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The use of compression stockings produces lower Interleukin-6 (IL-6) levels, Higher American Orthopaedic Foot and Ankle Society Score (AOFAS), and does not produce higher alkaline phosphatase level in postoperative patients with fracture around the ankle

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ABSTRACT

Background: Fractures around the ankles are common injuries. The use of compression stockings is one of the postoperative modalities that has been widely used in developing countries but is rarely used in Indonesia. This study aimed to determine the effect of using compression stockings on changes in inflammatory biomarkers level and functional outcomes in postoperative patients with fractures around the ankle.

Methods: This study was a randomized clinical trial (post-operative-only design) in 26 patients with fractures around the ankle. The study subjects were divided into groups using postoperative compression stockings and groups without compression stockings. Its efficacy was assessed by measuring levels of Interleukin-6 (IL-6), Alkaline Phosphatase (ALP), and American Orthopaedic Foot and Ankle Society (AOFAS) scores. Data were analyzed using SPSS version 20 for Windows.

Results: Postoperative 24-hour IL-6 levels were not significantly different ($p=0.200$; $-59.93-266.42$), but they were significantly different postoperatively in 3 days ($p = 0.001$; $8.76-30.21$), 14 days ($p=0.015$; $2.40-20.49$), and 30 days ($p=0.000$; $-15.49-[-5.03]$). ALP was not different significantly, both at 24 hours ($p=0.160$; $-16.0-2.80$), 3 days ($p=0.072$; $-0.65-14.19$), 14 days ($p=0.098$; $-1,310-12,54$), and 30 days ($p=0.419$; $-5.00-11.61$) after surgery. The AOFAS scores was different significantly 30 days postoperatively ($p=0.000$; $-3.915-[-1.469]$).

Conclusion: The use of compression stockings can be considered as postoperative therapy to lower the IL-6 levels but do not affect ALP levels in postoperative patients with fractures around the ankle. The use of compression stocking resulted in a higher AOFAS score than without wearing compression stockings in postoperative patients with fractures around the ankle.

Keywords: Fracture, Ankle, Compression Stockings, IL-6, ALP, AOFAS Score.

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INTRODUCTION

Fracture around the ankle is one of the most common injuries in daily practice and presents surgeons' challenges.¹ Although operative therapy has been carried out optimally and usually gives good results, long-term complications are often found in ankle fractures.² Various postoperative treatments have

been developed to maximize the healing process in patients who have undergone surgery.^{3,4} As a therapeutic modality that has not been widely used in Indonesia, compression stockings have been widely used in developing countries as an immobilization modality and reduce edema, inflammation, and improve circulation in the injured limb.⁵ However, there is no literature examining its efficacy

for postoperative ankle fracture patients in Indonesia.

Postoperative care plays an important role in healing fractures around the ankle. The use of compression stockings is one of many modalities that can be considered.⁶ In the research of Sultan MJ et al., compression therapy is useful to reduce the occurrence of venous hypertension in the immobilized leg so that it can optimize

soft tissue and bone healing process.⁶ Furthermore, this study also proved that pain movement, related to the release of Interleukin-6 (IL-6) and Alkaline Phosphatase (ALP), around the ankle and the American Orthopedic Foot and Ankle Society (AOFAS) score recovered faster than the group without intervention at the fourth to sixth week of examination.⁶⁻⁸

Based on the above explanation, and because there is not much literature comparing the efficacy of compression stockings on the healing of postoperative ankle fractures, especially in Indonesia, this study aims to determine the efficacy of these compression stockings and their effect on changes in the proinflammatory cytokines, such as IL-6 and ALP levels, as well as output functional as measured by the AOFAS score. If proven, this study is expected to be a basis for consideration in the choice of therapy in postoperative ankle fracture patients to improve control of inflammatory reactions and improve these patients' functional outcomes.

METHODS

This study is a randomized clinical trial (postoperative only) design. From the population of the research subjects, samples were enrolled that met the study's inclusion requirements and then randomized them to the control group and the treatment group. The study was conducted in the emergency, inpatient, and outpatient unit of the Orthopaedic Department Sanglah General Hospital between January - July 2020. The study population was patients with fractures around the ankle who came to the emergency room at Sanglah Hospital who received operative management open reduction - internal fixation (ORIF) during the study period.

Samples were taken from an affordable population with the following inclusion criteria: Adult patients aged 18-60 years, Body Mass Index (BMI) 18.5-25 kg/m², detected a fracture around the ankle determined from history, physical examination, and additional investigations, with diagnosis, includes the following: closed ankle fracture according to Weber classification types B and C, closed ankle fracture according to the Lauge-Hansen classification, closed tibial

Table 1. Baseline characteristics of respondents

Variable	Group (N=26)		P
	Treatment (N=13)	Control (N=13)	
Gender, n (%)			
Male	8 (62.00)	8 (62.00)	1.000
Female	5 (38.00)	5 (38.00)	
Age (Years) (Mean±SD)	48.00±13.65	48.15±13.17	0.842
IL-6 Post-Operation (pg/mL) (Mean±SD)			
24 Hours	379.26±122.09	482.50±251.23	0.200
3 Days	53.15±6.73	72.64±16.92	0.001*
14 Days	54.95±10.94	66.39±11.40	0.015*
30 Days	21.50±5.14	31.76±7.55	0.000*
ALP Post-Operation (IU/L) (Mean±SD)			
24 Hours	76,38 ± 8,45	69,77 ± 14,11	0.160
3 Days	68,62 ± 7,06	75,38 ± 10,87	0.072
14 Days	57,23 ± 4,28	62,85 ± 10,94	0,098
30 Days	58,00 ± 10,99	61,31 ± 9,48	0.419
AOFAS 30 Days-Post Operation (Mean±SD)	97,00 ± 1,73	94,31 ± 1,25	0.000*

IL: Interleukin; ALP: Alkaline Phosphatase; AOFAS: The American Orthopaedic Foot & Ankle Society; SD: Standard Deviation; *Statistically significant if p-value less than 0.05

plafond fracture and closed fracture of the distal tibia. The patient who underwent surgery did not have comorbid conditions that can affect the healing process, including diabetes mellitus, malnutrition, metabolic and hormonal disorders, malignancy, and immunosuppression. The patients were cooperative with the examination and can communicate well, and are willing to participate in the study by signing informed consent.

Exclusion criteria in this study included: patients diagnosed with pathological fractures, patient with congenital musculoskeletal disorders, patients with an exposed dislocation or fracture, patients with ankle osteoarthritis, patients with neglected fractures or patients who underwent revision surgery for trauma around their ankles, patients with peripheral artery disease, including a history of taking peripheral arteries for bypass grafting. Patients with severe peripheral neuropathy or other causes of sensory disturbances, patients allergic to stockings, patients with severe deformities of the limbs, patients who were not cooperative and had difficulty communicating, and patients who did not agree to participate in the study.

Sampling was obtained by stratified randomized sampling method from affordable populations. Using the Online Research Randomizer application

(randomizer.org), randomization was performed to determine which sample belongs to the intervention group and the control group. Variable identification is a characteristic of a research sample that is measured numerically or categorically. After the data was collected completely and re-evaluated, the collected data were analyzed with descriptive analysis to determine the proportion and basic characteristics of postoperative ankle trauma patients. An independent T-test was performed to investigate the relationship between the use of compression stockings and IL-6, ALP, and AOFAS scores in postoperative ankle trauma patients. Data were analyzed using SPSS version 20 for Windows.

RESULTS

This study's subjects were 26 patients who had fractures around the ankle who underwent operative management at Sanglah General Hospital Denpasar - Bali during the period January - July 2020 (Table 1). There was no significant difference in the proportion of gender and procedures performed in the two groups (p = 1.00). It was found that the mean age was 48.00±13.65 years and 48.15±13.17 years in each treatment and control group without any significant difference (p=0.842) (Table 1).

IL-6 levels were not significantly different at 24 hours postoperatively ($p=0.200$; 95%CI; -59.93-266.42), but significantly different at 3 days ($p=0.001$; 95%CI; 8.76-30.21), 14 days ($p=0.015$; 95%CI; 2.40-20.49), or 30 days ($p=0.000$; 95%CI; -15.49-[-5.03]) after surgery. Postoperative IL-6 levels were found to be significantly lower in the treatment group at each measurement time ($p<0.05$) (Table 1).

ALP levels were not significantly different, both at 24 hours ($p=0.160$; 95%CI; -16.03 - 2.80), 3 days ($p=0.072$; 95%CI; -0.65-14.19), and 14 days ($p=0.098$; 95%CI; -1.310-12.54), or 30 days ($p=0.419$; 95%CI; -5.00 - 11.61) post operation (Table 1). However, the AOFAS score was significantly different at 30 days after surgery ($p=0.000$; 95%CI; -3.915 - [-1.469]) compared with control group (Table 1).

DISCUSSION

In a study conducted by Shibuya N et al., on the epidemiology of fractures around the ankle in the United States (US), it was found that fractures around the ankles were the most common fractures found in trauma hospitals in the US.⁹ The previous study found that out of 280,933 cases of ankle fractures and dislocations, 119,787 patients were female, while 157,977 patients were male. The mean age of the subjects in the previous study was 43.87 ± 19.25 years old.²

In this study, it was found that IL-6 levels were not significantly different at 24 hours after surgery but differed significantly at 3 days, 14 days, or 30 days after surgery. Postoperative IL-6 levels were significantly lower in the treatment group at each measurement time (3, 14, and 30 days) ($p<0.05$).

Interleukin-6 (IL-6) is a type of interleukin produced in response to inflammation/inflammation, infection, and tissue injury.¹⁰ Human IL-6 comprises 212 amino acids, including 28 amino acids that act as peptide signaling, and the gene encoding IL-6 has been known to be located on chromosome 7p21. IL-6 contributes to the body's defense mechanisms by stimulating acute phase responses, hematopoiesis, and immune reactions.¹⁰ After being produced in

peripheral tissues, IL-6 will be circulated to the liver and induce the formation and release of C-reactive protein (CRP), serum amyloid-A (SAA), fibrinogen, haptoglobin, and α 1-antichymotrypsin.¹⁰ In addition, IL-6 will reduce the formation of fibronectin, albumin, and transferrin in liver cells.¹⁰

In conclusion, it was found that IL-6 levels reached their peak levels within 24 hours after trauma and the levels would decline at 48 hours. These results can lead to the assumption that measuring IL-6 levels in the first 24 hours after trauma will provide information about the injury's extent based on the previous study.¹¹ Measurement of IL-6 levels at 24 hours and 3 days after surgery because, based on the literature, the inflammatory process was still ongoing in that period.¹² Meanwhile, the measurement of IL-6 levels on day 14 and day 30 is still measured because a previous literature stated that there may be involvement of IL-6 in the bone healing process related to the stimulation process of osteoblasts, osteoclast differentiation, and other processes of bone healing, although the acute inflammatory process is over.¹³

This study found that ALP levels were not significantly different at 24 hours, 3 days, 14 days, or 30 days post-operation. Regarding the results of this study where ALP levels are not affected by the use of compression stockings, it is entirely in accordance with a previous literature which states that ALP is a bone turnover marker and is not a strong inflammatory mediator, so it is not affected by the degree of inflammation/inflammation that is influenced by the use of compression stockings.¹⁴ A study conducted by Nielsen et al. examining the effects of heparin therapy and compression stockings on serum aminotransferase and ALP levels found no significant increase in ALP levels between the conditions before and after therapy either on the administration of heparin therapy or the use of compression stockings.¹⁵ In this study, we continued to check ALP levels at 24 hours, 3 days, 14 days, and 30 days after surgery because in the literature, it is said that changes in ALP levels can be detected on 1-day post-trauma up to 4-6 weeks when the bone healing process has started.¹⁶

This study found that the AOFAS score at 30 days after surgery was significantly different in the two groups, where the AOFAS score was found to be higher in the treatment group. The AOFAS score relies on patient-reported questions about pain, activity, functional limitations, and footwear, and the examiner reported data on alignment, gait, and motion in 3 categories, namely (1) pain, (2) function, and (3) alignment. Each of the scores includes a clinical examination and contains 8 to 9 different questions with 3 to 4 answer choices.¹⁷ Each question is scored between 0 and a maximum that ranges from 5 and 40 depending on the specific question.¹⁷ There are no articles that clearly report the recommended timing of a good AOFAS assessment in patients after treatment of foot and ankle disorders. A previous study by Van Lieshout EM et al., divided the time for sampling in their study into 2 groups, the first group in post-treatment patients between 6 weeks and 3 months (ankle joint) or between 3 and 6 months (hindfoot); and the second group in post-treatment patients between 7 and 9 months (ankle joint) or between 6 and 24 months (hindfoot).¹⁸ The patients' clinical changes were assessed to be visible over a period of 5-6 months post-injury.^{18,19} Based on the above research, it is possible to measure the AOFAS score at 6 weeks to 9 months after surgery.

CONCLUSION

The use of compression stockings resulted in lower levels of interleukin-6 (IL-6) than without wearing compression stockings in post-ankle fracture surgery patients. The use of compression stockings does not result in higher alkaline phosphatase (ALP) levels than without wearing compression stockings in post-ankle fracture surgery patients. The use of compression stockings resulted in a higher American Orthopedic Foot and Ankle Society (AOFAS) score than without wearing compression stockings in post-ankle fracture surgery patients.

CONFLICTS OF INTEREST

The author states that there are no conflicts of interest regarding the material discussed in the manuscript.

ETHICS CONSIDERATION

The research protocol for Ethical Clearance from the Research Ethics Commission of the Medical Faculty of Universitas Udayana, Sanglah Hospital Denpasar, Bali, Indonesia, will be submitted before the research is carried out. Subjects who met the research criteria were explained the research objectives and asked to fill out the informed consent. Researchers have also attached a secondary data collection permit in the form of medical records at Sanglah Hospital, Denpasar.

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AUTHOR CONTRIBUTION

Gede Agung Krisna Yudha is responsible for finding research samples, carrying out actions, analyzing data, and reporting research results. Putu Astawa and I Ketut Suyasa are in charge of the research concept design and are the supervisor in this research.

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