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Editorial

Orthopaedic Surgeon and Engineer Research Collaboration

Asep Santoso

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Orthopaedic surgeon treats various pathology of musculoskeletal tissue. Not only bone, muscle, tendon, cartilage, ligament, meniscus, etc. Furthermore, the orthopedic field has various subspecialties with their special conditions and diseases. Several reasons for always needing research collaboration with an engineer are identified. Orthopaedic cases could be different and unique in every cases. Sometimes it needs a special instrument, implant, surgical technique, and rehabilitation. All surgery needs to be highly accurate. Orthopaedic surgeons commonly face difficulties intraoperatively. The ideas that come to mind in developing a special device/ implant/software by a surgeon need to be discussed with an engineer to convert to real solutions.

Another problem is related to the implants. Most of the available implants recently, especially arthroplasty, most commonly comes from a western country. Those implants are developed based on the anthropometry/ anatomy of western populations. Mismatches in size and design are commonly encountered intraoperatively by the performing surgeon [1]. The mismatched condition will affect the long-term clinical outcome and implant durability [2]. Another issue is that the available implant sometimes could not allow special conditions, such as some extreme movement needed by some particular populations [3]. Orthopaedic surgeons need to put some advice or develop the desired implants/devices based on the local population's anatomy and needs [4,5]. The relations between orthopaedic surgeons and engineer are mutualism. Orthopaedic surgeons need help from the engineer in designing and developing implants/devices in terms of material and all technical aspects. In other conditions, the developed implant/device to be used in clinical practice need to be tested in several research steps from laboratory study, animal study and clinical study where the orthopaedic surgeon have more knowledge [6]. The final goals are the results of the research can be used by another orthopaedic surgeon to have ideal surgery with improved clinical outcomes and patient satisfaction.

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Case Report

The Struggle of Infection Eradication in A 24-Year-Old Male with Chronic Femoral Osteomyelitis Treated with Masquelet Technique

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ABSTRACT

Introduction: Post-traumatic chronic osteomyelitis is a multi-factorial disease needing holistic and long-term care with the aim to fully eradicate infection and filling bone defects. Though meticulous debridement is urgently needed as a part of treatment, it often leaves a significant bone defect postoperatively. Until now, there has not been a lot of literatures describing the efficacy of Masquelet Technique in femoral osteomyelitis.

Case Presentation: Our case revealed a 24-year-old patient with this condition after numerous surgical and antibiotic treatments. Masquelet technique was finally used in order to fill the resultant femoral bone gap, after a subsequent two-staged procedure, the result seems promising in terms of infection eradication.

Discussion: Surgical intervention along with proper antibiotic therapy are the key to successful treatment. However, internal host factors also play important roles, such as the extent of soft tissue damage, sufficiency of blood supply, the condition of bacterial flora, fracture site instability, and host immunity. Masquelet procedure has the advantages of less X-Ray examination, faster union rate, and the healing time that is independent from the defect length. However, Masquelet technique is not suitable for limb length discrepancy and malalignment correction.

Conclusion: This case report presents the challenge of treating post-traumatic chronic femoral osteomyelitis through a series of surgical and antibiotic therapy. Masquelet technique, eventually, seems to be a promising surgical procedure of choice in eradicating the infection.

Keywords: chronic osteomyelitis, bone gap, masquelet
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INTRODUCTION

Osteomyelitis is a complex and challenging pathology in the field of orthopaedic surgery, especially in post-traumatic osteomyelitis of the long bone, where it is found in 10% of all open fractures and 1 % of all closed fractures. Direct inoculation, surgical contamination, vascular damage, and immunodeficiency have been some risk factors described in literatures. A series of surgeries and prolonged antibiotics therapy is usually needed, and the patients should still be counselled on the risks for complications, including non-union, hardware failure and recurrence.[1]

The reconstruction of diaphyseal bone defects is still a challenge to surgeons these days in order to restore limb length and function. Even though bone graft is effective in filling bone gap, it might not be sufficient for a defect more than 5 cm long.[2] In cases where large bone defect is found, Masquelet procedure has been used widely as the treatment of choice. It is a two-step procedure including an initial debridement of soft tissues and necrotic bone and the use of a polymethyl methacrylate (PMMA) cement spacer placed in the bony defect. The bone spacer works by preventing fibrous tissue invasion to the defect area, and stimulating the development of pseudo-synovial membrane as body's reaction to foreign bodies. This development of pseudo-synovial membrane is maintained for 6-8 weeks, after which the membrane is incised and the bone spacer is removed. Bone graft is then inserted into the membrane in which the membrane provides a vascular source for the bone graft. The membrane is also known to secrete growth factors such as BMP-2, VEGF and TGF-beta1. This mechanism allows osteoconduction, osteoinduction, as well as osteogenesis, which makes it a perfect procedure for large bone defects.[3]

Most of the cases treated with Masquelet Technique were tibial osteomyelitis.[4] Until now, there has been a scarcity of literatures describing the efficacy of Masquelet Technique, particularly in femoral osteomyelitis. Through this study, we aim to describe a case of a 24-year-old male with persistent post-traumatic chronic femoral osteomyelitis undergoing numerous surgical treatment and antibiotic therapy, in which infection eradication has been a real challenge for the treating surgeons. Masquelet procedure was finally chosen, where this two-staged surgery seems to result in promising outcome to overcome the infection.

CASE REPORT

This case presents a 24-year-old immunocompetent male patient with chronic osteomyelitis of the right femur. Five months prior to admission, he had a traffic accident where he was hit by a car from his right side. He was diagnosed with Open Fracture Right Femur Middle Third. He immediately underwent debridement and Open Reduction Internal Fixation using a Non-locking 10-hole Broad Plate and 8 screws. However, after two weeks, discharge was found over the postoperative wound. The discharge was seropurulent, despite routine proper wound care.

Figure 1. Initial X-Ray at presentation to our hospital, showing implant failure.

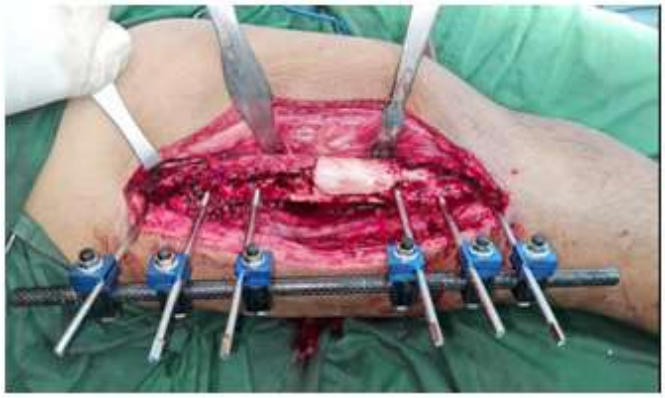

Figure 2. Intraoperative picture during debridement and application of external fixation.

Three months later, while he was walking at home with the help of 2 crutches, he accidentally slipped and fell down with his right thigh bumped to the floor. Plain X-Ray showed implant failure with irregular bone surface, supporting osteomyelitis as one of the likely causes of implant failure. Culture specimen was obtained in outpatient setting and *Serratia marcescens* was found

to be the colonialization bacteria. Antibiotic usage was not recommended, and routine wound care was advised. He then underwent debridement and the metalware was removed. Infected tissue and sequester were found intraoperatively. After thorough debridement, external fixation was applied using 6 Schanz screws. Bone defect was filled with antibiotic beads made of 2-gram Vancomycin and bone cement.

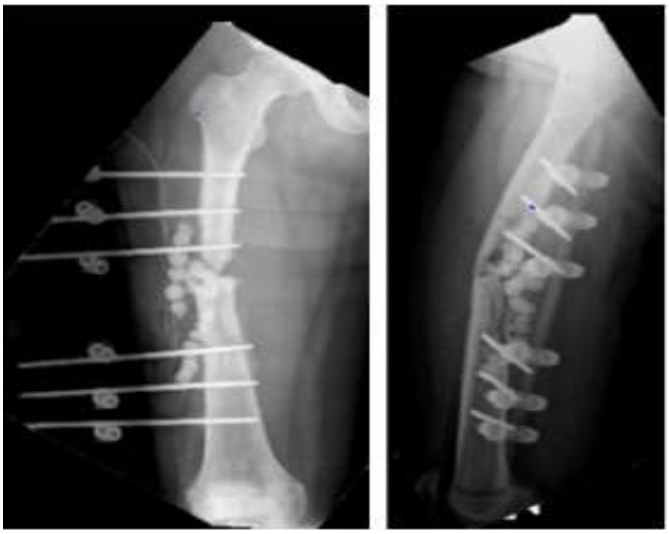

Figure 3. Post-operative X-Ray after debridement, application of antibiotic beads, and external fixation.

The external fixation and antibiotic beads were removed 11 days later. Sequestrectomy was performed to remove 9-cm dead bone and the patient was then immobilized with skeletal traction. Ten-kilogram load was used for immobilization, resulting in no leg length discrepancy. Culture specimen was obtained intraoperatively, showing Multidrug Resistant *Serratia marcescens* as the causative organism, and Ciprofloxacin was suggested as antibiotic treatment. After routine wound care and two weeks of therapy with Ciprofloxacin showing positive response with no fever, discharge, or other signs of infection, the next procedure was urgently needed in order to fill the bone defect and eradicate the chronic infection.

Figure 4. Intraoperative pictures during sequesterectomy, leaving a 9-cm bone gap.

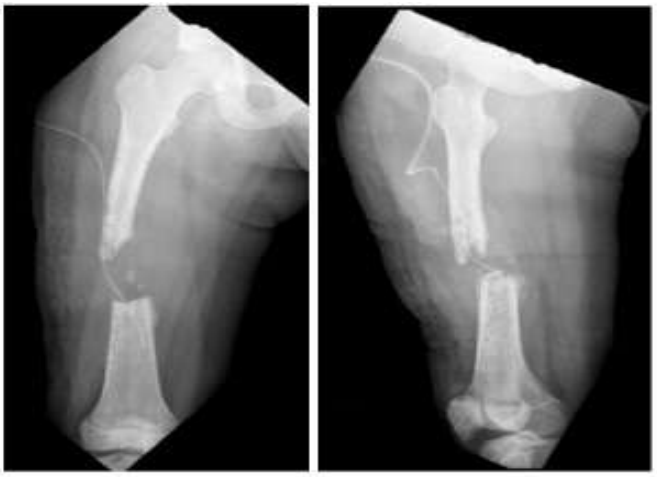

Figure 5. Post-operative X-Ray after sequesterectomy and the application of skeletal traction.

Figure 6. First stage of Masquelet procedure, before and after the application of bone cement with antibiotic (Vancomycin).

Masquelet procedure was chosen as the next treatment method 2 weeks later, where a 9 cm tube containing 20 mg Vancomycin per 40 g of bone cement was formed into a shape resembling the original bone in order to fill the bone gap and act as a bone spacer. A 13-hole Distal Femoral Locking Plate with 9 screws were utilized as fixation device. Culture specimen obtained during this last surgery showed Multidrug Resistant *Acinetobacter baumannii* as the causative organism, and this microorganism was found in significant amount, leading to the need to start another antibiotic therapy with Tigecycline.

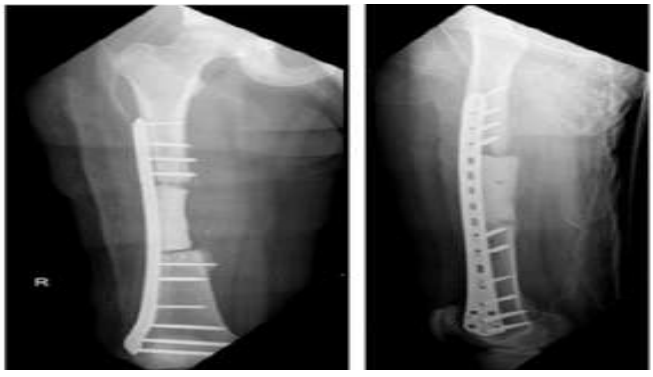

Figure 7. Plain radiograph after the first stage of Masquelet procedure.

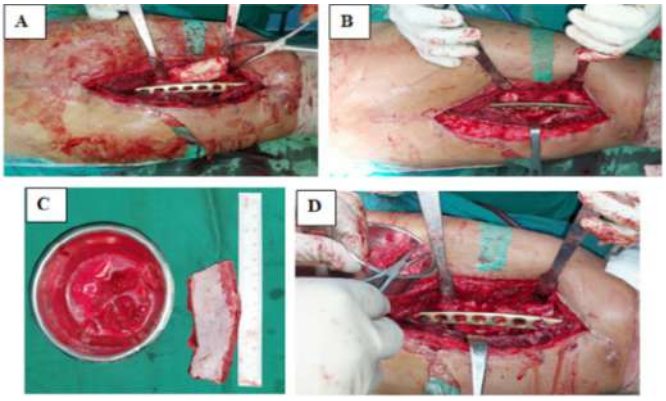

Figure 8. (A) Removal of bone spacer, resulting in (B) 9-cm gap. (C) Bio membrane formed after the first stage procedure. (D) Bone gap filling with "graft cocktails" from iliac bone graft, synthetic bone graft, and Vancomycin.

Figure 9. Plain radiograph after the second stage of Masquelet procedure.

Two months after the first stage surgery, the second stage surgery was performed, comprising of debridement, bone spacer removal, and bone grafting. Intraoperatively, bio membrane was found encapsulating the bone spacer. The membrane was then incised, and the bone spacer was extracted. The resulting nine-centimeter defect was then filled with iliac bone graft, combined with synthetic bone graft and 1 gram of Vancomycin. Bio membrane was then re-sutured and the implant was retained in place. Routine wound care and 1-week antibiotic therapy showed promising outcome, with no sign of infection neither wound discharge.

DISCUSSION

Post-traumatic osteomyelitis has always been a challenge for surgeons, as it requires a long-term treatment. Combination of surgical intervention and proper antibiotic therapy are the key to successful treatment. However, it is not always the case. Some factors contribute to the success of the treatment, such as the extent of soft tissue damage, sufficiency of blood supply, the condition of bacterial flora, fracture site instability, and host immunity.[5]

The eradication of infection on chronic osteomyelitis has also been a real challenge in the treatment. The bacteria within the biofilm enters osteoblasts and fibroblasts, prevents killing by antibiotics and immune system. Though considered as an additional measure, the use of local antibiotics as a mixture with PMMA is still controversial. PMMA cement spacer alone without antibiotics is adequate for membrane creation, and some literatures also stated that the presence of antibiotics in PMMA may alter osteogenic gene expression in the membrane. On the contrary, other studies proved that local antibiotic is effective in infection control, and a study by Shah *et al*. (2017) stated that the addition of antibiotics in the spacer reduced bacteria inoculation and promoted osteogenic gene expression.[6,7] In our case report, we used Vancomycin as an antibiotic mixture to bone cement.

Another highlight of our case report is the discovery of two different microorganisms isolated from two different surgical procedures: *Acinetobacter baumannii* and *Serratia marcescens. Serratia marcescens* is rarely found in immunocompetent patients. However, it may emerge as a result from spreading urinary tract infection or infected central catheters.[8] On the other hand, *Acinetobacter baumannii* is an important human pathogen with increasing number of multidrug-resistant (MDR) strains. McConnell *et al*. (2013) stated that most infections caused by *A. baumannii* are hospital-acquired due to long-term hospital stay.[9] These possibility should be evaluated further, and the possibility or nosocomial infection should always be considered in patients needing long-term hospital treatment like in our case.

As one of the popular surgical methods for bone defect, since its first invention in 1986, Masquelet procedure has been developed in many aspects and with different methodologies. A systematic review by Morelli *et al*. (2016) stated that the union rate using this technique reached 89.7%, and the infection eradication reached 91.1%. Another advantage of this procedure compared to other reconstruction technique is that the healing time is independent from the defect length. A study by Tong *et al*. (2017) showed that Masquelet procedure yielded

better functional outcome in femoral osteomyelitis compared to distraction osteogenesis, as well as less X-Ray examination and faster union rate. However, Masquelet technique is not suitable for limb length discrepancy and malalignment correction. Moreover, distraction osteogenesis allows immediate postoperative weight bearing, unlike Masquelet procedure.[3,4]

Masquelet procedure consists of 2 separate procedures with 4-8 weeks interval in between. The first stage includes meticulous debridement of bone and soft tissue, PMMA cement spacer implantation to cover the void, and bridging fixation of the defect using internal or external fixation device as well as soft-tissue defect reconstruction. The second stage includes removing bone spacer, debridement of the cavity, pseudomembrane preservation, and insertion of bone graft. Autologous bone graft is the gold standard to fill the cavity, but allograft or bone substitutes may also be added as graft expanders.[6]

Biofilm is another challenge related to implant selection, where steel surface should be covered with antibiotic cement whenever used. Locking plates have also been used as a method of temporary fixation in the first stage of treatment. However, in the second stage of treatment, intramedullary nailing is preferred to allow early mobilization and provide strong fixation.[10]

A case series by Wong *et al*. (2014) described the success of Masquelet procedure in 9 consecutive patients with post-traumatic bone defects, where it was described that this method was effective in maintaining well-defined void, preventing fibrous ingrowth, providing structural support, and facilitating biomembrane formation. Biomembrane, further, provides vascularity and corticalization needed for the placement of the bone graft. The series proved the efficacy of Masquelet procedure in various bones, including tibia, femur, humerus, olecranon, and calcaneus, with bone defect of 2-8 cm. No complication was observed postoperatively and radiographic consolidation was demonstrated in all patients.[11]

This case report confirms the efficacy of Masquelet technique for treating femoral osteomyelitis, however, it has several limitations. It is of Level IV evidence considering it only presents one patient. In addition, longer follow-up period is needed to ensure its efficacy and long-term outcome. However, this case report shows the struggle of eradicating chronic femoral osteomyelitis through surgical and antibiotic treatments. Eventually, by using Masquelet procedure, the short-term outcome is promising with no signs of infection one month after the second stage procedure. In the future, it is hoped that this study can be a basis for further study with bigger number of samples, and possible histopathological evaluation of the biofilm formed during the first stage of Masquelet procedure, as it may serve as an objective reasoning for the success of this technique in addition to long-term clinical evaluation.

CONCLUSION

This case report presents the challenge of treating post-traumatic chronic femoral osteomyelitis through a series of surgical and antibiotic therapy. Masquelet technique, eventually, seems to be a promising surgical procedure of choice in order to completely eradicate the infection.

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Original Research Article

Effect of COVID-19 Infection to Incidence of Thromboembolic Phenomenon in Hip and Knee Fracture or Arthroplasty Surgery Patients: A Systematic Review

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ABSTRACT

Introduction: COVID-19 is now recognized as an inflammatory disease with an increase in pro-coagulation factors. Orthopaedic procedures are also associated with high incidence of thromboembolism. This systematic review aims to give some perspective and consideration for orthopaedic surgeon when facing orthopaedic surgery patient with COVID-19.

Methods: A systematic literature search was done in PubMed, Cochrane central database, MedRvix, and PubMed Central up until 10th November 2020 using the following keywords: (COVID-19 OR SARS-CoV-2) AND (hip fracture OR femoral fracture OR TKA OR THA).

Results: Combination of soft tissue trauma, limited mobility, and pro-coagulation state of COVID-19 can overwhelm patient's biologic reserve and causing endothelial dysfunction, which creates fibrin deposition and thrombus. These findings reflected in D-dimer and C-reactive protein increase in COVID-19 patients. This group of patients usually experienced delay from injury to hospital admission and delay from admission to surgery time. Any delay can increase thromboembolic incidence due to limited mobilization. To reduce thromboembolism in this group of patients, some hospitals have implemented modification of the clinical pathway for trauma patients, perioperative thrombosis prophylaxis, and avoid surgical treatment with high risk of thromboembolism.

Conclusion: From limited data, it appears that COVID-19 infection may increase thromboembolic incidence in orthopaedic surgery patients. In facing orthopaedic surgery patients with COVID-19 infection, the risk/benefit and the chance of thromboembolic phenomenon should be evaluated carefully for perioperative treatment.

Keywords: COVID-19, SARS-CoV-2, Thromboembolism, Orthopaedic surgery, Complication
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INTRODUCTION

COVID-19 is an infectious disease by SARS-CoV-2 virus. COVID-19 has a wide range of clinical manifestations from mostly asymptomatic or mild to rapidly progressive and life-threatening conditions.[1] In severe cases of COVID-19, Cytokine release syndrome developed, which predisposed patients to thromboembolic disease.[2] Cytokine release will affect endothelial tissue and active platelet aggregation, creating a pro-coagulation state.[3] Pro-coagulation state of COVID-19 infection also mirrored in elevated D-dimer level of patients with SARS-CoV-2 Virus infection.[4]

A similar condition of pro-coagulation also occurs in traumatic patients and surgery patients, especially orthopaedic patients. Several factors contribute to this increase in pro-coagulation. Use of tourniquet, immobilization, and bed rest will cause venous blood stasis, and according to Virchow's triad will increase thrombi formation.[5] Surgical manipulation of the extremity will damage the vascular endothelial lining, trauma will increase thromboplastin agents.[6] Moreover, use of bone cement of polymethylmethacrylate (PMNA) also induces hypercoagulability.[6] From the available data, orthopedic cases such as trauma, fracture, and arthroplasty are found to be associated with higher thromboembolism events compared to medical cases.[6] Incidence of deep vein thrombosis (DVT) ranges from 40-60% in major orthopaedic surgery.[7]

Thromboembolism phenomenon complication can increase morbidity and mortality in orthopaedic surgery patients.[8] Patient with thromboembolism shows a high level of mortality with 6% of DVT patients and 12% of pulmonary embolism patients died in one month after diagnosis.[9] From an economic burden standpoint, the cost of venous thromboembolism (VTE) is substantial. Additionally, a complication from VTE such as post-thrombotic syndrome and heparin-induced thrombocytopenia also increase the cost.[10]

There were cases of COVID-19 patients who need orthopedic surgery.[11,12] The researchers hypothesize that a combination of COVID-19 infection and orthopedic surgery will increase the incidence of the thromboembolism phenomenon. There are still limited studies that try to look for the effects of both COVID-19 and orthopaedic surgery associated with thromboembolism events. Because of this reason, this systematic review aims to explore the effect of both COVID-19 infection and hip and knee fracture or arthroplasty in the incidence of thromboembolism events, the underlying reasons, and the method of thromboembolism events prevention in this group of patients. PRISMA 2020 guidelines were used to structure this systematic review.[13]

METHODS

In this systematic review, PRISMA guidelines were used to structure the research.[13]

2.1 Eligibility Criteria

In this research, we aim to find out if COVID-19 infection will affect thromboembolism phenomenon in hip or knee fracture or arthroplasty surgery compared to hip or knee fracture or arthroplasty surgery in patients without COVID-19. We included a research article that stated the diagnosis status of COVID-19 and the type of thromboembolism phenomenon in the lower extremity orthopaedic surgery procedure. We did not include abstracts only publications, review articles, commentaries, grey articles, and letters. Positive COVID 19 was defined as a positive oropharyngeal or nasopharyngeal swab test with real-time reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 before, during, or after hospitalization. The type of thromboembolism phenomenon that we were looking for was venous thromboembolism (VTE) and pulmonary thromboembolism (PTE) that happened perioperatively. Researcher excluded articles which do not use RT-PCR for COVID-19 diagnosis.

2.2 Search Strategy and Study Selection

We performed a systematic literature search in PubMed, Cochrane central database, MedRvix, and PubMed Central (PMC) up until 10th November 2020 using the following keyword: (COVID-19 OR SARS-CoV-2) AND (hip fracture OR femoral fracture OR TKA OR THA). We searched for research papers only in English language as the authors capability. Orthopaedic cases mentioned in the keyword represent the majority of thromboembolism event causes.[9] We excluded thromboembolism events associated with bone cancer to focus our result on trauma cases, as cancer has a different pathophysiology pathway to induce thrombosis compared to trauma.[14] After the removal of the duplicate article, two authors independently screened the titles and abstracts of the remaining articles based on the inclusion and exclusion criteria. Selected

articles will be checked for an additional research article, which is included in the relevant article, that might be missed from the literature search. There was no article focusing on single-blinded or double blinded process because some of this journal related to case report and systematic review.

2.3 Data Collection Process

After removal of duplicate article and checking for relevance to inclusion and exclusion criteria, 2 authors checked for any bias of the article and then decided whether the article would be included in the research. Disagreement between the authors was solved by consensus or by a third person. From all the included articles we listed the title, authors, year of publication, study design, number of subjects, age, sex, hypertension, diabetes mellitus, cardiovascular diseases, location of the fracture, percentage of thromboembolic events, COVID-19 status, and mortality. Unavailable data from selected articles would be marked with an X in Table 3. Articles that passed the inclusion and exclusion criteria but had some missing data were still included in the study to have a thorough discussion about the aim of the study.

RESULTS

The search result, which simplified into *Figure.1*, yielded a total of 677 articles, of which 537 articles came from PMC, 73 from PubMed, 33 from MedRvix, and 34 from the Cochrane central database. After screening duplicates and excluding irrelevant articles based on the title, 42 articles were examined for full-text availability and data associated with the aim of the study. After a full-text assessment, 13 articles were included for analysis.

3.1 Characteristics of Studies

The 13 articles included in the study consisting of 3 case series, 1 case report, 4 systematic reviews, 4 cohort studies, and 1 observational study. From the search for additional articles related to the aim of the study, we did not find any additional research articles. Each primary study was then grouped into positive and negative COVID-19. The suspect group was a group of patients with the clinical characteristic of COVID-19 but no data of RT-PCR.[14] Data of patients' characteristics were noted and elaborated in table 1. Data of patient's comorbidity, location of surgery, thromboembolism incidence, and mortality were included in table 3.

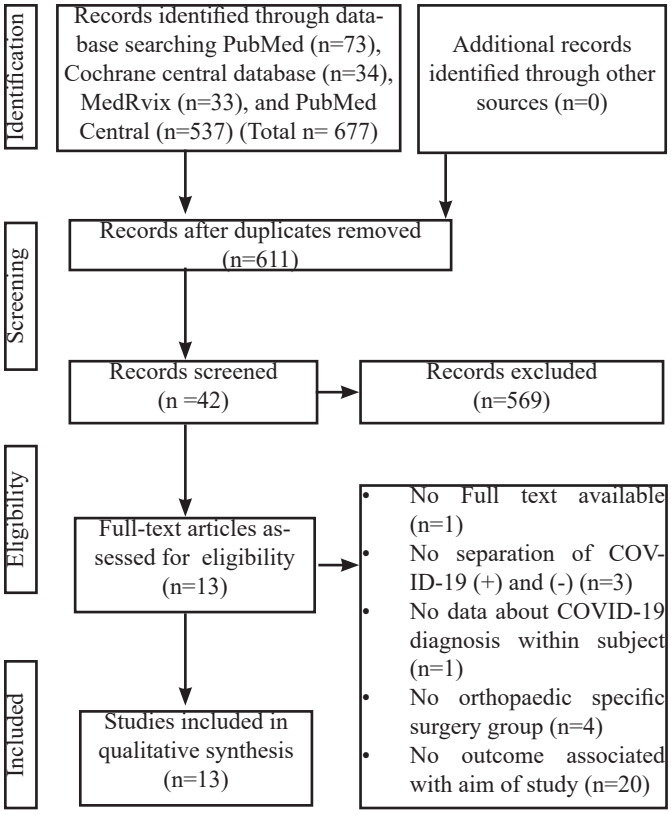

Figure 1. PRISMA diagram.

3.2 Risk of Bias Analysis

Analysis of individual research article was done according to the study design. The National Institute of Health (NIH) quality assessment tool was used for risk of bias analysis of case reports and case series studies.[15] The results of the case series risk of bias analysis are shown in Table 2. The Risk of Bias in Non-randomized Studies (ROBINS-I) was used for Cohort study.[16] The results of cohort study bias analysis are shown in Fig. 2.

3.3 Thromboembolism Incidence in COVID-19 and Orthopaedic Surgery Patients

There are limited cohort studies that mentioned the thromboembolism incidence in COVID-19 and Orthopaedic surgery patients. A retrospective multicenter cohort study documented 82 cases of hip and femur Fracture with COVID-19, which found 11 (13.4%) cases of thromboembolism postoperatively.[11] In this study, the use of thromboembolic prophylaxis and patients' comorbidity was not mentioned. Another prospective cohort study by Egol *et al*. found 2 VTE incidence out of 17 patients (11.8%) in hip and femur fracture and COVID-19 posi-

Table 1. List of Studies Included in the Review

Title	Authors	Publication Year	Study Design	Subject Number	COVID-19 Infection	Age	Sex	
							male (%)	female (%)
Early outcomes after hip fracture surgery in COVID-19 patients in New York City	Cheung et al.	2020	retrospective cohort study	10	+	67-90	2 (20)	8 (80)
Increased Mortality and Major Complications in Hip Fracture Care During the COVID-19 Pandemic: A New York City Perspective	Egol et al.	2020	prospective cohort study	17	+	82.4 +- 9.6	12 (70.6)	5 (29.4)
				12	Suspect	80.6 +- 9.9	2 (28.6)	10 (71.4)
				107	-	83.4 +- 10.4	34 (31.8)	73 (68.2)
Characteristics and early prognosis of covid-19 infection in fracture patients	Mi et al.	2020	case series	10	+	34-87	2 (20)	8 (80)
COVID-19: not a contraindication for surgery in patients with proximal femur fragility fractures.	Morelli et al.	2020	case series	10	+	72-98	2 (20)	8 (80)
Delayed surgery versus nonoperative treatment for hip fractures in post-COVID-19 arena: a retrospective study of 145 patients.	Mi et al.	2020	retrospective observational study	108	-	65-79	38 (35.1)	70 (64.8)
Fractures in Patients With COVID-19 Infection: Early Prognosis and Management. A Case Series of 20 Patients in a Single Institution in Lombardy, Northern Italy.	Jannelli et al.	2020	case series	20	+	82.06 (59-95)	4 (20)	16 (80)
Hip Fracture Outcomes During the COVID-19 Pandemic: Early Results From New York.	LeBrun et al.	2020	Multicenter retrospective cohort study	50	-	84.7	12 (24)	38 (76)
				9	+	86.5	3 (33.3)	6 (66.6)
The effects of COVID-19 on perioperative morbidity and mortality in patients with hip fractures.	Kayani et al.	2020	retrospective multicenter cohort study	82	+	71.9	31 (33.7)	51 (62.1)
Timing and Tips for Total Hip Arthroplasty in a Critically Ill Patient With Coronavirus Disease 2019 and a Femoral Neck Fracture.	Kaidi et al.	2020	case report	1	+	67	1 (100)	0 (0)
Coronavirus disease 2019 (COVID-19) markedly increased mortality in patients with hip fracture - A systematic review and meta-analysis.	Lim et al.	2020	systematic review					
COVID-19. An update for orthopedic surgeons	Abdelnasser et al.	2020	systematic review					
Fracture management during COVID-19 pandemic: A systematic review.	Kumar et al.	2020	systematic review					
Inflammatory and Coagulative Considerations for the Management of Orthopaedic Trauma Patients With COVID-19: A Review of the Current Evidence and Our Surgical Experience.	Puzzitiello et al.	2020	systematic review					

(+): Positive RT-PCR of SARS-CoV-2, (-): Negative RT-PCR of SARS-CoV-2, (-): Data not available

Table 2. Case Report & Case Series Risk of Bias Analysis

Major Components	Mi et al. 2020	Morelli et al. 2020	Jannelli et al. 2020	Kaidi et al. 2020
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	Cannot Determine	No	Yes	Not Applicable
4. Were the subjects comparable?	Yes	No	No	Not Applicable
5. Was the intervention clearly described?	Yes	Yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
7. Was the length of follow-up adequate?	Yes	Yes	Yes	Yes
8. Were the statistical methods well-described?	Yes	No	Yes	Not Applicable
9. Were the results well-described?	Yes	No	Yes	No
Quality Rating	**Good**	**Fair**	**Good**	**Fair**

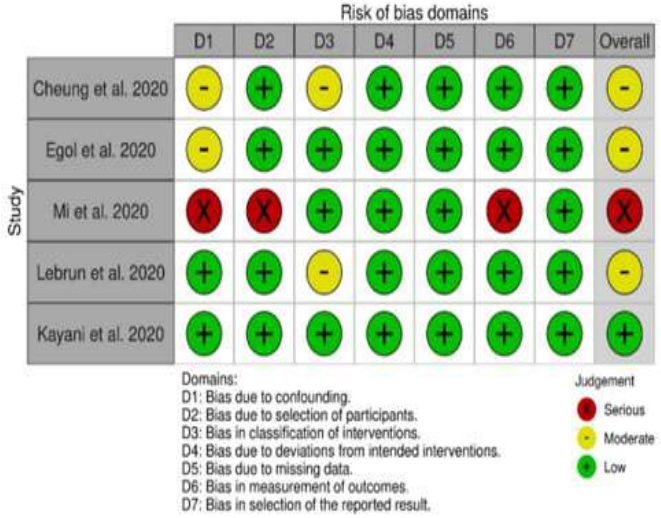

Figure 2. ROBINS-I Analysis for Cohort Studies

tive group. In the same study, VTE incidence was found in 3/107 (2.8%) of the COVID-19 negative group.[12] In this study, all patients with hip fractures received prophylactic level of low-molecular-weight heparin during admission until 1-month post-injury.[12] If compared to pre-pandemic era, the incidence of thromboembolic events were 2.8% in Total Knee Arthroplasty (TKA) from 2.1% pre-pandemic event, 1.9% in Total Hip Arthroplasty (THA) from 0.3% pre-pandemic event, 1.1%[17,18] in hip fracture surgery from 0.45% pre-pandemic event and 0.64% in simple fracture of lower extremities from 0.1% pre-pandemic event.[19] In this study, patients were given anticoagulant or antiplatelet agents and/or mechanical prophylaxis.[17] In another study, VTE incidence was 1.17% in the minor trauma group (ISS≤15) and 6.8% in the major trauma group (ISS>15).[20]

From the literature, most of the studies excluded patients less than 18 years of age at the time of injury, open fracture, periprosthetic fracture, and revision fracture surgery.[11] We only found one article that compares thromboembolism incidence in fracture patients with COVID-19 positive or negative. Comparing the results of the different articles cannot be performed because different articles have different inclusion and exclusion criteria and different data collection methods.

DISCUSSION

4.1 Pro-thromboembolism Factor in COVID-19 and Surgery Patients

4.1.1 Pathology of COVID-19 and Surgery Patients

In the two-hit concept introduced by Moore and Moore to explain the pathway for post-traumatic complication development, "first hit" is the physiological response to injury, and the second hit is the subsequent intervention or any ongoing physiologic disturbance.[21] From this principle, a damage control orthopedic in polytrauma patient is used to minimize the second hit and decrease any complication incidence.[22] COVID-19 infection can be a part of the "first hit" or elevate the "first hit" effect from trauma inpatient with orthopaedic surgery.[4] This effect be more prominent in patients with severe inflammatory responses associated with COVID-19.[4] COVID-19 infection in itself increases thromboembolic disease through direct and indirect effects.[3] Reports find elevation of Interleukin 2 (IL-2), IL-6, and tumor necrosis factor (TNF)-α in COVID-19 patients, which indicates an increased inflammatory response.[23] Diffuse alveolar damage and endothelial dysfunction can then occur.[24] Endothelial cells dysregulation and platelets & leukocytes activation result in excessive thrombin generation and inhibition of fibrinolysis. Causing fibrin deposition

and predisposing the patient to microangiopathy and microthrombi.[24,25]

The most common observed hemostatic abnormality inpatient with COVID-19 infection is elevated D-dimer level (>1µg/mL).[4,26] C-reactive protein (CRP) was found elevated in 90% of patients but prothrombin times are normal in 70% of patients.[4] In a case series of 10 patients with COVID-19 and hip fracture, it was found uniformly elevated D-dimer, ferritin, and Lactate dehydrogenase (LDH) but normal PT/INR and PTT.[4] One patient with DVT had markedly elevated CRP (194.1 mg/L) and elevated D-dimer, ferritin, and LDH (5.85 ug/mL, 223mg/mL, and 284 U/L, respectively).[4] Another case series by Mi *et al*. demonstrated 10 cases of COVID-19 positive patients with fracture had similar results, with 9 patients had high serum levels of D-dimer and CRP. High D-dimer is postulated to be caused by limited activity which all patients in the case series are in.[4] Another laboratory result that characterized fracture patients with COVID-19 positive are higher neutrophil count.[4]

Even with an asymptomatic patient, COVID-19 infection may amplify the initial inflammatory response to trauma.[27] A descriptive study by Cheung *et al*. reported 10 COVID-19 patients who underwent hip fracture surgery. The all ten patients were asymptomatic on admission and also presented similar laboratory results of elevated D-dimer, ferritin, and LDH on admission.[28] One patient had VTE in addition to respiratory failure and died postoperative at day 19.[28] High level of suspicion of COVID-19 status should be implemented as 4-18% of patients with positive swab assay for SARS-CoV-2 can be asymptomatic.[11,29]Additionally, COVID-19 has an incubation period of ten to 14 days, which in this period, patients are asymptomatic but highly contagious.[29]

4.1.2 VTE in Orthopaedic Trauma and Surgery

The Incidence of thrombosis caused by cast and immobilization is around 17%.[11] Injuries to the pelvis also increase the risk of thrombus. Pathophysiology of thrombus occurrence is caused by the Virchow factor consisting of venous stasis, endothelial injury, and hypercoagulability.[5] Immobilization of lower extremity, especially at the ankle, will decrease muscle pump function and increase venous stasis. Trauma and injury factors to the endothelial tissues are believed to support the occurrence of thrombus in the event of trauma and orthopedic surgical procedures. Recent studies support findings in the form of procoagulant particles and thrombogenic particles as well as a decrease in antithrombin III levels that support clotting.[30] Damaged tissue induces a local and systemic inflammatory response similar to COVID-19 infection, which elevates IL-6 and TNF-α.[27] This combination of soft tissue trauma and pro-coagulation state of COVID-19 that Puzzitiello *et al*. referred to as reaching a "tipping point", where patient's biologic reserve overwhelmed, causing alveolar damage, microvascular injury, interstitial edema, hemodynamic lability, and end-organ failure.[27,31] Damaged endothelium increases thrombus formation. This is supported by the incidence of pulmonary embolus in asymptomatic COVID-19 with relatively low intraoperative embolus burden.[27] Coagulation abnormalities also can be seen by increased D-dimer level, decrease prothrombin time, and international normalized ratio. [27]

4.1.3 Delayed Operation / Prolong Immobilization

One case series study of 43 orthopaedic surgery patients during the COVID pandemic explained a delay from admission to surgery time during the COVID-19 pandemic because of pre-operative screening of COVID-19, which is 2 days of COVID-19 RNA and antibody detection assays.[32] Average waiting time from admission to surgery was 5.3 ± 2.8 days, which is 2 days longer than the pre-COVID era.[32] Additional info from these patients, before arriving at the emergency room, they stayed at home for more than 10 days without anticoagulants. Although there is still not enough information to predict the incidence of thromboembolism in COVID-19 and surgery without prophylaxis, in patients who underwent hip surgery without prophylaxis before the COVID-19 pandemic, thromboembolism incidence was found at 40-60%.[7]

In the same study, they found delayed time from injury to hospital admission by 2.1 days. Delayed seek for hospital help maybe because most trauma patients are afraid to go outside because of local government advice to stay indoors during the pandemic.[32] Patients with trauma to lower extremity would likely be bed-bound or have limited mobility causing an increased chance of thromboembolism.[33]

Patients with severe infection with COVID-19 are also usually evaluated by orthopaedic surgeons to be unfit for surgery[4]. Although this decision would reduce the amount of soft tissue injury from the operation, it would increase immobilization time (> 7 days) and in turn,

could increase thromboembolic incidence.[34] A guide from WHO also recommends treating orthopedic trauma patients with COVID-19 who need surgery immediately because it reduces the risk of thromboembolism due to immobilization.[35]

Thromboembolism also can happen after the orthopaedic operation.[36] In One study, asymptomatic COVID-19 patients undergoing surgery were reported to have significant higher admission to the Intensive Care Unit (ICU) than non-surgical COVID-19 patients (44.1% vs 26.1%).[37] A collection of case studies stated that the presence of co-morbid COVID-19 is the biggest cause of thrombosis. This is due to the hypercoagulation process being exacerbated by the ICU care, which causes patients to be immobilized, subsequently increasing the risk or causing high incidence of venous thrombosis.[38]

As the review stated that the number one contributor of the thromboembolism event is the orthopaedic surgery itself, the COVID-19 disease is the co-factor that worsens the event by increasing the coagulability of the blood.

4.2 Methods to Decrease Thromboembolism Events

4.2.1 Modification of the Clinical Pathway

Since the COVID-19 outbreak, hospitals around the world designed a modification of the clinical pathway for trauma patients.[32] All patients with orthopaedic trauma should be tested for COVID-19.[19,27] Reason for this recommendation is that patients with COVID-19 infection can appear asymptomatic, as Zoe *et al*. found. Baseline inflammatory markers (IL-6, D-dimer, and CRP) can be used to predict disease progression.[27] Screening in patients with COVID-19 who have high risk of thromboembolism can be seen from D-Dimer, fibrinogen, and factor VIII levels.[35] In patients with positive COVID-19 and high-risk fracture, consider doing lower extremity duplex ultrasound to check for pre-existing thrombosis.[27] Vena cava filter is one method that is used as an alternative when anticoagulants are not available or contraindicated in the patients, but it is not recommended for first-line treatment.[39] Concern arising from emergent cases that need operation <24 hours. In these cases, COVID-19 screening with RT-PCR cannot be done. The solution is to treat all trauma and orthopaedic surgery emergent operations as positive COVID-19 until proved otherwise.[40]

4.2.2 Perioperative Thromboembolism Events Prophylaxis

As COVID-19 is associated with increased D-dimer level, experts from the American College of Cardiology support the use of empiric anticoagulation on therapeutic dose for inpatient with COVID-19 infection with highly elevated D-dimer level.[3] Based on the pre-COVID era, American College of Chest Physicians (ACCP) guidelines encourage using anticoagulation therapy for at least 10 to 14 days and up to 35 days in orthopaedic surgery patients to prevent thrombosis.[41] This recommendation was proven to be effective to reduce the incidence of the thromboembolic phenomenon in Egol *et al*. prospective cohort study that includes 138 patients with orthopaedic trauma. They found no difference in the rate of venous thromboembolism in COVID-19 positive with negative control (2 [11.8%] vs 3 [2.8%], p = 0.138). This is due to all patients with hip fracture getting chemical prophylaxis for at least 1 month after injury.[14] A case series reported that, in mild symptomatic COVID-19 cases, the use of the anti-thromboembolic drug in fracture patients may reduce thrombosis incidence although the patients had high D-dimer (>500μL/L) as out of 20 patients, they reported, there was no thromboembolism incidence.[42] This may be due to prophylaxis use on admission or immediate admission to operation time (1-4 days, only 1 case that delayed until 9 days).[42] Another article published administration of low molecular weight heparin (enoxaparin sodium 4000IU twice daily) before surgery.[43] Benefit of heparin use in trauma patients and COVID-19 also extent to reduce mortality of hospitalized patient with COVID 19 by 20%.[44] This is related to reduced microthrombi formation in pulmonary microcirculation and reducing the incidence of respiratory failure.[44] Use of prophylaxis is also recommended for surgery that is delayed up to 24 hours (MWH and UFH have similar efficacy and safety).[35] In patients who unfit for surgery (*eg*. major trauma), enoxaparin (LMWH) can be given until more appropriate time for surgery. The considerations for this procedure depend on age, comorbidities, immobilization and quality of injury of the patient.[35]

In post-operative time, the patient rehabilitation phase starts as soon as possible with a simple exercise.[45] This avoid complication and also preserve muscle strength and flexibility.[19] The patient also should try to maintain an active lifestyle and rapid mobilization.[46] Prophylaxis use is extended in one case report, which used enoxaparin 40mg per day for 28 days after the patient discharged.[36] Unfortunately, the patient developed non-occlusive thrombi in the right femoral and anterior tibial vein and occlusive thrombus in the right popliteal vein at

2 months postoperatively, which added to consideration of prolonged use of DVT prophylaxis from the standard 1 month in COVID-19 patients.[36]

4.2.3 Alteration of treatment method

Patients experiencing long bone fracture treated with intramedullary fixation are at risk for thromboembolism phenomenon.[47]Consider surgical treatment that avoids canal instrumentation and excessive rearming in intramedullary fixation.[27] Cementless technique in total hip arthroplasty (THA) is preferred over cemented THA in patients with decreased pulmonary function to avoid pulmonary emboli.[36] Cemented THA has been documented to have higher rates of cardiopulmonary complication with 5.7 times higher risk of pulmonary embolism.[48] Complication of emboli can be disastrous because patients with COVID-19 already have decreased cardiopulmonary reserve.[36]

Treatment of fracture non-operatively may lower the inflammation from surgical treatment and can be the choice of treatment in some patients.[49] But the non-operative treatment of the hip fracture is not recommended because of the long immobilization time for traction (8-12 weeks). In a retrospective observational study by Mi *et al*., it was reported that there was an increased incidence of deep venous thrombosis in the non-operative therapy group than the delayed surgery group (12/34 vs 13/99, p=0.004).[50] The highest incidence of thrombosis was in patients treated nonoperatively due to long immobilization. It is, therefore, recommended for operative management, or in delayed operative cases could be given antithrombotic first.[51] The Non-operative treatment of hip fracture is also associated with a higher risk of complications, such as pulmonary infection, pressure ulcers, UTI, which consequently leading to high mortality.[52]

4.2.4 Timing of Surgery

Timing of surgery in hip fracture and other lower extremity fractures has been extensively explored but an additional factor of COVID-19 status can alter the surgeon's decision of surgery timing. The optimal timing of surgery in a patient with COVID-19 still needs to be explored. With varying degrees of COVID-19 infection severity, it is difficult to determine the best time of surgery. The decision of surgery time should be individualized, and every patient should undergo medical optimization before surgery. Caution was reported for patients in the 7-10th day of COVID-19 infection when many patients acutely decompensated.[26] This was observed in non-survivor COVID-19 patients with an upward trend of laboratory results from day 4 to 19 of infection.[26] Similar suggestion was also made by a group of Singaporean orthopaedic surgeons to look at single result of inflammatory markers when planning surgery (TNF-α, IL-1, and IL-10).[53] As worsening systemic inflammation associated with surgery complication[54], upward trend of inflammatory markers can be considered to delay orthopaedic surgery.[55] In a hip fracture patient who is not critically ill, the fracture should be definitively fixed within 24 hours.[56,57]

Up to the moment, there are still no guidelines to choose one method of treatment over another in COVID-19 patients with orthopaedic surgery. Careful consideration for risk/benefit in COVID-19 patients with orthopaedic surgery should be evaluated and treatment should be customized on a patient-to-patient basis.

4.3 Limitation of the study

There is still limited long-term studies on complications in COVID-19 and hip and knee fracture or arthroplasty surgery patients. From studies included in this research, not all studies mentioned the severity of infection or inflammation markers of the subjects. This can bias the conclusion as the severity of infection or inflammation can affect the thromboembolism phenomenon.[28] Not all articles reported the type and the extent of the soft tissue injuries severity, which include in the factors that contribute to the thromboembolic phenomenon. There are also limited RCT studies on thromboembolism prophylaxis in COVID-19 and fracture patients.

4.4. Strength of Study

Our study involved the latest journal related to COVID-19, thromboembolism phenomenon and orthopaedic surgery with the population focus on geriatric population, as the common incidence of thromboembolism and the high prevalence of fracture are usually in the geriatric patients. Further research is needed, focusing on the systematic algorithm of patient selection, and better-quality evidence for perioperative treatment to reduce thromboembolism events and, subsequently, reduce the mortality and morbidity in hip and knee fracture or arthroplasty surgery with COVID-19 infection.

CONCLUSION

It appears that COVID-19 infection may increase thromboembolic incidence in hip and knee fracture or arthroplasty patients. The combination of pro-coagulation condition of COVID-19 and orthopaedic surgery, and delayed trauma to surgery time, may contribute to the increasing thromboembolic incidence. To reduce the thromboembolic incidence, the use of thrombosis prophylaxis perioperatively, avoidance of high-risk procedure and optimizing the patient's condition before surgery may be beneficial. In facing orthopaedic surgery patients with COVID-19 infection, the risk/benefit and the chance of thromboembolic phenomenon should be evaluated carefully for perioperative treatment. Further study needs to search for optimal timing of surgery and perioperative medical intervention in fracture patients with COVID-19 to reduce mortality.

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Original Research Article

Outcomes of Posterior Cruciate Ligament Retaining versus Posterior Cruciate Ligament Sacrificing in Total Knee Replacement in Young Population -Meta-Analysis of 10 Years of Studies

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ABSTRACT

Introduction: Total knee arthroplasty (TKA) is a common procedure performed especially in end-stage knee osteoarthritis (OA). Since the posterior cruciate ligament (PCL) may affect knee stability, it has been debated whether the PCL needs to be preserved or sacrificed. This study aims to systematically analyze the clinical and functional outcomes following TKA with PCL retaining (PCLR) and sacrificing (PCLS).

Methods: A systematic search was performed through online databases (PubMed, Google Scholar and Cochrane Library) based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline within the searching period from 2011 to 2021. Studies involving patients undergoing total knee replacement with PCL retaining or sacrificing method for knee OA with minimum follow-up of 12 months were included. Non-comparative studies, animal studies and non-English studies were excluded. Review Manager (RevMan) Version 5.3 was used to analyze mean difference (MD) and odds ratio (OR) with a 95% confidence interval (CI).

Results: There were 194 studies on the initial search, 72 duplicates were removed and the final remaining 7 studies were used for inclusion**.** Seven studies with a total of 3346 patients were included. There were 2220 patients (66.35%) underwent TKA with PCL retaining method. Analyses revealed no significant difference in range of motion (ROM), knee score, maximum flexion, the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and pain score between PCLR and PCLS with p-values of 0.10, 0.56, 0.42, 0.33 and 0.67, respectively. Only function score, hospital for special surgery (HSS) score and flexion contracture showed significant differences with p-values of 0.0002, 0.002 and 0.004, respectively. Further studies are needed.

Conclusion: Analysis between PCLR and PCLS showed no significant difference on the clinical or functional outcomes except in postoperative function score, flexion contracture and HSS score. PCLR had significantly higher function and HSS score with lower flexion contracture compared to PCLS.

Keywords: total knee arthroplasty, posterior cruciate ligament, PCL-retaining, PCL-sacrificing
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INTRODUCTION

Knee osteoarthritis (OA) has been the main indication for total knee arthroplasty (TKA).[1] Knee OA with radiographic classification of Kellgren-Lawrence grades III and IV are of the most common indication to perform TKA.[2] The requirement for TKA has been predicted to increase rapidly and significantly due to the increasing prevalence of knee OA globally, to be approximately 1.26 million procedures within the next ten years.[3] It is important to bear in mind that to correct knee deformity and to obtain a stable knee resulting in satisfactory functional improvement are the main goals of TKA. Two distinct methods are available to reach these purposes, including the use of cruciate retaining (CR) technique and posterior-stabilized technique, which is also known as cruciate sacrificing (CS) technique.[4] It is important to ensure stability following TKA procedure, since instability may lead to devastating consequences requiring revision surgery. Posterior stability is achieved by retaining the posterior cruciate ligament (PCLR). However, it can also be reached by PCL-sacrificing (PCLS) method.[5]

Studies have reported several advantages of each procedure. PCLR has been shown to provide inherent stability, less load between bone and cement, better proprioception and kinematics, higher degree of bone preservation and better stabilization of the implant. Meanwhile, easier ligament balancing, conforming articulation, better knee flexion, more predictable kinematics and reproducible rollback, lower range of axial rotation and condylar translation and less risk of PCL insufficiency are the superiorities of PCLS method. It is essential to thoroughly evaluate the condition of PCL intraoperatively to determine which technique to perform. PCLR is contraindicated in patients with PCL insufficiency and poor elasticity, bone defects, or the need for augments.[4] The PCL is usually released if there is anterior tibial translation of 90^0 in flexion with the presence of tight flexion gap.[5]

There have been numerous studies assessing the outcomes of PCL retaining (PCLR) and PCL sacrificing (PCLS) methods in which some have demonstrated that PCLR resulted in less consistent success, while in some meta-analyses better proprioception and kinematics were

Table 1. Population-Intervention-Comparison-Outcome, Table Describing Inclusion and Exclusion Criteria

Study Component	Inclusion	Exclusion
Population	• Patients with knee OA • At least 12 months follow-up	• Animal studies • Less than 12 months follow-up • Patients with causes other than primary OA
Intervention and Comparison	• TKA with PCLR or PCLS method	• Other methods of treatment • Studies with only one method of treatment (non-comparative studies)
Outcome	• ROM • Knee score • Function score • Flexion contracture • Maximum flexion • HSS score • WOMAC • Pain score	No outcome mentioned or different outcomes
Publication	Studies published in English in peer-reviewed journals	• Abstracts, editorials, letters • Duplicate publications of the same study that do not report on different outcomes • Meeting presentations or proceedings • Non-English studies
Study Design	All study design except case reports and review articles	Case reports and review articles

observed in PCLR method.[6] Due to scarcity of literature comparing the two methods, this study was aimed to provide an objective comparison between the two methods in the form of meta-analysis. This study focused mainly on postoperative outcome measures, including postoperative clinical and functional outcomes.

METHODS

This is a meta-analysis of relevant studies comparing between PCL retaining and PCL sacrificing in total knee replacement. A thorough and systematic search was conducted within the searching period from 2011 to 2021 to obtain and identify relevant studies through several online databases, including PubMed, Google Scholar and Cochrane Library, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Figure 1). The keywords utilized were "Total knee replacement" AND "PCL Retaining" AND "PCL Sacrificing" AND "Outcome".

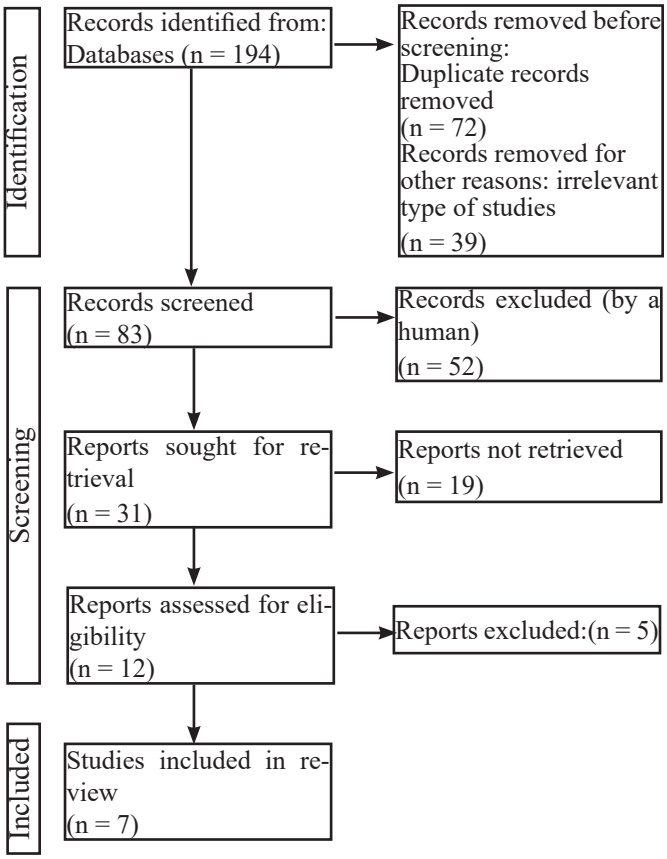

Figure 1. Flow chart for article selection process

The obtained articles following the search were then manually scanned and reviewed by the authors according to PICO method to determine the inclusion and exclusion criteria (Table 1). Studies involving patients undergoing total knee replacement with PCL retaining or sacrificing method for knee OA with minimum follow-up of 12 months were included. Non-comparative studies, animal studies and non-English studies were excluded.

Data extraction was performed for basic characteristics and outcomes. Review Manager (RevMan) [Computer program, Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014] was used to analyze mean difference (MD) and odds ratio (OR) with a 95% confidence interval (CI). Fixed effect model was used when the heterogeneity was <50%, whereas random effect model was used when the heterogeneity was >50%.

Abbreviations: PICO, Population-Intervention-Comparison-Outcome. OA, osteoarthritis. TKA, total knee arthroplasty. PCLR, posterior cruciate ligament retaining. PCLS, posterior cruciate ligament sacrificing. ROM, range of motion. HSS, hospital for special surgery. WOMAC, the Western Ontario and McMaster Universities Arthritis Index (WOMAC).

RESULTS

After an initial search of 194 studies, 72 duplicates were removed, and eventually there were remaining 7 studies used for inclusion. Seven studies with a total of 3346 patients were included. Out of the seven studies, only one study was a randomized controlled trial (RCT) (Level I evidence), whereas three were prospective cohort studies (Level II evidence) and the rest three other studies were retrospective cohort studies (Level III evidence) (Table 2.). Approximately 2220 patients (66.35%) underwent TKA with PCL retaining method. There was a female predominance (61.98%) in subjects involved.

An analysis on ROM was made from five studies with a total sample of 687 patients. Calculation showed a mean ROM of 118.21^0 for PCLS group and 120.31^0 for PCLR group. Figure 2 shows, however, no significant difference in terms of postoperative ROM between the two groups (Heterogeneity, $I^2 = 67\%$; WMD -2.56; 95%CI,-5.57 – 0.45; p=0.10).

As for analysis of knee score, four studies were included, comprised of a total sample of 2864 patients. In PCLS group, the mean knee score was 91.03 while in PCLR mean knee score was 91.98. Analysis showed no signif-

Table 2. Studies included in the analysis

No	Authors	Study design (Level of evidence)	No of Knees	Mean age (range) (years)		Publication Year	Journal
1	Ishii et al.	Cohort prospective (Level II)	108	71	74	2011	Knee Surg Sports Traumatol Arthrosc
2	Bae et al.	Cohort retrospective (Level III)	137	67.5 ± 4.6	65.8 ± 9.0	2011	The Journal of Arthroplasty
3	Roh et al.	Randomized controlled trial (Level I)	90	69.8 ± 4.7	71.0 ± 4.9	2012	Knee Surg Sports Traumatol Arthrosc
4	Ritter et al.	Cohort prospective (Level II)	105	66.8	67.2	2012	BONE & JOINT RESEARCH
5	Ünkar et al.	Cohort prospective (Level II)	112	69.7 ± 5.9	68.2 ± 6.8	2017	Acta Orthopaedica et Traumatologica Turcica
6	Kim et al.	Cohort retrospective (Level III)	253	69.6 ± 7.1	68.3 ± 7.2	2021	Scientific Reports
7	Saleh et al.	Cohort retrospective (Level III)		64.8 ± 13.185	67.63± 8.416	2021	Hip Knee Journal

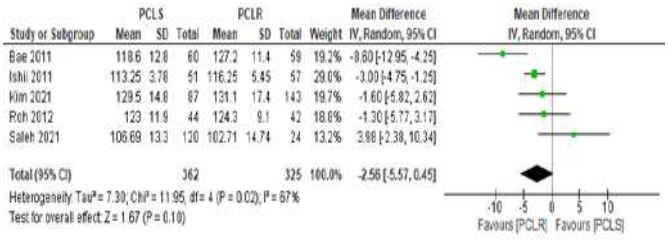

Figure 2. Forest plot for range of motion (ROM)

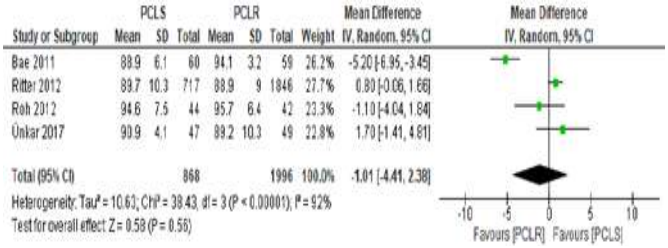

Figure 3. Forest plot for knee score

icant difference in knee score between the two groups (Figure 3) (I^2 = 92%; WMD -1.01; 95%CI, -4.41 – 2.38; p=0.56).

Five studies were included in the analysis of function score, involving a total number of 3094 patients. Mean function score in PCLS group was 82.74 whereas in PCLR group was 84.54. Analysis showed significantly higher function score in PCLR group compared to PCLS group (I^2 = 0%; WMD -2.58; 95%CI, -3.94 – -1.22; p=0.0002) (Figure 4).

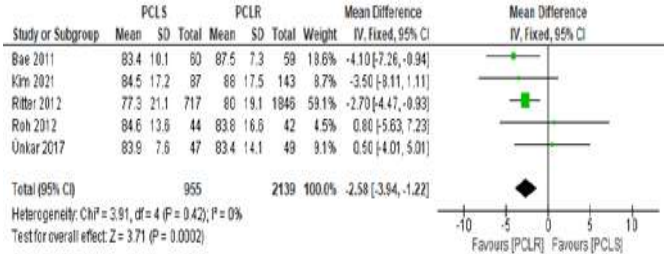

Figure 4. Forest plot for function score

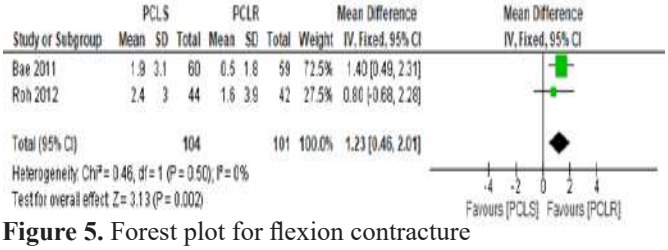

Figure 5. Forest plot for flexion contracture

Only two studies evaluated flexion contracture as outcome following TKA with PCLR or PCLS method. Calculation was performed from a total of 205 samples, revealing a mean flexion contracture of 2.15 in PCLS group and 1.05 in PCLR group. Analysis showed a significantly higher flexion contracture in PCLR group compared to PCLS group (I^2 = 0%; WMD 1.23; 95%CI, 0.46 – 2.01; p=0.002) (Figure 5).

Maximum flexion was evaluated in four studies. A to-

tal of 2853 patients were included. The mean maximum flexion in PCLS group was 120.1^0 and 118.04^0 in PCLR group. As depicted in Figure 6, analysis showed no statistically significant difference in terms of maximum flexion between PCLR and PCLS group (I^2 = 97%; WMD 2.15; 95%CI, -3.06 – 7.36; p=0.42).

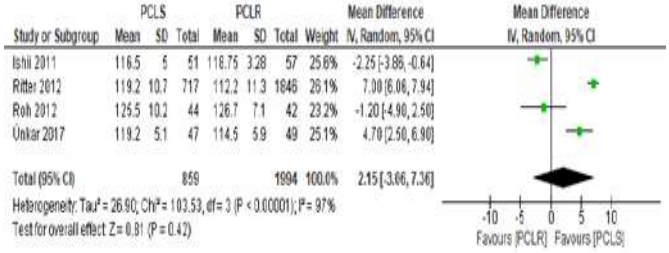

Figure 6. Forest plot for maximum flexion

We estimated HSS score from three studies, comprised of 424 patients. The mean HSS score in PCLS group was 90.07 and 90.9 in PCLR group. Analysis revealed a significantly higher HSS score in PCLR group compared to PCLS group (I^2 = 9%; WMD -1.52; 95%CI, -2.55 – -0.49; p=0.004) (Figure 7).

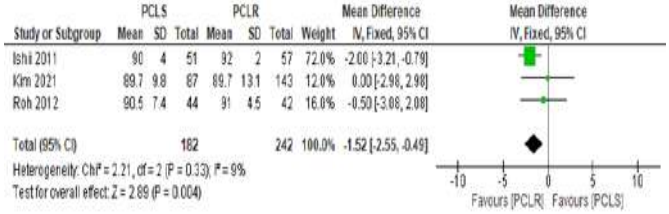

Figure 7. Forest plot for HSS score

WOMAC score was assessed in two studies involving 316 patients. A mean WOMAC score of 14.51 and 13.3 were observed in PCLS and PCLR group, respectively. Figure 8 shows no significantly different mean between the two groups (I^2 = 0%; WMD 1.24; 95%CI, -1.28 – 3.76; p=0.33).

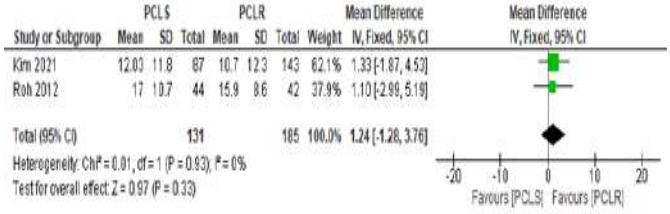

Figure 8. Forest plot for WOMAC score

Calculation and analysis of two studies with a total of 2793 patients assessing pain score revealed a mean pain score of 45.2 and 45.4 in PCLS and PCLR group, respectively. Analysis showed no significant difference in pain score between the two groups (I^2 = 0%; WMD 0.14; 95%CI, -0.52 – 0.80; p=0.67).

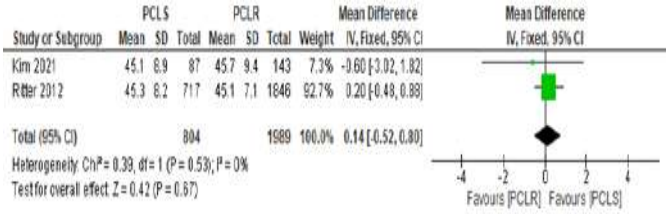

Figure 9. Forest plot for pain score

DISCUSSION

Total knee arthroplasty (TKA) has become the most common treatment for knee osteoarthritis (OA), especially the at the end-stage ones. The increasing prevalence of knee OA, especially due to aging population, has resulted in a significant increase in the rate of TKA.[1,3] TKA is performed by resecting the defected articular knee surface and placing a prosthetic implant. The posterior cruciate ligament (PCL) may be removed or retained, depending on the type of implant used.[7] The role of PCL is, however, still debatable since some argued that it increases proprioception, stability, mechanical properties of the quadriceps and femoral rollback. This results in reduced excessive wear of the polyethylene along with loosening due to decreased stress on the joint surfaces. The ligament can also be completely removed, this has been believed to simplify the correction of fixed deformities.[8]

Postoperative functional outcome in TKA includes postoperative range of motion (ROM). Knee ROM is important for a patient to be able to perform daily activities. In this study, we analyzed postoperative ROM from five studies and found no significant difference between PCLR and PCLS. Bae *et al*., observed a statistically significant difference in postoperative ROM between PCLR and PCLS. However, the increased amount of ROM was not significant between the two groups.[9] On the contrary, Ishii *et al*., also concluded that postoperative ROM had no significant difference at any time point during the follow-up period.[10] Similarly, in a study by Kim *et al*., postoperative ROM at final follow-up at 1 year following the surgery did not show any significant difference between PCLR and PCLS.[11] There was also no significant difference in the postoperative ROM between PCLR and PCLS according to Roh *et al*.[12]

Knee score was found to be not significant among the PCLR and PCLS group and this was in accordance with the results from previous studies.[6,12,13] Bae *et al*., however, observed a significantly higher postoperative knee score in PCLR group compared to PCLS group (94.1 ±

3.2 vs 88.9 ± 6.1, p<0.001). But this difference turned out to be insignificant when the improvement of knee score between the two groups were compared (33.3 ± 5.8 in PCLR and 30.5 ± 11.8 in PCLS, p=0.108).[9] Knee score is an essential postoperative assessment for evaluating patient's ability to perform basic daily tasks, including walking, stair climbing, and it also assesses the necessity for walking aids, pain, ROM and stability.[14]

On the contrary to the knee score, the mean function score according to our meta-analysis on five studies showed a significant difference. The function score being higher in PCLR group compared to PCLS group (p=0.0002). Function score was used to evaluate the pain and the function of the knee and similar to the knee score, this also included the measurement of ROM. Interestingly, however, when each study was individually assessed, it was observed that postoperative function score was statistically not significant between PCLR and PCLS in each included study.[6,9,11–13] This might result from a greater summed sample size included in the analysis.

Flexion contracture was significantly higher in PCLS compared to PCLR according to the data obtained from two studies (p=0.002). In accordance with this, Bae *et al*., reported higher flexion contracture in PCLS (1.9 ± 3.1 degrees vs 0.5 ± 1.8 degrees; p=0.001).[9] On the other hand, Roh reported that the difference in flexion contracture between the two groups was not significant.[12] Nevertheless, maximum flexion was not significantly different between PCLR and PCLS postoperatively. Out of four studies included in the analysis for maximum flexion, only one study reported a significantly higher maximum flexion in PCLS group.[6,10,12,13]

Our analysis on HSS score showed a significant difference in postoperative HSS score, with it being higher in PCLR group. In contrast to our result, previous study concluded that postoperative HSS score was not different between the two groups. However, it was estimated that in longer term PCLR may result in worse clinical outcome due to ongoing degenerative changes of the PCL, contributing to worsening of clinical outcomes.[10–12] WOMAC score also showed no significant difference in our study, similar to previously reported results.[11,12]

Pain, as one of the most commonly reported symptoms of OA, may significantly affect patient's quality of life since it limits their ability to perform daily activities and they may depend on pain-relieving medication on a daily basis to lessen the pain. Following the surgery, the patient may not be completely free of pain, but surgery aids in overall improvement, including much less pain. However, according to our meta-analysis, postoperative pain score did not significantly differ between PCLR and PCLS. This finding was similarly observed in previous studies.[6,11]

Like any medical procedure, TKA with either PCLR or PCLS technique is also at risk of complications, intra- or post-operatively. Frequently reported complications include infection, periprosthetic femoral fracture, periprosthetic patellar fracture, instability, and aseptic loosening. Previous studies reported that postoperative complications between the two groups were not significantly different.[9,11–13]

Our study included a sufficiently large number of subjects to conduct adequate analysis on the outcome following TKA with PCLR and PCLS technique. Nevertheless, we only included one RCT study, having the highest level of evidence, while the rest included were of those with lower level of evidence. Further investigations using multiple studies with better study designs are necessary for evaluating outcomes following TKA with PCLR and PCLS technique. The limitation of this research is that only a small number of variables studied, thus the data coverage is not yet broad and deep.

CONCLUSION

In general, analysis between PCLR and PCLS showed no significant difference on the clinical or functional outcomes except in postoperative function score, flexion contracture and HSS score. PCLR had significantly higher function and HSS scores with lower flexion contracture compared to PCLS. Further research involving studies with better study designs is necessary to aid surgeons in determining whether to retain or sacrifice the PCL in TKA.

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Original Research Article

The Effect of Vitamin C, E, and B12 on the reduction of Ischemic Skeletal Muscle Damage on Rat (Rattus norvegicus) due to Reperfusion Injury

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ABSTRACT

Introduction: Tourniquet is usually used in limb surgery, both orthopaedic surgery and plastic surgery.[1] The use of pneumatic tourniquets has become a standard for creating bloodless fields in the upper and the lower limb surgery. However, the use of tourniquets is dangerous because it causes complications. Complications of tourniquet use occur due to mechanical suppression of the underlying tissue, ischemia, and reperfusion effects. This causes local and systemic complications.

Objectives: This study aims to determine the effect of vitamin C, vitamin E and B12 in reducing rat skeletal muscle damage due to tourniquets.

Methods: This research is an experimental laboratory with a post-test-controlled group design. The sample consisted of 20 female Wistar rats divided into 4 groups, where each group consisted of controlled group, vitamin C group, vitamin E group, and vitamin B12 group. All the rats were anesthetized and then a tourniquet (orthodontic rubber) was placed on the thigh of each rat for 2 hours and continued reperfusion was performed for 1 hour after the tourniquet was released. Histological picture of the muscle cells (myocytes) was observed and the number of the damaged cells and the healthy ones were counted. Data were analyzed using the One-Way ANOVA test ($\alpha = 0.05$) and continued with the Post Hoc Multiple Comparisons (LSD) test ($\alpha = 0.05$).

Results: The result of One-Way ANOVA test showed significant differences between the four treatment groups. The result of Post Hoc test showed significant differences between the control group and the groups P2, P3 and P4. Whereas the P3 group showed significant difference with the P2 and P4 groups.

Conclusions: Oral administration of vitamins C, E and B12 for 5 days reduces histological damage of rat myocytes in ischemic reperfusion injuries due to tourniquet. Vitamin E has the best effectiveness compared to vitamins C and B12.

Keywords: antioxidants, myocyte damage, reperfusion injury
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INTRODUCTION

Tourniquet is usually used in limb surgery, both orthopaedic surgery and plastic surgery.[1] The use of pneumatic tourniquets has become a standard for creating bloodless fields in the upper and the lower limb surgery.[2] However, the use of tourniquets is dangerous because it causes complications. Complications of tourniquet use occur due to mechanical suppression of the underlying tissue, ischemia, and reperfusion effects. This causes local and systemic complications.[3]

Skeletal muscles in the extremities are very sensitive to ischaemic changes.[4] Ischaemic-reperfusion (IR) injuries due to tourniquet use increase with greater inflationary pressure, as well as an increase in the duration of ischemia.[3] The molecular mechanisms underlying IR injury have been extensively investigated over the past few decades. It has been shown that reactive oxygen species (ROS), polymorphonuclear neutrophils (PMN) and nitric oxide (NO) play an important role in IR injury.[5,6]

The ROS formed can be reduced using antioxidants.[7] Researches on antioxidants and IR injuries have been carried out, but there are no recommendations regarding the type of antioxidant and the dosage needed to prevent IR injury to skeletal muscles. This study aims to determine the effect of enteral antioxidants (vitamin C, vitamin E, and vitamin B12) in the prevention of skeletal muscle ischaemic-reperfusion injuries due to the use of tourniquets.

MATERIAL AND METHODS

This study was a true experimental study, post-test controlled-group design. This study was conducted in Integrated Research and Testing Laboratory, Gadjah Mada University, Indonesia, for maintenance, experiment, and sacrifice of experimental animals, and in Pathology Anatomy Laboratory, Faculty of Medicine, Sebelas Maret University, Indonesia, for myocyte count, in February 2020. Ethical permission for undertaking this study was granted by Gadjah Mada University, with certificate number: 00072/04/LPPT/2020.

Animals

Twenty healthy, actively moved, and were not disabled in the extremities, female white rats (*Rattus norvegicus Wistar strain*), 2-3 months old (weighing about 180-200 g) were purchased from The Pre-clinical Research Service Unit, Integrated Testing Research Laboratory, Gadjah Mada University. These rats were selected randomly and divided into control, Vitamin C, Vitamin E, and Vitamin B12 groups. The rats had infection or died before this study completed were excluded. The animals were quarantined and acclimatized for one week before the experiment. The animals were kept in the animal room where the temperature was automatically maintained at temperature 25 ± 2°C, relative humidity 70-90%, and a dark/light cycle 12 hours per day. We maintained the rats with food and water *ad libitum*. Rats were kept in a cage with a size of 50 x 40 x 20 cm^3. The cage was placed in a quiet condition and the outside noise was minimized.

Procedure

Administration of Enteral Antioxidants

All groups were given a standard diet for 5 days. In addition to the standard diet, the experiment group 2 (P2), group 3 (P3) and group 4 (P4) were given additional oral vitamin C, vitamin E, and vitamin B12, respectively, for 5 days. The reference dose of vitamin C used is 2 g per kg for 5 days.[8] The reference dose of vitamin E is 1 x 200 mg,[9] and the dose of vitamin B12 is 6 mcg.[10] After the dose conversion from human to mice,[11] we got doses of vitamin C, vitamin E, and vitamin B12 per 200 g of rat weight, 36 mg, 3.6 mg, and 108 mcg, respectively. We gave the vitamins in 2 cc volume via enteral using syringe.

Torniqueting and Specimen Collection

In day 5, all animals were fasted for 3 hours before the surgery with ketamine hydroxychloride (ketalar) as anesthesia, 100 mg/kg, then the surgical preparation was performed. Once all the rats were anesthetized, the procedure were performed asepsis, a tourniquet (orthodontic rubber 4.0-4.5 oz) was then placed on the thigh of each rat for 2 hours and continued reperfusion was performed for 1 hour after the tourniquet was released.

Samples were collected under the tourniquet location with a lateral incision of the proximal femur up to the muscle, then the muscle tissues were taken 0.5-0.5 cm. The preparations were fixed with 4% paraformaldehyde and stored overnight at 4°C. The preparations were subsequently cut transversely into 4 μm thick with a

microtome and stained with hematoxylin-eosin (HE). The wound was cleaned, sutured and closed with a wound dressing. The rats that had been given the action were sacrificed by giving a triple dose of ketamine. The carcasses of the rats were then put in an incinerator to burn to ashes.

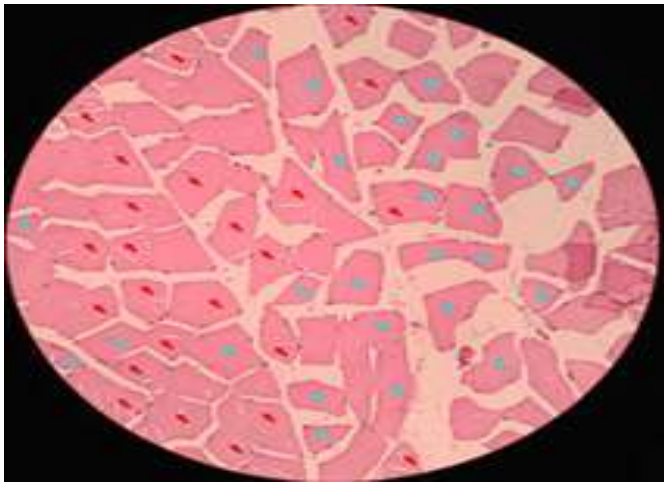

Figure 1. Histology of skeletal muscle tissue with ischemic reperfusion injury (control group). Red arrow: damaged myocyte (72%); blue arrow: normal myocyte (28%).

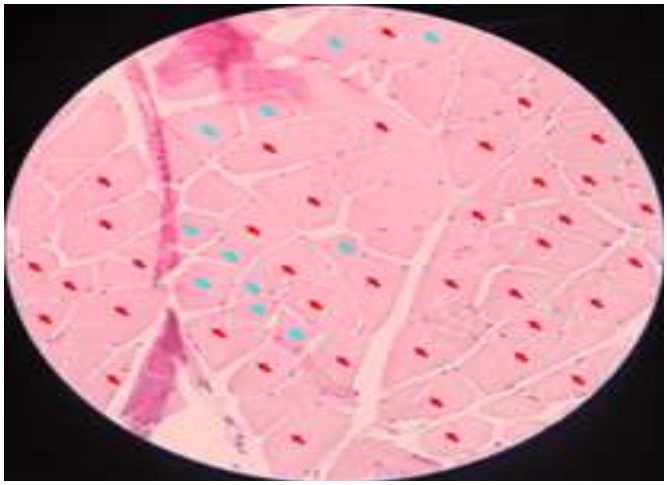

Figure 2. Histology of skeletal muscle tissuewith ischemic reperfusion injury (Vitamin C group). Red arrow: damaged myocyte (45%); blue arrow: normal myocyte (55%).

Histological Examination

Histological examination was carried out on specimens obtained at the Laboratory of Pathology Anatomy, Sebelas Maret University. The preparations were observed under a microscope with a magnification of 400x. The tissue damage assessment was measured in percent, the percentile of the number of defect myocytes in the total number of myocytes examined. Myocytes were categorized into injured and uninjured based on the morphological assessment of each individual myocyte. Uninjured myocytes had firm edges, consistent texture, and uniformity in the myocyte unity. Pericellular or satellite cells can sometimes be seen in healthy myocytes. Injured myocytes were described with uneven edges, inconsistent textures and colors (not artifacts), and/or lost nuclei.[12] Each experimental animal was made into one preparation, therefore there were five preparations in each group. The number of damaged (injured) and healthy (uninjured) cells were counted in a total of 100 myocytes counted from the entire field of view.

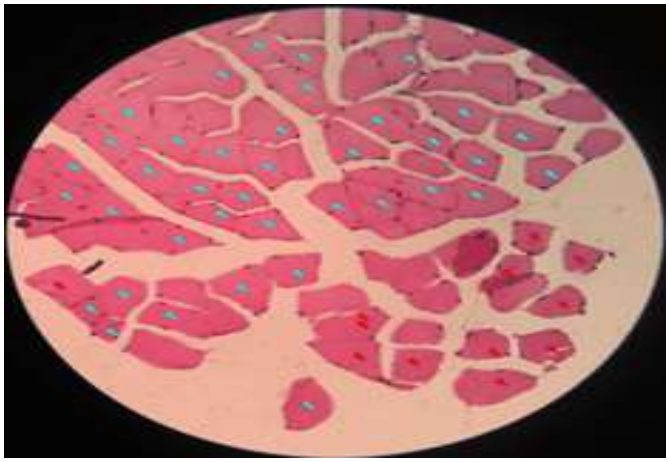

Figure 3. Histology of skeletal muscle tissue with ischemic reperfusion injury (Vitamin E group). Red arrow: damaged myocyte (22%); blue arrow: normal myocyte (78%).

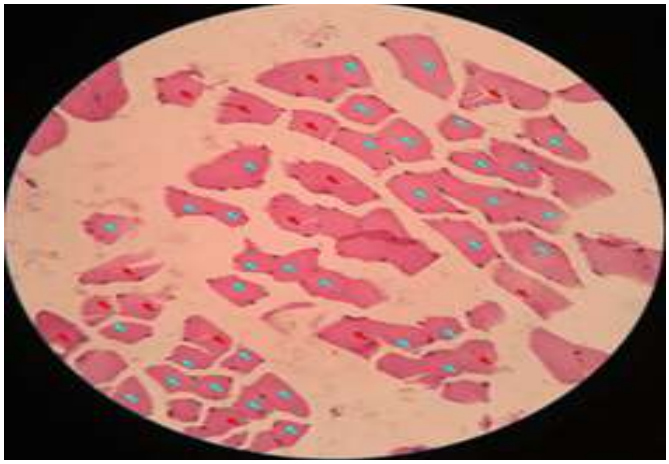

Figure 4. Histology of skeletal muscle tissue with ischemic reperfusion injury (Vitamin B12 group). Red arrow: damaged myocyte (33%); blue arrow: normal myocyte (67%).

Data Analysis

Statistical analysis was performed using One Way ANOVA to see the difference between the number of myocytes in each group and the significance level was

set at p<0.05. If the difference obtained was significant, the analysis proceeded with The Post Hoc Multiple Comparison test

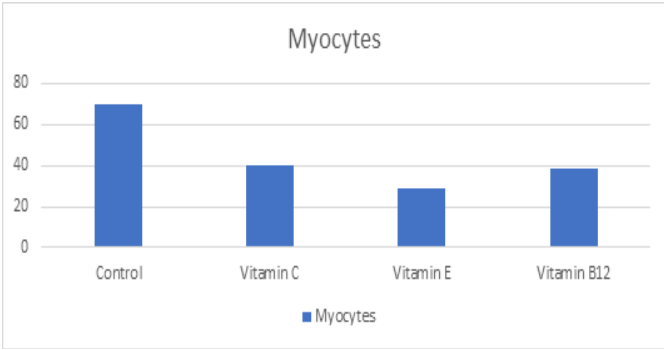

Figure 5. Diagram of Myocyte Damage on Various Treatment Preparations

RESULTS

In this study, a histological examination of 100 myocytes was performed under a microscope magnification of 400x. The myocytes were categorized into damaged and healthy based on the morphology of the myocytes.

Table 1. Myocyte Damage on Various Treatment Preparations

Group	Mean (myocytes)
Control	70,00 + 4,64
Vitamin C	40,40 +6,11
Vitamin E	29,20 +4,21
Vitamin B12	38,60 +6,80
p-value	<0.001*

Table 2. Myocytes Damage Comparrison on Various Treatment Preparations

Myocytes	p-value		
	Vitamin C	Vitamin C	Vitamin C
Control	<0,001*	<0,001*	<0,001*
Vitamin C		0,006*	0,615
Vitamin E			0,016*

Based on Table 1, it is showed that the rats taken Vitamin E had the least damage of all with an average damage of 29.20+4.21. While the most damage occurred in the control group with an average damage of 70.00+4.64. ANOVA test showed a value of p = <0.001 (p <0.05) which indicated a significant difference in myocytes damage between the four groups.

Based on the post hoc multiple comparisons test, there was a significant difference in the group of rats given vitamin C (p = <0.001), vitamin E (p = <0.001), and vitamin B12 (p = <0.001) (Table 2). This study shows that treatment with antioxidants vitamin C, Vitamin E, and Vitamin B12 can prevent an increase in myocyte damage. The post hoc test also demonstrated that the Vitamin E, vitamin C (p = 0.006), and vitamin B12 (p = 0.016) groups showed significant difference. From this study, it was found that compared to the other three groups, Vitamin E, as an antioxidant, showed the best effectiveness in preventing myocyte damage.

DISCUSSION

The results of statistical test using one way ANOVA (α = 0.05) showed significant differences between the four treatment groups. The control group was the group with the most damage, while the vitamin E group had the lowest number of myocyte damage, followed by vitamin B12 and vitamin C groups, respectively. The results of the Post Hoc test with LSD test showed a significant difference (p> 0.05) in the P1-P2, P1-P3, P1-P4 groups. This showed that giving antioxidants, *i.e.* vitamin C, vitamin E, and vitamin B12, can reduce myocyte damage. The results of the post hoc test also showed significant difference between P2-P3 and P3-P4. However, the P2-P4 groups did not show any significant difference. This study is in accordance with the theory that the administration of antioxidants can reduce the explosion of ROS that occurs due to ischemic-reperfusion injuries in the use of tourniquets on skeletal muscles and, as the consequences, will reduce the damage to the muscle cells.

The effect of oral vitamin C on prevention of IR injury in rat cremaster muscle was studied[8] by using cross-clamping for 2 hours and reperfusion was performed for 1 hour, and the muscle function was assessed electrophysiologically by electric field stimulation, infiltration by neutrophils was determined by tissue myeloperoxidase (MPO) activity, and tissue edema was determined with wet-dry ratio. In this study, pre-treatment with vitamin C maintained muscle function and reduced tissue edema and neutrophil infiltration. Neutrophil infiltration blast activity was reduced in the vitamin C-treated group compared to the control group. It can be concluded from this study that pre-treatment with oral vitamin C protects muscles against acute IR injury by attenuating neutrophil infiltration activity.

However, the safety of administering vitamin C has also

been questioned because of its contradictory role in IR injury. In a model of IR injury-induced liver damage, ascorbic acid was shown to have anti- and pro-oxidant properties. After IR injury, decreased glutathione oxidation ratio is reduced and increased lipid peroxidation levels and mitochondrial swelling can be prevented by exposure to ascorbic acid at a dose of 0.5 mM. On the contrary, a dose of 2.0 mM ascorbic acid increases tissue injury.[5]

Several studies on the protection of vitamin E in IR injury to various organs have been conducted. Kohler, in his study, stated that enteral pre-treatment of vitamin E reduced ischemic reperfusion injury in the rat jejenum, which was indicated by less loss of villi height and weakened neutrophil infiltration.[5] Meanwhile, the group given with vitamin C did not show any significant results.

Research conducted by Medling showed that vitamin E infusion had a protective effect in preventing IR injury in mouse muscle as measured by increased muscle viability and reperfused blood flow compared to control.[13] Vitamin E also had the effect of reducing edema, although the results were not significant. Furthermore, Medling *et al*. revealed that, apart from the release of ROS, the tissue damage that occurred during reperfusion was potentiated by the infiltration of inflammatory cells and the release of humoral mediators.[13] In addition to necrotic mortality, apoptosis appears to be induced by activation of the signal transduction cascade promoted by the changing environment observed during reperfusion. The transduction cascade is a delayed process that can potentially be reversed if the pathway can be interrupted. The initiation and spread of IR injury depends on the activation of transcription factors which, in turn, are responsible for the induction of inflammatory genes required for the rapid production of proteins (cytokines, adhesion molecules, complement factors, and induced nitric oxide synthase). Vitamin E has been shown to function not only as an antioxidant but also as a regulator of this signal transduction.

Vitamin B12 or cobalamin protects against oxidative stress induced by hydrogen peroxide. The antioxidant effect of cobalamin is likely to result from a combination of direct and indirect effects: stimulation of methionine synthetase (MS) activity, direct reaction with reactive oxygen and nitrogen species, glutathione sparing effects, and modification of molecular signals.[14] Vitamin B12 is a cofactor of the MS enzyme. MS plays a key role in homocysteine metabolism (L-Hcy, Hcy). Impaired MS activity due to cobalamin deficiency leads to increased Hcy or hyperhomocysteinemia (HHcy / HHCY).[15] HHcy is known to produce oxidative stress, which interferes with different signaling pathways and also inhibits methylation reactions. Research by Moreira suggested that a combination supplement with folic acid, vitamin B6, and vitamin B12 is a very effective treatment for HHcy patients. From the study, it can be concluded that intervention with B12 combined with other B vitamins could be a treatment for skeletal muscle dysfunction in HHcy condition. But how ROS affects skeletal muscle during HHcy is not clear. Further research must be done to confirm this association.

Antioxidant, together with the results of previous studies, support the results of this study, where in this study all groups that were pre-treated with antioxidant showed significant results in protection against histological damage to rat skeletal muscle cells (myocytes) due to IR injury caused by the use of tourniquets. In addition, in this study, the group treated with vitamin E gave the most effective results compared to vitamins C and B12. Because of the effect of vitamin E, vitamin C, and vitamin B12 in preventing reperfusion ischemic injury, their readily available preparations, and low cost, it is hoped that this study can become a reference in developing new therapies for the prevention of complications of tourniquets in muscles.

The results of this study are consistent with the theory that the administration of antioxidants can reduce the explosion of ROS that occurs due to ischemic-reperfusion injuries in the use of tourniquets on skeletal muscles so that it can reduce muscle cell damage.

CONCLUSION

The administration of vitamin C, vitamin E and vitamin B12 can significantly reduce the histological damage to rat myocytes due to the use of tourniquets, and vitamin E shows the best effectiveness compared to vitamins C and B12. Additionally, giving vitamin C and vitamin B12 has the same effectiveness in preventing the increase in rat myocyte damage.

Acknowledgments

Nil

Disclosure

The author reports no conflicts of interest in this work.

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Original Research Article

Non-drug Non-invasive Treatment in the Management of Tennis Elbow: RICE and Guided Rehabilitation

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ABSTRACT

Introduction: Tennis elbow is a common disorder of upper extremity. Majority of the patients can be treated conservatively. It is the major cause of disability and time off work, after low back pain. The disease impacts upon activities of daily living, ultimately leading to a loss of functional independence and quality of life.

Purpose: The main purpose of this study was to assess the results of non-drug non-invasive treatment in the management of tennis elbow.

Methods: This study was conducted in the Department of Orthopaedics from December 2010 to December 2015. One hundred and ten outpatients of tennis elbow with a mean age of 45 years were studied. They were managed with non-invasive treatment and were followed for twelve months.

Results: At the twelve-month follow-up visit, the intensity of tennis elbow pain and disability were assessed by using Quick DASH scoring system and Patient-rated elbow evaluation system. According to the physician global evaluation, up to the age of 40 years at twelve-month follow-up, the results were excellent. At 40 to 60 years of age, the results were good to excellent. Over the age of 60 years, the results were good. The patient global evaluation was found very good up to the age of 40 years at twelve-month follow-up, good to very good between 40 to 60 years, and over the age of 60 years it was good.

Conclusions: Non-drug non-invasive interventions can reduce pain and improve function in tennis elbow.

Keywords: non-drug, non-invasive, tennis elbow, treatment
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INTRODUCTION

Tennis elbow is a common pathology of both athletes and non-athletes, affecting 1 to 3% of the population at large [1, 2]. It is the most common cause of lateral elbow pain, mostly affecting middle-aged patients. It is characterized by pain in the lateral epicondyle of the humerus, which is aggravated during wrist dorsiflexion, supination, and sustained power grip. It could lead to a substantial loss of labour due to the pain experienced by the patients. It usually occurs in the 4th and 5th decade of life without gender disposition. It is caused by generalized extensor inflammation at the lateral epicondyle of the humerus, with resulting microcracks and histological changes of angio-fibroblastic hyperplasia. Extensor carpi radialis brevis (ECRB) and extensor digitorum communis (EDC) are considered to be the most commonly affected tendons. The lack of pathological evidence of inflammation in these types of injuries has led most authors now to refer to this condition as an epicondylitis, abandoning the mislabelled "itis" [3, 4, 5 and 6].

Conservative treatment strategies aim to reduce inflammation through rest, local ice application, activity modification, pain relief, splints, injections, and more recently, extracorporeal shock wave therapy. Nonsurgical treatment of lateral epicondylitis is successful in 70-80% of cases within a year. Various types of orthotics have been developed and popularized for the treatment of tennis elbow. The most commonly used devices include a splint placed around the abdomen of the wrist extensors and a wrist extensor splint. Both of these braces have been used successfully with significant symptom reduction. The paucity of evidence on treatments for lateral epicondylitis may stem from several sources, including the self-limiting nature of the condition, the lack of pathophysiological data, the methodological shortcomings of the current studies, and the existence of multiple factors which may influence the outcome [1, 7].

The aim of our study was to find out the outcome of non-drug non-invasive treatment in the management of tennis elbow.

METHODS

This prospective study was carried out at Orthopaedics Department from December 2010 to December 2015. Institutional medical ethics committee approval was obtained. In this series, 110 patients were enrolled. The average age of patients was 45 years (ranging from 20 to 75 years) **[Table 1]**. The average follow-up was done up to twelve months.

Inclusion criteria

• Age between 20 to 75 years

• No general illnesses or use of medication

• A characteristic history and symptoms of tennis elbow: This is a condition characterized by pain and tenderness at the lateral epicondyle of the humerus due to non-specific inflammation at the origin of the extensor muscles of the forearm. Although, it is sometimes seen in tennis players, other activities such as squeezing clothes, carrying a suitcase etc. are frequently responsible.

• Characteristic clinical signs of tennis elbow local tenderness at lateral epicondyle of humerus: Pain is aggravated by putting the extensor tendons to a stretch; for example, by palmar-flexing the wrist and fingers with the forearm pronated. Cozen's test - Painful resisted extension of the wrist - with elbow in full extension elicits pain at the lateral elbow. Elbow movements are normal.

Exclusion criteria

• Cases were excluded if there had been previous surgery or other elbow pathology such as rheumatoid arthritis, osteoarthritis, or radial tunnel syndrome (pain, paraesthesia, and weakness).

• Investigations are usually not performed in the straightforward case of lateral elbow pain. However, in longstanding cases, plain X-ray (AP and lateral views) of the elbow may show osteochondritis dissecans, degenerative joint changes or evidence of heterotopic calcification. CT scan and MRI are also prescribed to all cases to exclude other abnormality.

A written informed consent was obtained from all the patients; they were explained the treatment plan. The common objectives of all conservative measures are relief of pain and reduction of inflammation followed by guided rehabilitation. Conservative measures have two phases, first phase is for relief of pain and reduction of inflammation and the second phase is for guided rehabilitation. Duration of the first phase is 1-2 weeks

and the second phase is from 2 weeks to 3 months. Follow-up assessments were done at 2 weeks, 6 weeks, 3 months, 6 months, and 12 months. Relief of pain and inflammation is the primary goal of the first phase of nonsurgical treatment. Cessation of the offending activity is required initially, but complete inactivity or immobilization is avoided as this may lead to disuse atrophy, which compromises later rehabilitation. Ice is recommended for its local vasoconstrictive and analgesic effects.

Rest and watchful waiting. Sometimes taking a break from the activity(ies) that triggered tennis elbow symptoms is sufficient to alleviate the symptoms. **RICE protocol**, or the combination of **R**est, **I**ce, **C**ompression, and **E**levation is often employed as a first-line treatment for tennis elbow [8-11]. Analgesics and anti-inflammatory drugs were not formally prescribed for patients during the study period; however, patients were occasionally allowed to take over-the-counter acetaminophen as needed. In addition to rest, cloth-covered ice packs can be applied to the affected area for no more than twenty minutes at a time every two to three hours, two to three times per day. ACE bandages, compression sleeves, or other similar devices can be worn on the affected arm, and the arm can be elevated on a cushion, high table, or other type of platform. This protocol can provide pain relief while also reducing swelling and promoting healing. All patients received wrist extensor stretching, ultrasound, cross-friction massage, heat, and ice during their physical therapy visits.

Upon relief of initial pain and inflammation, the second phase of nonsurgical treatment is begun. This phase emphasizes on continued tissue healing through avoidance of the abusive aspects of the causative activity and guided rehabilitation. If the patient uses aberrant techniques in sports or occupational activities, these should be identified and corrected.

In second phase, the Standard Treatment Group performed isotonic wrist extensor strengthening and the Eccentric Group performed isolated eccentric wrist extensor strengthening. The strengthening and stretching exercises were also prescribed as a home exercise program. Treatments were continued until patients had resolution of symptoms or they were referred back to their physician with continued symptoms. The isolated eccentric strengthening exercise was performed using a rubber bar (Thera-Band Flex Bar; The Hygenic Corporation, Akron OH) which was twisted using wrist flexion of the uninvolved limb and slowly allowed to untwist with eccentric wrist extension by the involved limb. Each eccentric wrist extensor contraction lasted approximately 4 seconds (i.e., slow release). Both upper extremities were reset for the subsequent repetitions. A 30-second rest period was timed between each set of 15 repetitions, and 3 sets of 15 repetitions were performed daily. Intensity was increased by giving the patient a thicker rubber bar if the patient reported no longer experiencing discomfort during the exercise. Exercise protocols with two or three sets of 10 or 15 repetitions were commonly used. The frequency of exercise ranged from three times a week to twice a day, and the duration of intervention ranged from 2 weeks to 3 months. Operative treatment is indicated for debilitating pain that is diagnosed after the exclusion of other pathologic causes for pain and that persists in spite of a well-managed nonoperative regimen spanning a minimum of 6 months.

The results were assessed by quick dash scoring system and the patient-rated elbow evaluation system. The quick DASH [12] is a shortened version of the dash scoring system. It consists of 11 items to measure physical function and symptoms in people with any or multiple musculoskeletal disorders of the upper limb. Similar to the DASH, each item has five response options (1 = no difficulty; 2 = mild difficulty; 3 = moderate difficulty; 4 = severe difficulty; 5 = unable to do). From the item scores, a summative score is calculated. The final score ranges between 0 (no disability) and 100 (the greatest possible disability). Only one missing item can be tolerated, and, if two or more items are missing, the score cannot be calculated [13]. The patient-rated elbow evaluation [14] (PREE) consists of two sections investigating pain and function. All questions are scored on a 10-point scale. The pain section has four questions that rate pain from ‘no pain’ to ‘worst ever’. In addition, there is a question that rates how often the patient has pain (‘never’ to ‘always’). The scale for the function questions ranges from ‘no difficulty’ to ‘unable to do’. The function section has 11 questions regarding specific activities of daily living, and four questions regarding personal care, household work, occupational work and recreational activities. Higher scores represent worse functioning [15, 16].

RESULTS

There were 140 elbows of 110 patients (54 males and 56

females) with tennis elbow admitted to our institute were included in the present study. Fifty-six patients (56.11%) were women and fifty-four patients (49.09%) were male. Thirty patients had bilateral tennis elbow and 80 patients had unilateral tennis elbow. There were 90 cases of tennis elbow found on the right side and 50 cases seen on the left side. All the patients were divided into three age groups. In the age group between 20-40 years, there were 22 females and 20 males. In the age group between 40-60 years, there were 16 females and 18 males and in the age group between 60-75 years, there were 18 females and 16 males. The average age of patients was 45 years (ranging from 15 to 75 years) [Table 1]. All patients were followed for twelve months. At the twelve-month follow-up visit, the intensity of tennis elbow pain and disability were assessed by using Quick dash scoring system and Patient-rated elbow evaluation system [Table 2].

Table 1. Age and sex variations in study group (n=110)

Age	Male	Female	Total
20-40	20	22	42
40-60	18	16	34
60-75	16	18	34
Total	54	56	110

Before the treatment, pain, disability and unable to do were severe and worst in both evaluation system scales, in all 100% cases. At the twelve-month follow-up, it was performed the patient-rated elbow evaluation [14] (PREE), which was consisted of two sections investigating the pain and the function. All questions were scored on a 10-point scale. The pain section had four questions that rate pain from 'no pain' to 'worst ever' compared to before the treatment with significant *P* value (P = 0.16, 0.73, and 0.079, respectively, for each age group). After the treatment, the subjective overall assessment below the age of 40 years was done, 100% of the patients were given one point. Between 40-60 years, 75% of the patient had one point, 15% had four to six points and 10% had seven to eight points. Over the age of 60 years, 50% of the patients had one point, 30% had four to six points and 20% had four to five points.

In Quick DASH scoring functional disability scale [12, 13], below the age of 40 years, 100% had full recovery (0% disability). Between 40-60 years, 75% of the patient had full recovery (0% disability), 25% had minor recovery (<20% disability). Above the age of 60 years, 50% had full recovery (0% disability) and 50% had minor recovery (<20% disability). (Table 2)

Table 2. Pre- and post-management evaluation of tennis elbow (n=110)

Age group	Quick dash scoring system		Patient-rated elbow evaluation system	
	Before treatment	After treatment	Before treatment	After treatment
20-40	100% had Severe difficulty to Unable to do	100% had No difficulty	100% had Worst pain and Unable to do	100% had No pain and No difficulty
40-60	100% had Severe difficulty to Unable to do	75% had No difficulty and 25% had Mild difficulty	100% had Worst pain and Unable to do	75% had No pain and difficulty, 25% had Mild pain and Mild difficulty
60-75	100% had Severe difficulty to Unable to do	50% had No difficulty and 50% had Mild difficulty	100% had Worst pain and Unable to do	50% had No pain and difficulty, 50% had Mild pain and Mild difficulty

In Global Assessment of tennis elbow, below the age of 40 years, 100% had full improvement. Between 40-60 years, 75% of the patient had full improvement, 25% had minor improvement. Above the age of 60 years, 50% had full improvement and 50% had minor improvement. In objective physician global evaluation, below the age of 40 years, 100% had full improvement. Between 40-60 years, 75% of the patients had full improvement, 25% had minor improvement. Above the age of 60 years, 50% had full improvement and 50% had minor improvement. In the patient global evaluation, below the age of 40 years, 100% had no difficulty. Between 40-60 years, 75% of the patient had no difficulty, 25% had minor difficulty. Above the age of 60 years, 50% had no difficulty and 50% had minor difficulty. Below the age of 40 years, at 6 months, complete subjective, functional, and clinical recovery had occurred in almost 100% of the patients. From 40 to 60 years of age at 6 months,

Table 3. Results in study group (n=110)

Age group	Subjective overall assessment [Patient-rated elbow evaluation system]	Quick dash scoring system functional disability scale	Global Assessment of tennis elbow	Physician global evaluation	Patient global evaluation
20-40	100% full recovery	100% full recovery	100% full recovery	Excellent	Very good
40-60	75% full recovery	75% full recovery	75% full recovery	Good-excellent	Good-very good
	25% minor recovery	25% minor recovery	25% minor recovery		
60-75	50% full recovery	50% full recovery	50% full recovery	Good	Good
	50% minor recovery	50% minor recovery	50% minor recovery		

complete subjective, functional, and clinical recovery had occurred in almost 75% of the patients. Twenty percent of the patients had minor recovery even at 24 months, but their severity became lowered significantly. Over the age of 60 years at 6 months, complete subjective, functional, and clinical recovery had occurred in almost 50% of the patients, the other 50% had minor recovery even at 24 months, but their severity became lowered significantly. According to the result of the physician global evaluation, up to the age of 40 years at 2-year follow-up were excellent. At 40 to 60 years of age, it was good to excellent. Over the age of 60 years, it was good. The patient global evaluation were found very good up to the age of 40 years at 2-year follow-up, good to very good between 40 to 60 years and over the age of 60 years it was good [Table 3].

DISCUSSION

Tennis elbow (Lateral epicondylitis) is an overuse injury involving the extensor muscles, especially in the extensor carpi radialis brevis. Histopathological finding is fibrous granulation tissue at the origin of the common extensor tendon [17] and vascular infiltration and degeneration of the common tendon origin [18, 19]. Others claimed that the main pathology in tennis elbow was entrapment of the anterior interosseous branch of the radial nerve and suggested surgical decompression of the nerve [20, 21]. Tennis elbow occurs most commonly in people aged 40 to 50 years with an equal distribution between men and women [3, 22, and 23]. The dominant arm is involved in 75% of patients, and the incidence most directly relates to playing time in amateur players [3]. In our study, fifty-six patients (56.11%) were women and fifty-four patients (49.09%) were male. 30 patients had bilateral tennis elbow and 80 patients had unilateral tennis elbow. There were 90 cases of tennis elbow found on the right side and 50 cases seen on the left side. The average age of patients was 45 years (ranging from 20 to 75 years).

It has been reported that nearly 50% of all tennis players over 35 years old and 60% of players over 50 years old suffer from tennis elbow at some point in their career [3]. Most such injuries are related to direct trauma or repetitive stress, and account for a significant amount of "down time" for the athlete in sports where the arm is utilized for throwing, catching, or swinging. Elbow biomechanics play a very important role in many overhead sporting activities, including tennis. The amount of tension and the location of the stress within the elbow joint are dependent on the stroke used and the mechanics of each stroke [24]. Electromyographic (EMG) studies of elbow function in tennis have shown that the serving motion creates a larger demand on the elbow than does the groundstroke [24]. That being said, it is well known amongst tennis players that improper backhand mechanics is one of the main causes for elbow injuries. In fact, the incidence of lateral epicondylitis has been clinically linked to a one-handed backhand, and greater wrist extension and pronation activity [24]. Some tennis instructors teach a double-hand backstroke, a stroke which minimizes wrist pronation, and/or a stroke that avoids leading with the elbow to minimize the potential for improper mechanics.

Traditionally, the term tennis elbow has been synonymous with lateral epicondylitis. However, the term epicondylitis suggests an inflammatory process, and as Boyer has pointed out – there is no evidence of acute or chronic inflammation in the publications examining the pathological specimens of patients who were operated on for this condition [25]. Repetitive muscle contraction will produce tensile forces within a tendon of an involved muscle, potentially causing micro trauma. If the natural healing process fails, pathological alteration of tissue results in a fibroblastic and vascular response called angiofibroblastic degeneration [3, 4, 5

and 6]. The pathology of tennis elbow is thus most likely to be angiofibroblastic degeneration at the origin of the wrist extensors, and more suitably referred to as lateral epicondylosis [3, 4, 5 and 6]. The current understanding of this condition places the specific pathology at the extensor carpi radialis brevis [3, 4, 26 and 27]. The origin of the extensor carpi radialis brevis is covered by the extensor carpi radialis longus and the extensor communis origin. In fact, the common extensor origin consists of the fused tendons of extensor carpi radialis brevis, extensor digitorum, extensor digiti minimi, and extensor carpi ulnaris.

Biomechanical studies of tensile force at the lateral epicondyle further indicate that stretching extensor carpi radialis brevis, extensor digitorum communis and the superficial head of the supinator produce a large increase in tensile force at the epicondyle [28]. Obviously, a thorough understanding of the anatomical arrangement of these muscles and their specific actions is necessary to make a correct diagnosis. Additionally, it is important to rule out other differential diagnoses such as capitellum fracture, lateral collateral ligament injury, osteochondritis dissecans, posterior interosseus nerve syndrome, radial head fracture and synovitis [26].

Radiographic analysis of lateral epicondylitis may reveal calcification along the lateral epicondyle. However, radiographs, as an initial step in diagnosing lateral epicondylosis, is not necessary [29]. On the other hand, a diagnostic ultrasound of the common extensor origin can be used to confirm lateral epicondylitis in patients with elbow pain and add additional information in regards to the severity [30].

Most authors suggest that over 90% of patients will respond to conservative care, which may include rest, bracing, strengthening, therapeutic modalities, and steroid injections [3, 31, 32, 33 and 34]. In our study, below the age of 40 years, at 6 months, complete subjective, functional, and clinical recovery had occurred in almost 100% of the patients. From 40 to 60 years of age at 6 months, complete subjective, functional, and clinical recovery had occurred in almost 75% of the patients. Twenty percent of the patients had minor recovery even at 24 months, but their severity became lowered significantly. Over the age of 60 years at 6 months, complete subjective, functional, and clinical recovery had occurred in almost 50% of the patients, the other 50% had minor recovery even at 24 months, but their severity became lowered significantly.

Additionally, it has been reported in cases where surgery was required that over 90% of patients responded well [35]. The attempted meta-analysis in 1992 by Labelle *et al*. reviewed 185 articles on the subject of tennis elbow treatment. However, only a single paper was considered to be of a good quality design for controlled therapeutic trials. They concluded that there was insufficient evidence to support any single current method of treatment [36]. This conclusion was reiterated even more recently in the meta-analysis by Bisset *et al.* that identified 28 randomized controlled trials, which met their minimum criteria [7]. These authors suggested that there was a lack of evidence for the long-term benefit of physical interventions in general [7]. There have been a number of studies comparing therapeutic modalities with placebo for the treatment of soft tissue injuries such as lateral epicondylosis. There is insufficient evidence to support the use of most physiotherapy interventions and only weak evidence for the efficacy of therapeutic ultrasound in the treatment of tennis elbow [7, 36, 37 and 38]. Basford *et al.* assessed patients for pain, tenderness to palpation, grip strength, medication usage, and subjective perception of pain after a double masked, placebo controlled, randomized trial utilizing a low intensity laser. The results of this study showed that there were no significant differences, and they concluded that there was no demonstrable beneficial effect of laser therapy [39]. The 2004 systematic review for the efficacy of splinting for lateral epicondylitis identified early positive, but not conclusive evidence supporting the effectiveness of splinting [40]. Similarly, there have been conflicting results on the use of braces and orthotic devices, which may be useful in the initial stages of therapy [41, 42 and 43]. The ability to control the pain associated with lateral epicondylalgia may be achieved through acupuncture.

A recent systematic review suggested that acupuncture was effective in the short-term relief of lateral epicondyle pain [44]. The Fink *et al*. randomized controlled trial for chronic epicondylitis also showed that real acupuncture points showed a reduction of pain and an improvement of function at early follow-up [45]. More long-term follow-up would be useful to assess whether acupuncture has a greater role than simply pain modulation. In addition to the acupuncture findings, manipulations and/or mobilizations have been suggested to have a hypoalgesic effect.

The works of Strujis *et al*. and Paungmali *et al*. have shown that manipulation of the wrist and mobilization of the elbow may play a role in the management of the pain associated with lateral epicondylitis [46, 47]. The preliminary evidence does suggest that manipulation and mobilization may have some positive effects in the reduction of pain and improvement of function [37]. Historically, a popular choice for treating tendonitis have been deep friction massages. However, as evidenced by the 2002 Cochrane review, there was simply not a large enough sample size to draw any conclusions in regards to control of pain or improvement in function [48]. The concepts of cross-friction techniques have since evolved into an augmented soft tissue mobilization, more commonly known as the "Graston Technique Instrument-Assisted Soft Tissue Mobilization" or simply Graston [49]. The Graston protocol for epicondylosis uses specifically designed stainless steel instruments, which are moved with multidirectional strokes around the bony prominence of the elbow. Preliminary studies utilizing this Graston technique had shown promising results when compared to a traditional physiotherapy protocol in the treatment of lateral epicondylitis [50]. Perhaps the most popular of soft tissue techniques to gain recent notoriety is Active Release Technique or ART®. This therapy is based on the observation that the anatomy of the forearm has traversing tissues situated at oblique angles to one another that are prone to reactive changes producing adhesions, fibrosis, and local edema, and thus pain and tenderness [51, 52]. During active release therapy, the clinician applies a combination of deep digital tension at the area of tenderness and the patient actively moves the tissue through the adhesion site from a shortened to a lengthened position [51, 52]. For example, in order to treat extensor carpi radialis brevis, the clinician applies proximal tension distal to the lateral epicondyle while the patient extends the elbow and pronates and flexes the wrist [51]. In the present study, the physician global evaluation up to the age of 40 years at 2-year follow-up were excellent. At 40 to 60 years of age, it was good to excellent. Over the age of 60 years, it was good. The patient global evaluation was found very good up to the age of 40 years at 2-year follow-up, good to very good between 40 to 60 years and over the age of 60 years it was good.

CONCLUSION

The majority of tennis elbow patients can be treated with non-drug non-invasive forms of treatment, and only selected cases may benefit from more invasive operative treatments. Tennis elbow is certainly a challenging musculoskeletal condition to treat and this is largely due to the lack of definitive evidence for the clinical efficacy of the myriad of treatment approaches seen within the literature.

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Nil

Conflict of interest

Nil

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