Clinical Research

The relationship between tourniquet duration and Il-6, d-dimer and visual analogue scale in Total knee arthroplasty

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ABSTRACT

Introduction: Total knee arthroplasty (TKA) is commonly done with tourniquet device placed around the thigh. The use of tourniquet during TKA, aside, from having several advantages, is also accompanied by several risks. Some of these complications are increasing pain due to tourniquet inflation, reperfusion syndrome that leads to the increase of several pro inflammatory cytokines, such as IL-6, as well as increasing D-dimer as a marker for thromboembolic events.

Methods: This study is a cross-sectional analytical experimental research performed in patients with primary osteoarthritis of the knee who failed conservative treatment and agreed to undergo Total Knee Arthroplasty. Blood samples were taken from the patients and IL-6 cytokine and D-dimer levels were identified using ELISA method. Visual Analogue Scale (VAS) was assessed at 12 hours and 24 hours post operation.

Results: The result of this study showed a positive correlation between the length of tourniquet used with IL-6 at 12 hours post operation (r=0.359) and 24 hours post operation (r=0.658); with D-dimer at 12 hours post operation (r=0.491) and 24 hours post operation (r=0.483); and with VAS at 12 hours post operation (r=0.647) and 24 hours post operation (r=0.507) with $p < 0,05$.

Conclusion: A positive correlation was found between tourniquet time and the level of IL-6 and D-dimer, and VAS. The duration of tourniquet cut-off time of more than 122.5 minutes elevated IL-6 and D-Dimer levels which increased the risk for SIRS and DVT.

ABSTRAK

Pendahuluan: *Prosedur TKA banyak dilakukan dengan bantuan alat* tourniquet *yang dipasang di sekitar paha. Penggunaan* tourniquet *selama TKA disamping memiliki manfaat juga tidak terlepas dari beberapa risiko dan dampak buruk yang diakibatkannya. Beberapa komplikasi dari penggunaan* tourniquet *adalah meningkatnya rasa nyeri akibat inflasi* tourniquet*, peningkatan beberapa sitokin pro-inflamasi seperti IL-6, akibat terjadinya sindrom reperfusi, serta peningkatan penanda trombotik yang bersirkulasi, seperti D-Dimer.*

Metode: *Penelitian ini adalah penelitian eksperimental yang dirancang menggunakan rancangan* cross-sectional *analitik pada pasien penyandang* Osteoarthritis *lutut primer yang akan menjalani operasi Total* Knee Arthroplasty*. Darah sampel diambil dengan metode ELISA untuk memeriksa kadar sitokin IL-6 , D-Dimer dan* Visual Analogue Scale *(VAS) pada 12 jam dan 24 jam pasca-operasi.*

Hasil: *Hasil dari penelitian ini menunjukkan korelasi antara durasi penggunaan* tourniquet *dengan IL-6 pada 12 jam pasca-operasi (r = 0,359) dan 24 jam pasca-operasi (r = 0,658); dengan D-dimer pada 12 jam pasca-operasi (r = 0.491) dan 24 jam pasca-operasi (r = 0.483); dan dengan VAS pada 12 jam pasca-operasi (r = 0,647) dan 24 jam pasca-operasi (r = 0,507) dengan p <0,05*

Kesimpulan: *Korelasi positif ditemukan antara durasi penggunaan* tourniquet *terhadap kadar IL-6, D-dimer dan VAS. Durasi waktu* cut-off *penggunaan* tourniquet *lebih dari 122,5 menit meningkatkan IL-6 dan D-Dimer, yang berisiko tinggi untuk SIRS dan DVT.*

Keywords: Total Knee Arthroplasty, Tourniquet, D-Dimer, IL-6, Visual Analogue Scale

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INTRODUCTION

Total Knee Arthroplasty (TKA) is a general surgical procedure performed to treat patients with pain due to osteoarthritis and rheumatoid arthritis. In Europe, TKA operation in 2013 increased with an estimated of 91,703 cases in England, Wales and Northern Ireland. Currently, majority of TKA procedures are carried out with the help of a tourniquet device that is installed around the thigh.[1–3]

The use of tourniquet in lower limb surgery in the orthopedics field has developed rapidly since it was first introduced. One of the complications of using a tourniquet is increased pain due to tourniquet inflation. Another complication is increase in several proinflammatory cytokines due to the occurrence of reperfusion syndrome. Tissue damage induces local and systemic response characterized by the release of mediators, such as pro-inflammatory cytokines, to maintain immune integrity and stimulate reparative mechanisms. The acute phase response begins locally at the site of surgical trauma by macrophages and monocytes, which release proinflammatory cytokines, specifically Tumor Necrosis Factor alpha (TNFα) and Interleukin-1 beta (IL-1β). In tissues during the acute phase response caused by trauma, TNF-α and IL-1β cytokines stimulate the production and release of other cytokines, including Interleukin-6 (IL-6) which reaches a peak of 4-48 hours after surgery.[1,2,4]

In addition to increasing cytokines, a number of physiological disorders that occur with the use of tourniquets can predispose patients to thrombotic conditions. The use of tourniquet can induce an increase in circulating thrombotic markers such as D-Dimer, tissue plasminogen activator, angiotensin-converting enzyme, antithrombin-III and protein C.[1,5]

The use of tourniquet during TKA, besides having benefits, also comes with some inherent risks and adverse effects. Determining the duration of use of a safe tourniquet is very important to prevent the occurrence of complications of reperfusion syndrome which can trigger inflammatory reactions and tissue damage. The use of tourniquet in a safe period of time is expected to minimize the incidence of complications, such as post-operative pain associated with blood vessel and nerve suppression, muscle damage, and a number of other physiological disorders that predispose to thrombotic conditions.[1,5,6]

Considering that tourniquet is routinely used in TKA procedures at Sanglah Hospital and thatonly limited studies found discussing the relationship between the use of tourniquet and the treatment response, the inflammatory response, and the thrombotic markers, the authors considered it necessary to conduct a study in order to determine the relationship between torniquet usage and the level of IL-6 and D-Dimer, and pain assessment using VAS, also the safe cut-off point for torniquet usage.

MATERIALS AND METHODS

This research was conducted at Central Surgical Installation of Sanglah General Hospital from July to September 2018. Examination of IL-6, D-Dimer and VAS was carried out at the Clinical Pathology Laboratory at Sanglah Hospital and a Visual Analogue Scale examination was performed at inpatient ward of Sanglah General Hospital.

This study used an analytical cross-sectional design. A consecutive sample selection was carried out from a pool of patient population undergoing Total Knee Arthroplasty procedure. Materials, such as blood samples, collection, measurement, and observation were carried out simultaneously at a certain point in time. Inclusion criteria were patients with primary knee osteoarthritis failing to improve with conservative therapy and undergoing Total Knee Arthroplasty at Sanglah General Hospital, patients with torniquet application during TKA for <3 hours, the use of spinal and/or epidural anaesthesia during procedure, age of 50-65 years old, and ASA 1 or 2 status. Exclusion criteria included patients with inflammatory arthritis, autoimmune disease, cancer, and other chronic systemic diseases, general anesthesia usage during surgery, history of DVT, thrombositopenia, heart disease, stroke, ASA 3,4,5, or 6 status, and patients deceased after TKA procedure. Patients withdraw from the research or deceased during research were included in drop out criteria.

Samples were taken by consecutive sampling according to inclusion criteria and exclusion criteria. The minimum amount of sample needed was 34, according to Taro Yamane formula.

The patients selected as samples were then underwent spinal anesthesia. Afterwards, a pneumatic tourniquet is applied to the thigh of the affected lower extremity. In all samples, a tourniquet was placed on the treatment

group's femur with a pressure of 350 mmHg from the beginning of the operation until finished. Tourniquet application was used by fulfilling the Bruner's Ten Rules for safe use of tourniquet (recommended by Kutty and McElwain). Tourniquets used in all patients were 12.5 cm wide. The surgical technique used was medial parapatellar approach, extending throughout the entire knee and allowing excellent access to most structures. Parts of the incision couldbe used to gain access to the suprapatellar pouch, patella, and medial side of the joint.

Blood samples of 5 cc were taken 12 hours and 24 hours after TKA surgery for IL-6 and D-Dimer levels determination. Evaluation of pain scale using VAS was done 12 hours postoperatively after the first epidural analgesia and 24 hours postoperatively after the second epidural analgesia. The patients received information with regards to the research and informed consent was obtained from each subject.

RESULTS

The results obtained, which were used as basic data in this study,were then analyzed, including statistically using SPSS for Windows version 23.0. In this discussion, normality test, homogeneity test, comparability test, and treatment effects will be described. The research analysis is presented asdescriptive data distribution.

Descriptive analysis

Table 1. Descriptive statistics of age, sex and duration of tourniquet[1]

Subject Characteristics	Mean ± SD (N=34)			Minimum	Maximum	p
Age	66.588	±	7.336	50.00	81.00	0.602
Sex						
Male	4 (11.8%)					
Female	30 (88.2%)					0.550
Duration of tourniquet use	130.735	±	12.740	105.00	150.00	0.001

Table 2. Descriptive statistics for IL-6 and D-Dimer levels and VAS at 12 hours and 24 hours postoperatively

Variable	Mean ± SD (N=34)			Minimum	Maximum	p
IL-6 Level						0.000
24 hours postoperatively	365.180	±	89.947	200.06	500.00	
12 hours postoperatively	437.219	±	44.785	345.99	500.00	
D-dimer Level						0.000
24 hours postoperatively	5.085	±	1.559	2.30	8.64	
12 hours postoperatively	16.917	±	1.868	12.28	19.83	
VAS Score						0.014
24 hours postoperatively	4.411	±	1.616	2.00	8.00	
12 hours postoperatively	5.382	±	1.435	3.00	8.00	

Descriptive data analysis aims to obtain a clearer pictureonthe distribution and standard deviation of each research variable.

Inferential analysis

This analysis aims to generalize the results of this research to the population. The inferential statistical test used in this study was ANOVA with normal and homogeneous data. Assessment of the test results was performed by using 95% CI and *p value* at significance levelof 0.05. Pearson correlation test was also carried out.

Normality test

The research variables in the treatment and control groups were tested for normality with total of 34 samples (n <50), the normality test used was Shapiro-Wilk test.

Table 3. Normality test of research variables using Shapiro-Wilk

Variable	Shapiro-Wilk		
	Statistic Z	p	Explanation
Duration of tourniquet use	0.955	0.177	Normal
IL-6 Levels			
24 hours postoperatively	0.948	0.106	Normal
12 hours postoperatively	0.943	0.077	Normal
D-dimer Levels			
24 hours postoperatively	0.972	0.510	Normal
12 hours postoperatively	0.967	0.386	Normal
VAS Score			
24 hours postoperatively	0.944	0.079	Normal
12 hours postoperatively	0.938	0.053	Normal

Correlation test

To assess the strength and linear relationship of the variables, Pearson correlation test was performed.

Table 4. Correlation between the duration of tourniquet use andeach variable

Variable	Pearson correlation	p
Duration of Tourniquet use and IL - 6 Level		
24 hours postoperatively	0.658	0.000
12 hours postoperatively	0.359	0.037
Duration of Tourniquet use and D-dimer Level		
24 hours postoperatively	0.483	0.004
12 hours postoperatively	0.491	0.003
Duration of Tourniquet use and VAS score		
24 hours postoperatively	0.507	0.002
12 hours postoperatively	0.647	0.000

The relationship between cut-off point of tourniquet use andil-6 and d-dimer levels

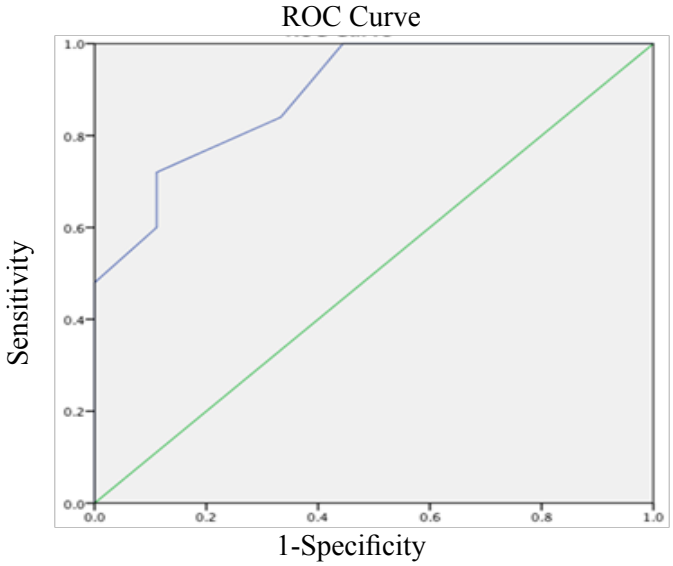
To determine the relation between the cut-off point for using a tourniquet and IL-6 and D-Dimer levels, analysis of the ROC Curve was carried out. The test revealed a significant relationship between the duration of tourniquet use and IL-6 and D-Dimer levels.

From Table 5, it is shown that the value of Area Under Curve (AUC) obtained from the ROC method is 0.891

Table 5. Area Under the Curve of Duration of using a tourniquet and IL-6 level 24 hours postoperatively

Area Under Curve (AUC)	P Value	95% Confidence Interval	
		Lower	Upper
0.891	0.001	0.772	1.000

with a p-value = 0.001 (95% CI; 0.772-1,000). Statistically, the AUC value of 89.1% is classified as good. The optimal value of the cut-off point was determined by the sensitivity and specificity values close to the value of AUC with minimal differences. The following are ROC curve and table.



Diagonal segments are produced by ties

Figure 1. ROC curve of the duration of tourniquet use and IL-6 level 24 hours postoperatively

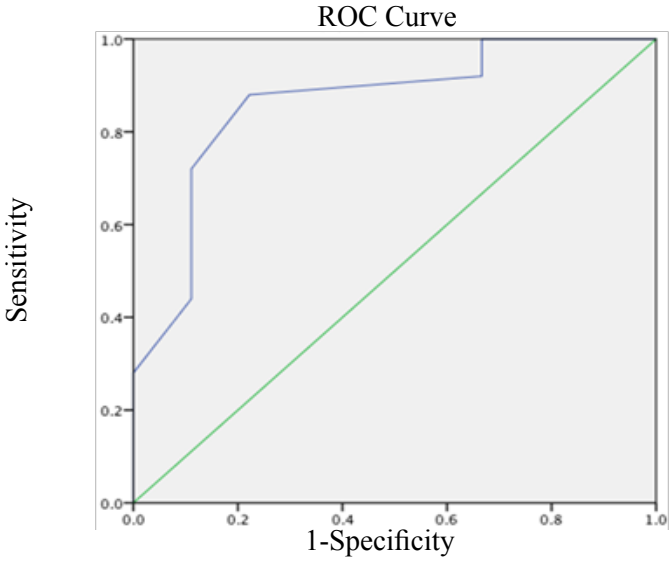
Table 6. Duration of tourniquet use and IL-6 level 24 hours postoperatively

Positive if Greater than or Equal to[a]	Sensitivity	1 - Specificity
104,0000	1.000	1.000
107,5000	1.000	0.889
112,5000	1.000	0.667
117,5000	1.000	0.444
122,5000	0.840	0.333
127,5000	0.720	0.111
132,5000	0.600	0.111
137,5000	0.480	0.000
142,5000	0.280	0.000
147,5000	0.160	0.000
151,0000	0.000	0.000

From table 6 above, the cut-off point obtained was 122.5 minutes, which means torniquet duration exceeding 122.5 minutes may result in IL-6 level 24 hours post operative to reach more than 300 pg /ml, thereby increasing the risk of SIRS (Stensballe J et al.).

Table 7. Area Under the Curve of Duration of using tourniquet and D-Dimer level 24 hours postoperatively

Area Under Curve (AUC)	P Value	95% Confidence Interval	
		Lower	Upper
0.862	0.075	0.716	1.000



Diagonal segments are produced by ties

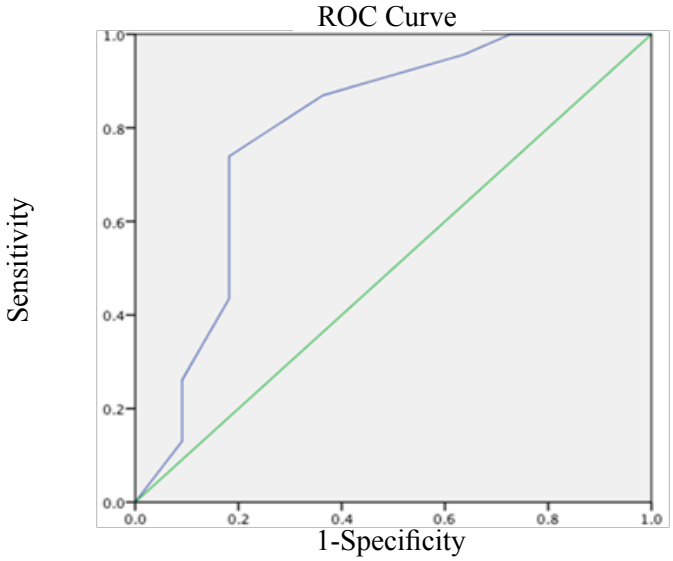
Figure 2. ROC Curve of Duration of tourniquet use andD Dimer level 24 hours postoperatively

From these data, the value of Area Under Curve (AUC) obtained from ROC method was 86.2%, p <0.001. Statistically, the AUC value of 86.2% is classified as good

From Table 8, the intersection is obtained at 122.5 minutes, which means torniquet duration exceeding 122.5 minutes may result in D-dimer level 24 hours postoperativeto reach more than 4 g/mL, which will increase the risk of DVT (LW TicK et al.).

Table 8. Duration of tourniquet use andD-Dimer level 24 hours postoperatively

Positive if Greater than or Equal to[a]	Sensitivity	1 - Specificity
104,0000	1.000	1.000
107,5000	1.000	0.889
112,5000	1.000	0.667
117,5000	0.880	0.667
122,5000	0.880	0.222
127,5000	0.720	0.111
132,5000	0.600	0.111
137,5000	0.440	0.111
142,5000	0.280	0.000
147,5000	0.160	0.000
151,0000	0.000	0.000



Diagonal segments are produced by ties

Figure 3. ROC Curve of Duration of tourniquet use and VAS 24 hours postoperatively

Table 9. Area Under Curve of Duration of tourniquet use and VAS 24 hours postoperatively

Area Under Curve (AUC) P value	P value	95% Confidence Interval	
		Lower	Upper
0.794	0.095	0.608	0.981

From the data above, the value of Area Under Curve (AUC) obtained from the ROC method was 79.4%, p <0.05. Statistically, the AUC value of 79.4% is classified as moderate.

From Table 10, the intersection is obtained at 122.5 minutes, which means torniquet duration exceeding 122.5 minutes may result in VAS24 hours postoperative to reach more than 3 (Haghighi M et al.).

Tabel 10. Duration of tourniquet use and VAS 24 hours postoperatively

Positive if Greater than or Equal to[a]	Sensitivity	1 - Specificity
104.0000	1.000	1.000
107.5000	1.000	0.709
112.5000	1.000	0.677
117.5000	0.957	0.636
122.5000	0.870	0.624
127.5000	0.739	0.182
132.5000	0.609	0.182
137.5000	0.435	0.182
142.5000	0.261	0.091
147.5000	0.130	0.091
151.0000	0.000	0.000

The duration of tourniquet use is related to il-6 level in patients undergoing TKA

In this study, higher IL-6 level was obtained at 12 hours postoperatively and proved to be significantly different as compared to IL-6 level at 24 hours postoperatively. The value of correlation coefficient (r) between the duration of tourniquet use and IL-6 level 24 hours postoperatively is 0.658, whereas IL-6 12 hours postoperative level is 0.359, and both are statistically significant with p values of 0.000 and 0.037, respectively ($p < 0.05$). Linear relationship with significant positive correlation was found especially between the duration of tourniquet use and IL-6 level at 24 hours postoperatively.

The acute phase response begins locally at the site of surgical trauma by macrophages and monocytes, which release proinflammatory cytokines, specifically TNFα and IL-1β. In cytokine tissue, during acute trauma-induced phase responses, TNFα and IL-1β stimulate the production and release of other cytokines, including IL-6, which reaches itspeak 4-48 hours after surgery.[7–10] A consistency with previous studies has shown that the tourniquet in TKA does not worsen systemic improvement in C-reactive protein. However, the findings by Matziolis et al. in a study showed an excessive inflammatory response occurred within 24 hours after the tourniquet release process in TKA. Thus, the systemic inflammatory response to the tourniquet in TKA depends on the first 24 hours after surgery.[7,9,11]

Duration of tourniquet use is related to d-dimer level in patients undergoing TKA

In this study, higher D-Dimer level was obtained at 12 hours postoperative and proved to be significantly different as compared to D-Dimer level at 24 hours postoperative in patients undergoing primary TKA surgery. Correlation coefficient (r) value between the duration of tourniquet use and D-Dimer level at 24 hours after operation is 0.483 while the D-Dimer level 12 hours after operationis 0.491, and both are statistically significant with p values of 0.004 and 0.003 ($p < 0.05$), respectively.

In the research of Tick L.W et al. it was mentioned that higher risk for DVTarise with the increase in D-Dimer above 4 µg/mL. This is also supported by a research carried out by Naem M.A et al. where all samples experienced increased D-Dimer in the first day after operation. In this study, the intersection was obtained at 122.5 minutes, which means if the use of a tourniquet exceeding 122.5 minutes, the D-dimer level at 24 hours postoperatively will be more than 4 g/mL and the risk of DVT is increased.[10,12–14]

The duration of tourniquet use is related to the scale of vas in patients undergoing TKA

In this study, higher VAS value was obtained at 12 hours postoperative and proved to be significantly different compared to VAS value at 24 hours postoperative in patients undergoing primary TKA surgery. Correlation coefficient (r) value between the duration of tourniquet use and VAS value 24 hours postoperative is 0.507 and 12 hours postoperative is 0.647, and both are statistically significant with p values of 0.000 and 0.002, respectively ($p < 0.05$). Linear relationship with significant positive strong correlation was obtained especially between the length of the tourniquet installation and the VAS value at 12 hours postoperatively.

Tai et al., 2012 stated that the use of tourniquet at TKA could reduce the time of surgery and bleeding and caused extensive muscle damage, which could result in postoperative pain. However, Marcos George et al. reported an opposite result in his study (2016) that there was no significance between the use of tourniquet and pain complications with p value of 0.174.[15–18]

CONCLUSION

A strong positive correlation between the duration of tourniquet use and IL 6 and D-Dimer levels and VAS scale are shown. The clinical and practice duration

of tourniquet use should be a parameter that must be considered to minimize the inflammatory response, prothrombotic conditions & postoperative pain in TKA procedure.

This study can be used as a baseline to examine the role of tourniquet duration on inflammatory response, prothrombotic conditions and postoperative pain. A similar study with higher number of samples should be conducted in the future.

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