study, there were no significant results with the incidence of PTS and it is a rare complication, however, in other studies, the study subjects who were included in the inclusion criteria had received anticoagulant therapy for at least 6-12 weeks due to the surgery. This might affect the results of the study because previous administration of anticoagulants reduces the incidence of thromboembolism, thus other advanced complications such as venous valve damage and venous obstruction that are closely related to the incidence of PTS can be prevented.

CONFLICT OF INTEREST

ETHICAL CLEARANCE

Ethics approval was obtained by the ethics commission, Faculty of Medicine, Udayana University, Sanglah Hospital, Bali, Indonesia before this research was carried out.

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