Clinical Research

Time to surgery increases pre-operative il-6 and fibrinogen levels in elderly patient with proximal femoral fracture

Ida Bagus Gede Arimbawa,[1] Putu Astawa,[2] I Wayan Suryanto Dusak,[3] I Ketut Suyasa[4]

[1,2,3,4]Department of Orthopaedic and Traumatology, Faculty of Medicine, Udayana University
Sanglah General Hospital, Bali-Indonesia

ABSTRACT

Introduction: Proximal femoral fractures are often found in elderly patients who often suffer from other diseases too. Therefore, comprehensive perioperative management is needed. Preparation for pre-operation will result in a longer waiting time than the time recommended in general. Time to surgery is associated with an increased risk of inflammation and thromboembolism, but many studies show contradictory results.

Methods: to find out the correlation between time to surgery and interleukin-6 and fibrinogen levels pre-operatively in elderly patients with proximal femoral fractures. This study was an analytic cross-sectional study in 31 elderly patients with proximal femoral fractures. Interleukin-6 and fibrinogen levels were measured one hour before surgery.

Results : Of the 31 patients aged ≥ 60 years with a proximal femoral fracture, the average age was 74 years old and the incidence of fracture was most common in women compared to men. The time to surgery is determined from the time the trauma occurred until surgery. There is a significant correlation between time to surgery and IL-6 levels (r 0.673; p <0.05). A significant correlation also found between time to surgery and fibrinogen levels (r 0.747; p <0.05).

Conclusion: From the results of statistical analysis, it was concluded that the time to surgery was significantly associated with an increase in Interleukin-6 as an inflammatory marker and also with fibrinogen as a possible marker of venous thromboembolism.

ABSTRAK

Pendahuluan: *Fraktur femur proksimal sering ditemukan pada pasien lanjut usia yang juga sering menderita penyakit lain, sehingga diperlukan manajemen perioperatif yang baik. Persiapan pre operasi akan mengakibatkan waktu tunggu lebih lama dari rekomendasi pada umumnya. Lama waktu tunggu pembedahan dikaitkan dengan peningkatan risiko inflamasi dan tromboemboli, tetapi banyak penelitian menunjukkan hasil yang kontroversial.*

Metode: *Penelitian ini merupakan studi potong lintangan alitik pada 31 sampel, untuk mencari hubungan antara lama waktu tunggu pembedahan dengan kadar Interleukin-6 dan fibrinogen diukur 1 jam sebelum operasi, pasien lanjut usia dengan fraktur femur proksimal.*

Hasil: *Dari 31 pasien umur ≥ 60 tahun dengan fraktur femur proksimal, usia rata-rata adalah 74 tahun dan kejadian fraktur paling banyak ditemukan pada wanita dibandingkan laki-laki. Semua pasien yang memenuhi criteria inklusi diperiksa kadar IL-6 dan fibrinogen serum, 1 jam pre operasi. Lama waktu tunggu pembedahan ditentukan dari saat trauma terjadi sampai operasi. Didapatkan korelasi kuat dan signifikan antara lama waktu tunggu pembedahan dengan kadar IL-6 (r 0,673; p <0,05). Sedangkan antara lama waktu tunggu pembedahan dan kadar fibrinogen didapatkan korelasi kuat dan signifikan (r 0,747; p <0,05).*

Kesimpulan: *Dari hasil analisis statistic tersebut didapatkan adanya korelasi yang signifikan antara lama waktu tunggu pembedahan dengan kadar IL-6 sebagai penanda inflamasi dan juga dengan kadar fibrinogen sebagai penanda kemungkinan tromboemboli vena.*

Keywords: proximal femoral fracture, elderly patients, time to surgery, Interleukin-6, fibrinogen.

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Corresponding author : Ida Bagus Arimbawa, MD. ibg.arimbawa@gmail.com

INTRODUCTION

Proximal femoral fractures cause a large proportion of hospitalizations among trauma cases and are a public health problem that is often found especially in elderly patients. Until now, there is no definitive therapeutic guide in determining the optimal length of time for surgical waiting in cases of proximal femoral fractures. Injury to tissue due to fractures increases local and systemic inflammatory responses and prolonged immobilization increases the risk of venous thromboembolism. The incidence of pelvic fracture in Spain is 500 per 100,000 in people aged ≥ 65 years, occurring more in female sex. Mortality in the following month after fracture ranges from 5% to 10%, reaching 30% after a year, with 30% of patients experiencing severe disability complications.[2] International recommendations suggest that patients with proximal femoral fractures should undergo surgery within 24-48 hours after trauma.[3] One complication often found due to delayed surgery is an increased risk of inflammation, and one of the most studied pro-inflammatory cytokines is IL-6. The study by Karakaya et al., 2013 included determining changes in serum IL-6 levels in blood samples taken from patients at 6, 24 and 48 hours after trauma involving lower limb bone fractures found that the serum IL-6 levels were 50.14 ± 2.93, 86.84 ± 6.78 and 32.45 ± 3.13 pg / mL.[4] Longer waiting time for surgery in the population of elderly with proximal femur fractures, besides being feared to increase the likelihood of inflammation and infection, are also said to have a greater risk of the occurrence of venous thromboembolism. Research has shown DVT incidence of 54% to 62% inpatients with acute fractures who experienced delayed surgery. One marker of the possibility of preoperative thromboembolism is high levels of fibrinogen in delayed surgery.[5]

METHODS

This study used a cross-sectional analytic study design. All elderly patients with proximal femur fractures who came to the Emergency Installation (IGD) Surgery and were treated in the patient care room at Sanglah Central General Hospital (RSUP), Denpasar, and the patients who had fulfilled the inclusion criteria for Interleukin-6 (IL-6) were examined and the fibrinogen level was measured at 1 hour before surgery. Sampling was done by consecutive sampling method in patients who met the inclusion criteria and were not included in the exclusion criteria. Samples (patients) that had received an explanation of the research procedure and signed the informed consent and fulfilled the inclusion criteria were taken for blood samples for IL-6 and fibrinogen examination 1 hour before surgery. The total number of research samples is 31 subjects.

RESULTS

Basic characteristics of the subjects is shown in Table 1. The average surgery waiting time needed since the on set of trauma until the surgery was 96 hours. The average value of Interleukin-6 level in subjects with proximal femoral fracture was 79.92 pg/mL and the average level of fibrinogen was 454.00 mg/dL (Table 2).

Table 1. Basic characteristic of the subject

Characteristic	Mean ± SB or median (Minimum and maximum value) or frequency	p value
Age (year)	74 (61-92)	0.711
Sex		0.643
Male	9 (29.0%)	
Female	22 (71.0%)	
Type/site fracture anatomy		0.604
Fracture of Neck Femur or Hip	10 (32.3%)	
Fracture ofIntertrochanter	20 (64.5%)	
Fracture of Subtrochanter	1 (3.2%)	

Table 2. Characteristic of time to surgery, IL-6, and Fibrinogen level

Characteristic	Mean ± SB, 25 and75 percentileor frequency	p value
Surgery waiting time (hours)	96 (72-120)	
IL-6 level (mg/dL)	79.92 (37.95-343.63)	0.000
Fibrinogen level (pg/mL)	454.00 (385.00-583.00)	0.001

The correlation between surgery waiting time and IL-6 and fibrinogen levels are shown in Table 3. Based on the data above, there is a strong and significant positive correlation between the surgery waiting time and the level of IL-6 and fibrinogen. The correlation coefficient value

(r) between the surgery waiting time and the IL-6 level is 0.673 with p value of 0.000 (p<0.05). The correlation coefficient value (r) between the surgery waiting time and the fibrinogen level is 0.747 with p value of 0.000 (p<0,05).

Table 3. Correlation between time to surgery with IL-6 and Fibrinogen level

Variable	Spearman correlation	p value
Surgery waiting time to IL-6 level	0.673	0.000
Surgery waiting time to fibrinogen level	0.747	0.000

Table 4. Area Under Curve (AUC) of time to surgery with IL-6 Level

Area Under Curve (AUC)	p Value	95% Confidence Interval	
		Lower	Upper
0.777	0.087	0.608	0.947

Table 5. ROC curve coordinate time to surgery with IL-6

Positive if greater than or equal to	Sensitivity	1-Specificity
47.00	1.000	1.000
60.00	1.000	0.739
84.00	0.875	0.391
108.00	0.625	0.217
132.00	0.500	0.130
156.00	0.000	0.087
169.00	0.000	0.000

To assess the cut-off point of surgery waiting time in association with IL-6 and fibrinogen levelwas done by using Receiver Operating Characteristic (ROC) curve (Figure 1 and 2).

Based on the Table 4, AUC is 0,777 with p value 0.087 (95% CI, 0.608 – 0.947). Based on the Table 6, AUC is 0.780 with p value of 0.088 (95% CI, 0.607 – 0.954). From the Table 5 and 7 it is indicated that the time to surgery that has low sensitivity and specificity is 84 hours after the trauma.

Table 6. AUC of time to surgery and fibrinogen level

Area Under Curve (AUC)	p Value	95% Confidence Interval	
		Lower	Upper
0.780	0.088	0.607	0.654

Table 7. ROC curve coordinate of time to surgery and fibrinogen level

Positive if greater than or equal to	Sensitivity	1-Specificity
47.00	1.000	1.000
60.00	0.909	0.556
84.00	0.636	0.222
108.00	0.409	0.111
132.00	0.318	0.000
156.00	0.091	0.000
169.00	0.000	0.000

DISCUSSION

The incidence of proximal femoral fractures increases significantly in the last decade and is estimated to double in the next 25 years due to increase inlife expectancy, and 9 over 10 incidences of fracture happened in individuals older than 65 years old.[6] In an experiment carried out by Smektala et al. the highest incidence of proximal femur fractures happened at an average age of 82.1 years old, and female (79.7%) are more affected than men (20.3%).[7] In this study, the incidence of proximal femoral fractures was obtained at an average age of 74 years old and the youngest age was 61 years old, the oldest was 92 years old. The incidence of proximal femur fractures was more often in female subjects (71.0%) compared to male subjects (29.0%).

Based on the anatomical location of the fracture, this study found: femoral neck fracture (32.3%), intertrochanter femur (64.5%), and subtrochanter femur (3.2%). Among proximal femur fractures, intertrochanter fracture is considered as the mostimportant, because it is the most frequent and usually affects weak patients such as the elderly population. This fracture is defined anatomically as a fracture that occurs in an area that extends from extracapsular area at the base of the neck femur to the proximal region alongside the minor trochanter. This type of fracture often occurs in elderly population due to osteoporosis and is often caused by low energy trauma.

Various literature and studies have shown that fractures and surgery are factors that can stimulate systemic inflammatory responses.[8] Interleukin-6 is the main regulator for most protein in acute phase and regulates local and systemic inflammatory responses, including acute phase reactant synthesis by the liver, such as C-reactive protein.[9] Evidence showedthat Interleukin-6 (IL-6) increases at the beginning of hip fracture andin patients suffering from SIRS and lung trauma.

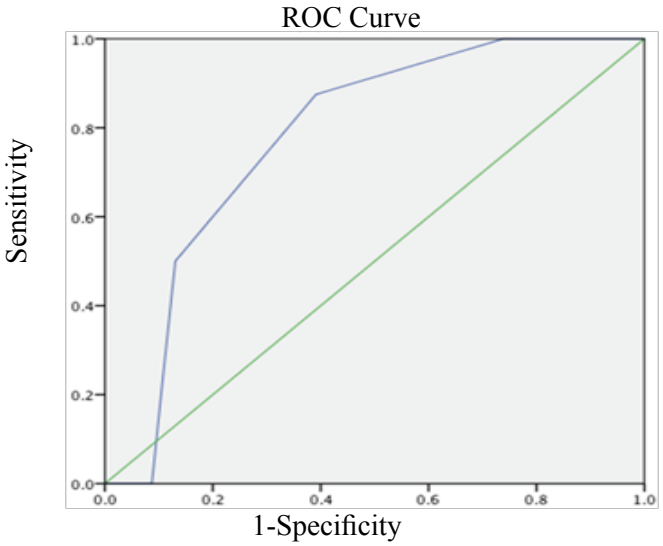

Figure 1. ROC curve of time to surgery with IL-6 level

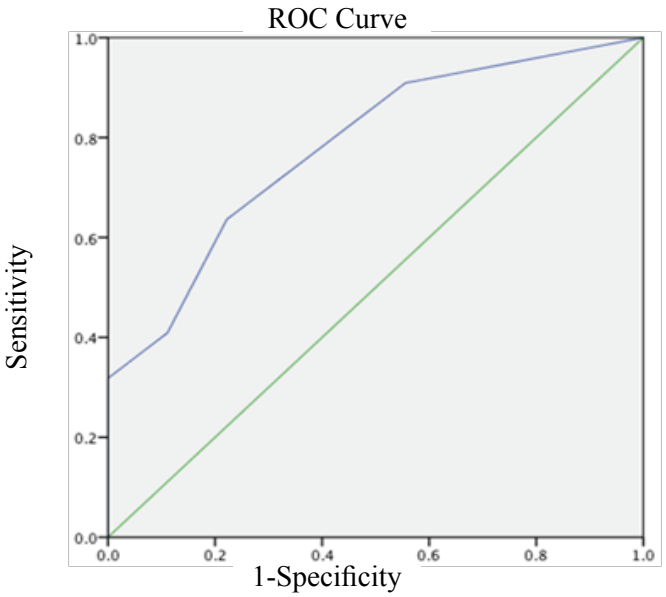

Figure 2. ROC curve of time to surgery and fibrinogen level

A study by Karakaya et al., 2013 defined changes in serum IL-6 levels in blood samples from patients taken at 6, 24, and 48 hours after trauma involving lower limb fractures. It was found that the average serum IL-6 levels at 6, 24, and 48 hours after trauma were 50.14 ± 2.93, 86.84 ± 6.78, and 32.45 ± 3.13 pg / mL. It was found that IL-6 reached peak levels within 24 hours after trauma and then decreased at 48 hours and reached the level below the 6th hour.[4]

In this study, the tendency of IL-6 levels to increase with the duration of surgical waiting time was found. This is probably caused by several diseases suffered by many patients aged > 65 years old, with a prevalence of 70% suffering from multiple chronic diseases in elderly population. Age is an independent risk factor for metabolic syndrome, diabetes, and heart disease. These affect the production of several pro-inflammatory cytokines, which can be independent risk factors for other diseases.[10] Other factors that can influence this production before hospital admission are alternative or traditional treatments as well as inadequate immobilization before and after hospital admission.

Prolonged immobilization after trauma accelerates thrombus formation.[11] High levels of fibrinogen are associated with an increased risk of arterial thrombosis, while the importance of hyperfibrinogenemia in the pathogenesis of deep venous thrombosis has not been determined. In one study, Koenig postulated several mechanisms that might explain the increased risk of venous thrombosis associated with increased levels of fibrinogen. Increased levels of fibrinogen can cause an increase in thrombus size, formation of dense and rigid tissue structures, and fibrinolysis disorders because they affect the binding of plasminogen to its receptors.

High levels of fibrinogen are associated with an increased risk of venous thrombosis, as proven in a study carried out in 1994 to 199 patients from the Leiden Thrombophilia Study (LETS). Individuals with fibrinogen level of > 4 g/L had a more than 2-fold increased risk of venous thrombosis compared to lower levels, and fibrinogen level of> 5 g/L show a stronger association with venous thrombosis.[8]

The findings in this study are in line with the results of a study conducted by Vlieg & Rosendaal in 2003, namely: the risk of venous thrombosis is associated with increased levels of fibrinogen, where the subjects are grouped by sex and age. The risk of thrombosis increased by 2.8-fold for individuals with fibrinogen levels above 95% (4.49 g/L), compared to individuals with fibrinogen levels below 95% [odds ratio (OR) 2.8, 95% CI 1.7,

4.6]. There is no difference in risks for men and women with high levels of fibrinogen. Age-based stratification shows that the risk of venous thrombosis associated with hyperfibrinogenemia is especially increased in older individuals.[8]

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