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Clinical Research

# The Protective Effect of Vitamin E for Reducing Intra-Hospital Mortality in Acute Limb Ischemia Patients

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**Abstract**

**Background:** Management of acute limb ischemia (ALI) is still a huge challenge. Current advances of endovascular therapeutic approach in management of ALI have decreased the overall amputation rate, nevertheless, mortality rate remains high which may be caused by metabolic consequences of reperfusion injury. Aim, To understand the role of vitamin E to intra-hospital and 30-day mortality among acute limb ischemia patients

**Methods:** This retrospective cohort study included all patients with ALI between 2015 to 2018. Vitamin E 2x400 mg orally for seven days was given based on physician preference after ALI diagnosis was confirmed. Data were collected from Vascular Registries of National Cardiovascular Center Harapan Kita (NCCHK), Jakarta, Indonesia. Univariate analysis and logistic regression models were used to explore factors that contribute to intra-hospital and 30-day mortality.

**Results:** A total of 160 patients with ALI involving 192 limbs were admitted to our hospital. Mostly were male (63.1%) and mean age were 56±13 years old. Majority of the patients had unilateral lesion (80%), and were diagnosed with Rutherford stage IIA (36.3%), followed by stage IIB (33.8%), stage I (20%), and stage III (10%) respectively. Intra-hospital and 30-day mortality were 28.1% and 36.9%, respectively. Low treatment of vitamin E increased intra-hospital mortality (HR 5.6 95%CI 1.7-18.3), however, it did not affect 30-day mortality. Other factors including IABP insertion, arrhythmia, bleeding requiring transfusion and acute renal failure were associated with higher intra-hospital and 30-day mortality. In addition, menopause (HR 3.2; CI 1.16-8.85) was also a predictor of 30-day mortality.

**Conclusion:** Vitamin E administration reduced intra-hospital mortality but not on 30-day mortality in acute limb ischemia patients.

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**Keywords:** Acute Limb Ischemia, vitamin E, mortality, reperfusion injury

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## Introdution

A sudden decrease in limb perfusion which threatened the viability of the limb namely acute limb ischemia (ALI), remains one of the major emergencies in vascular disease.[1] Despite its relatively lower incidence in comparison to acute coronary syndrome (ACS), 1.5 cases per 10,000 persons per year,[2] it has high morbidity and mortality if not well treated. Mortality rate reached 15% within the first 30-days and amputation, as the direct consequence of ALI, may reach up to 25% within the first month after the acute onset.[3]

Even nowadays, the management of acute limb ischemia remains a challenge. The goal of ALI management is to restore arterial flow and viability of the limb. The treatment of choice for non-viable ALI is amputation, whereas treatment options for viable and threatened ALI may include endovascular (i.e., intra-arterial thrombolysis, aspiration or rheolytic thrombectomy and/or angioplasty) or surgical (i.e., thrombo-embolectomy, endarterectomy and/or bypass) revascularization. Current advances of endovascular therapeutic approach in the management of ALI have decreased the overall amputation rates, nevertheless, mortality rate remains high and has not had any significant improvement after hospital discharge.[4]

Vitamin E is one of antioxidants and considered to have an important role in the prevention and treatment of illnesses related to oxidative stress such as cardiovascular disease, atherosclerosis, cancer, and diabetes.[5] This positive antioxidant effect has been proved by research data on chronic and acute model. There is no consensus using vitamin E routinely in the management of acute limb ischemia in recent guidelines.

The primary objective of this study was to know the effect of administration of vitamin E after acute limb ischemia event to intra-hospital and 30-day mortality. Whereas, the secondary objective was to identify other risk factors that are related with intra-hospital and 30-day mortality in ALI patients.

## Methods

### Study Design and Data Collection

This study was a retrospective cohort study in patients admitted to our hospitals with acute limb ischemia or newly diagnosed as acute limb ischemia after intra-hospital procedure between January 1, 2015 and December 31, 2018. All of the data were collected from Vascular Registries of National Cardiovascular Center Harapan Kita (NCCHK). The database includes baseline characteristics, diagnosis, comorbidities, procedures performed and outcome. Acute limb ischemia diagnosis was based on clinical history, physical examination and Doppler studies of all extremities. All patients were treated according to the standard management on recent guideline. Since vitamin E was not recommended in any guideline of acute limb ischemia yet, so the administration of vitamin E depends on physician discretion. Vitamin E was administered once acute limb ischemia was diagnosed with doses 2x400 mg orally for seven days. All patients with incomplete data were excluded. The study has been approved by the institutional review board. No informed consent was required for this study.

### Statistical Analysis

We performed univariate analysis to identify factors associated with intra-hospital mortality and amputation using Chi-Square and independent t-test analysis. Variables with p-value <0.25 will be included in multivariate logistic regression analysis to identify the most influencing factors related to intra-hospital mortality. We considered a two-sided p-value of less than 0.05 as statistically significant. All analyses were conducted using SPSS version 23.0.

## Results

A total of 160 patients involving 192 limbs were admitted to our hospital with the diagnosis of ALI, 63.1% were male and the mean age was 56 ± 13 years old. Intra-hospital and 30-day mortality were 28.1% and 36.9% respectively (Figure 1). Baseline characteristics of our study population are shown in Table 1. Most patients presented to our hospital with unilateral lesion (80%)

and Rutherford stage IIA (36.3%) and IIB (38.3%).

Table 2 shows the result of univariate and multivariate analysis of variables related to intra-hospital mortality. In the univariate analysis, insertion of IABP (Intra-Aortic Balloon Pump), no treatment of bicarbonate sodium and vitamin E, complication of arrhythmia, bleeding requiring transfusion and acute renal failure were related to intra-hospital mortality. In the multivariate analysis, the predictors for intra-hospital mortality were insertion of IABP (HR 3.4; 95% CI 1.0-11.3); lack of vitamin E treatment (HR 5.6; CI 1.7-18.3); complication of arrhythmia (HR 12.00; CI 3.8-37.7); and acute renal failure (HR 6.70; CI 1.88-24.3). Bleeding requiring transfusion was not a significant factor.

Table 3 shows the result of univariate and multivariate analysis of variables related to 30-day mortality. In the univariate analysis, risk factor of menopause in women, acute renal failure, arrhythmia, and bleeding requiring transfusion were related to 30-day mortality. In the multivariate analysis, the predictors for 30-day mortality were menopause (HR 3.2; CI 1.16-8.85); IABP insertion (HR 4.51; CI (1.14-17.92); complication of arrhythmia (HR 0.11; CI 0.04-0.32); bleeding requiring transfusion (HR 3.77; CI (0.10-14.28); and acute renal failure (HR 5.5; CI 1.79-16.95)

## Discussion

This study showed that administration of vitamin E in acute limb ischemia patients was related to intra-hospital death but had no effect on 30-day mortality. Low treatment of vitamin E could increase intra-hospital mortality with OR 5,6 (CI 1.7-18.3). Vitamin E was given 200 mg twice a day orally from the day of diagnosis of acute limb ischemia were established and continued for 7 days. This is the first study that analyzed the relationship between administration of vitamin E in real acute setting of limb ischemia and its effect on intra-hospital mortality.

In our institution, intra-hospital and 30-day mortality rate of acute limb ischemia remained as high as 28.1% and 36.9% respectively in the last three years (2015-2018). High mortality in acute limb ischemia may be caused by the contribution of metabolic consequences of reperfusion injury.[6] Acute ischemia of extremities can lead to necrosis of the cells and further promote inflammatory process.[7] Restoration of blood flow after occlusion and tissue ischemia may then paradoxically aggravate previous ischemic damage by overt inflammatory response that promotes local tissue destruction and remote organ dysfunction.[8,9] Oxidative stress parameters such as malondialdehyde level and lipid peroxidation will increase significantly after ischemia and in 24 hours of reperfusion and these values will decrease gradually to the end of the first week.[10]

Vitamin E has been known for its antioxidant effect and reducing ischemic reperfusion injury. Vitamin E can inactivate reactive oxygen species (ROS) where its production increased after reperfusion occurred. Reperfusion will increase the release of ROS, infiltration of inflammatory cells and humoral mediators which further potentiates cellular damage.[11] Initiation and propagation of ischemic reperfusion injury depend upon transcription factor activation which in turn is responsible for the induction of inflammatory genes required for rapid production of some proteins such as cytokine, adhesion molecules, complement factors, and NO synthase.[12,13]

Vitamin E also has an effect as a regulator of signal transduction and modification of NF-KB as predominant transcription factor activation during reperfusion.[14] This is why we gave vitamin E for ameliorating ischemia reperfusion injury for seven days after diagnosis was established.

Several studies have shown the effect of pretreatment of vitamin E to ischemic reperfusion injury in animal models or human samples (muscle and blood). Arato, et al (2009) studied the effect of pretreatment of vitamin E 200 mg once a day in 16 patients underwent revascularization operation of lower limb due to chronic obliterative arterial stenosis from preoperative day till the 7th post-operative day. They concluded that the administration of vitamin E could decrease the rate of oxidative stress forming as a result of ischemia-reperfusion as well as overturning the prooxidant-antioxidant balance, and reduce white blood cell activation (MPO activation, free-radicals production, expression of adhesion molecules).[10] Earlier, Formigli, et al (1997) also studied the effect of administration of pretreatment vitamin E but in a model of ischemic-reperfusion of lower limb muscle of patients undergoing aortic cross-clamp during surgical repair of aortic abdominal aneurysm. They found that administration of vitamin E could prevent the accumulation of

neutrophils within ischemic and reperfused muscle by reducing expression of endothelial adhesion proteins such as E-selectin and ICAM-1.[15]

In our registry, the beneficial effect of vitamin E administration was limited to intra-hospital only. On 30 day-mortality, this effect was no longer seen. Our hypothesis is because of; 1. the effect on ameliorating of ischemic-reperfusion injury happened in acute setting after reperfusion was performed and not persisted in the long term; 2. The administration of vitamin E is only for 5-7 days; 3. 30-day mortality was depended on other stronger factors such as IABP insertion, acute renal failure, bleeding, and arrhythmia.

Other factors that contributed to higher intra-hospital mortality in ALI patients in our institution include IABP insertion, arrhythmia, bleeding requiring transfusion, and acute renal failure during hospitalization. Predictors for 30-day mortality were menopause, IABP insertion, complication of arrhythmia, bleeding requiring transfusion, and acute renal failure. Clason AE, et al found several factors contributing to 30 days mortality and amputation were increasing age, level of occlusion, recent myocardial infarction, pre-existing peripheral arterial disease, and cardiopulmonary functional class.[16] From the United States Medicare registries, predictors of 30-day mortality include advanced age, chronic renal failure, dementia, cancer, and atrial fibrillation.4 Nevertheless, in our study, all of these factors failed to showed significant association with intra-hospital mortality.

Insertion of IABP is one factor that is related to intra-hospital mortality (OR 3.4). IABP was inserted right before or after operation and in cardiogenic shock patients. In 30% of the population, IABP was inserted related to cardiac surgery. Such finding also supported by Allen RC, et al who found that IABP inserted during cardiac surgery patients is a strong risk factor for acute leg ischemia. Morbidity and mortality of ALI after cardiac surgery were 92% and 46% subsequently.[17] Folkert IW, et al (2018) also found similar findings whereas ALI was associated with significant morbidity, mortality and lower long-term survival. Insertion of IABP contributes to developing acute limb ischemia with OR 4.7 (CI 2.9-7.5).[18]

Reperfusion to severely ischemic muscles may induce the release of toxic metabolites such as potassium, free radicals, and myoglobin, and it may lead to life-threatening systemic complications including renal, cardiac and pulmonary failure.[19,20] Reperfusion to rhabdomyolytic muscle induces release of myoglobin, a potential renal toxin causing acute tubular necrosis. Reperfusion also induces overflow of intracellular potassium and hydrogen ions due to the destroyed potassium-sodium pump causing metabolic acidosis and cardiac arrythmia.[19] Acute renal injury and fatal arrhythmia is one of the most serious complications of ALI and may lead to death. In our registry, complication of acute renal injury and fatal arrhythmia were highly contributed to intra-hospital mortality with OR[6.7] (CI 1.88-24.3) and OR 12 (CI 3.8 – 37.7) respectively.

The correlation between menopause and 30-day mortality in acute limb ischemia patients is still not clear yet. Atherosclerotic burden is greater in postmenopausal women than premenopausal women with a higher proportion of obstructive coronary artery disease and multivessel disease due to the protective effect of endogenous estrogen on vascular endothelium.[21] One of the causes of high mortality in women with acute myocardial infarction is late or delay between onset of symptoms and arrival at the hospital.[22] Subgroup analysis in our registry also showed that menopausal women presented late to the hospital than the others with mean 100.57 hours, and 77.29 hours subsequently.

The limitation of our study is that our registry was only conducted in one center. All the data were collected both prospective and retrospectively from medical records. Some of them were incomplete and lost during the follow-up. Treatments of the patients were based on physician personal preference nevertheless it showed real-world practice data on treatment of ALI. There is a possibility of selection bias, in which patients that receive Vit E has better clinical profile

## Conclusion

Vitamin E administration had a protective effect to intra-hospital mortality but not on 30-day mortality. Other risk factors contributed to the intra-hospital mortality were including IABP insertion, arrhythmia, bleeding requiring transfusion and acute renal failure. Predictors for 30-day mortality were menopause; IABP insertion; complication of arrhythmia; bleeding requiring transfusion; and acute renal failure.

## Conflict of Interest

The authors declare that there is no conflict of interests.

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