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The effect of blood flow restriction in low-intensity load exercise on isokinetic strength of the quadriceps muscles in knee osteoarthritis

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ABSTRACT

Introduction: Cartilage destruction in knee osteoarthritis (KOA) caused the inflammation process. It makes the patient complain of knee pain, tends to immobilize, and induced neural inhibition (Arthrogenic muscle inhibition) on the quadriceps muscle as a knee stabilator and shock absorbent. These caused quadriceps weakness. The combination of blood flow restriction (BFR) and low-intensity resistance training (LIRT) showed an improvement in isotonic peak torque significantly, but the prescription is varied and limited in Indonesia.

Patient and Methods: This was a clinical experimental study with randomized control trial with pre and post-test design. The subjects were 28 KOA patients (50-70 years old). The intervention group (n=14) received a combination of low-load resistance training (30% 1-RM; 75 repetitions) and BFR (50 mmHg). The control group (n=14) received low load resistance training only (30% 1-RM; 75 repetitions). Both groups received training 2 times per week with a Q-bench machine for 6 weeks. Isokinetic peak torque was assessed before and after the training program.

Results: There was a significant improvement in isokinetic peak torque before and after the training program in both groups (intervention group p=0.001; control group p=0.000). There was a significant improvement of delta isokinetic peak torque between both groups (p=0.018) and post-test between both groups (p=0.044). The effect size value of the intervention group was 1.22 (very large) and the control group was 0.89 (large).

Conclusions: The addition of BFR on LIRT for 6 weeks can improve isokinetic quadriceps strength in patients with knee osteoarthritis.

Keywords: blood flow restriction, isokinetic peak torque, knee osteoarthritis, knee extensor strength, low-intensity resistance exercise.

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INTRODUCTION

The inflammatory process of knee osteoarthritis (OA) will cause pain and joint stiffness which results in immobilization.[1] Immobilization causes reduced activation of muscle fibers and atrophy, resulting in reduced muscle strength, especially quadriceps.[2,3] Weakness of the quadriceps will increase the load and instability of the knee, thereby exacerbating joint cartilage damage result in increasing degrees of osteoarthritis.[4] Inflammation will trigger a process of neural inhibition to inhibit the activation of the quadriceps known as Arthrogenic Muscle Inhibition (AMI). This inhibition does not only occur on the injured side but also affects the contralateral side.

AMI occurs soon after trauma or injury and can last months to years from onset depending on the severity of joint damage. AMI can disappear over time but the resulting weakness can persist, especially if there is no intervention, resulting in disruption of the subject's function and activity.[5] Weakness of quadriceps muscle in the affected knee showed a prevalence of 11-59%, while in the unaffected knee is 16%.[6] Decrease in quadriceps muscle mass was dominant in the elderly population with knee OA.[4] American College of Sports Medicine recommends weight training of 60% to 80% of 1 maximum repetition (1-RM) for at least 8 weeks to increase strength and muscle hypertrophy to reduce the risk and symptoms of knee OA, but this high-intensity weight training can exacerbate pain and joint damage, results in reduced patient compliance and hinder the rehabilitation process.[2,7]

The combination of low-intensity weight training (20-40% 1-RM) and blood flow resistance (BFR) can increase strength and muscle hypertrophy through the mechanism of tissue ischemia.[8] The use of low-intensity loads is expected to reduce the burden on the joints and increase exercise tolerance.[3,7] Ferlito J *et al* compared high-intensity loads, low-intensity loads, and a combination of BFR with low-intensity loads exercise and showed BFR has a similar effect on muscle strength, muscle mass, and pain with the high-intensity load group. The combination of BFR and low-intensity loads group has a better outcome than the low-intensity loads group. In this systematic review by Ferlito J *et al,* the period of training was a variation between 4 and 12 weeks. The cuff pressure was 100 mmHg until 200 mmHg.[9] Study by Sumide A *et al* compared different cuff pressure of BFR (50, 150, and 250 mmHg) and the result was 50 mmHg could significantly increase muscle strength meanwhile subjects that were given 250 mmHg reported increasing pain.[10] The standard prescription of BFR exercises combined with low-intensity weight training in patients with knee OA is still limited. This study aims to analyze the efficacy and safety of BFR exercises combined with low-intensity weight training in patients with knee OA.

METHOD

This is a clinical experimental study with a randomized control trial, single-blind, pre and post-test design. The research was carried out starting in December 2022 until March 2023 at the Medical Rehabilitation Outpatient Clinic Dr. Soetomo Surabaya Hospital. The inclusion criteria for this study are: 1) Patients with knee OA confirmed by the clinical criteria of the American College of Rheumatology and Radiology according to Kellgren and Lawrence grade II-III criteria both unilaterally and bilaterally. If bilateral, then the leg with the higher pain score (VAS) will be included in the study assessment. 2) Male or female aged 50 – 70 years old. 3) Do not have cognitive impairment (MoCA-Ina score or the Indonesian version of the Montreal Cognitive Assessment ≥ 26). 4) Willing to participate in this study by signing an informed consent form. Exclusion criteria for this study are 1) History of blood coagulation disorder. 2) History or increased risk of deep vein thrombosis in both legs. 3) Peripheral arterial disease in both legs. 4) Peripheral neuropathy and/or polyneuropathy in the leg. 5) Cardiorespiratory disease. 6) Uncontrolled blood pressure (systolic > 140 mmHg or < 100 mmHg and/or diastolic > 100 mmHg). 7) Uncontrolled Diabetes Mellitus (HbA1c > 6.5) 8) History of thrombotic stroke, hemorrhagic stroke, and transient ischemic attack. 9) Pain in the knee joint and/or the surrounding tissue with a VAS score > 60 (mm), with or without inflammation and there is a limitation of the range of motion of the knee joint in the leg to be trained. 10) Currently undergoing or have undergone a lower limb muscle strengthening exercise program within the last 1 month. 11) History of injuries, fractures, surgery, or other musculoskeletal diseases in the lower extremities that will be trained in the last 6 months. 12) Impaired vision and hearing. 13) Currently taking statin class drugs or in chemotherapy intervention or oral contraceptives. 14) Balance disorder. The criteria for Drop Out in this study include: 1) Subjects are not willing to continue research for any reason. 2) Subject cannot complete the intervention according to research protocol (missed > 2 sessions). 3) Subject experienced complications during the intervention which makes it impossible to continue.

This study used consecutive proportional random sampling. Subjects were informed about the objectives of the research and signed the informed consent. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2) and was categorized based on Asia-Pacific BMI criteria. Daily physical activity was assessed using the IPAQ-SF questionnaire. Subjects were randomly divided into two groups intervention group and control group. The subject was not blind to the group allocation. Both the Intervention and Control group received low-intensity weight training using Q-bench twice a week with an interval of 48-120 hours between sessions. Exercise intensity using 20% 1-RM in weeks 1-2 and 30% 1-RM in weeks 3-6. Each session consists of 4 sets x 15 reps in week 1, and 5 sets x 15 reps in weeks 2-6. Given a 60-second rest period between each set with a maximum time of 1 practice session is 10 minutes. In the intervention group, low-intensity weight training was combined with blood flow restriction using a 21 centimeter width of blood pressure cuff (50 mmHg pressure applied). Pre-intervention maximum torque extension of the knee joint was measured with the Cybex Isokinetic Test by a blinded assessor and determination of 1 Maximum Repetition (1-RM) using the Delorme method.

Before and after the exercise intervention, a vital sign examination was performed. The subject also explained the Borg scale and Visual Analog Scale. The subject warmed up using a static cycle for 5 minutes and stretched the hamstring, quadriceps, triceps surae, and tibialis anterior muscles for 5 minutes. In the middle of the exercise intervention (rest period between sets 2 and 3), fatigue levels were assessed using the Borg scale, and pain levels elicited by cuff pressure using the Visual Analog Scale, as well as oxygen saturation. After the exercise intervention, the subjects cooled down with a static cycle for 5 minutes and stretched the hamstring, quadriceps, triceps surae, and tibialis anterior muscles for 5 minutes. Safety and emergency kits are prepared in case of an emergency according to the protocol. At the end of the 6th week of training (96 hours after the last exercise), a post-intervention maximum knee extension torque was measured with the Cybex Isokinetic Test by a blinded assessor. The maximum torque of knee joint extension before and after the intervention was compared in each group using a paired-t-test and between groups using independent-t-test.

RESULT

In this study, a total of 30 subjects were included with 15 subjects for each group. 1 subject from each group dropped out due to work. At the end of the study, there were 28 subjects, consisting of 14 subjects in each group. The characteristic of the subject is shown in Table 1.

At baseline, the mean isokinetic peak torque in the intervention group was 19 ± 12.22 Newton meters, while the control group was 17.78 ± 9.05 Newton meters. There was no significant difference in the isokinetic peak torque between the two groups (p-value = 0.768). The isokinetic peak torque after six weeks of intervention in the intervention group was 34 ± 17.76 Newton meters, while in the control group was 24.21 ± 2.52 Newton meters. There is a significant improvement in isokinetic peak torque in both groups (p-value = 0.001 and 0.000) after 6 weeks of intervention (table 2).

There was also a significant difference in the isokinetic peak torque in the intervention group compared to the control groups (p-value = 0.044) after 6 weeks of intervention (table 3).

Delta of the isokinetic peak torque value of the intervention group was 15 ± 12.26 Newton meters, while the control group was 6.42 ± 3.27 Newton meters. There was a significant difference in the improvement of isokinetic peak torque values between groups (p-value = 0.018) (table 4).

The magnitude of the effect size in the intervention group is calculated by Cohen's d of 1.22 which shows that exercise in the intervention group has a very large effect on improving isokinetic peak torque values, whereas the effect size in the control group was 0.89 which indicated that exercise in the control group had a large effect on improving the isokinetic peak torque value.

DISCUSSION

This study was dominated by female subjects similar to the study by Susanti *et al* which was also conducted in Dr. Soetomo Hospital.[11] Studies by Neogi T *et al* and Tschon M *et al* stated that women have a greater risk of osteoarthritis after the age of more than 50 years and the menopausal period. This is influenced by hormonal, genetic, and anatomical differences and a history of previous trauma.[12,13] Decreased estrogen in postmenopausal women will reduce muscle mass and inhibit the repair process of muscle damage and the presence of pro-inflammatory agents including interleukins, which are greater than men, causing more severe pain in women.[13,14] Women have a greater Femorotibial angle (FTA) and Hip-knee-ankle angle than men so the knee valgus moment on the medial side of the knee joint is larger, thereby increasing the risk of knee osteoarthritis due to matrix metalloprotease damage, but varus deformity of the knee joint in

Table 1. Characteristics of the subject

Variable	Control Group (n = 14)	Intervention Group (n = 14)	*p-value*
Gender			
Male	2 (14.3%)	3 (21.4%)	0.622
Female	12 (85.7%)	11 (78.6%)	
Age (Years)	61.42 ± 5.70	57.71 ± 5.25	0.085
Category			
Elderly	4 (28.6%)	8 (57.1%)	0.127
Pre-Elderly	10 (71.4%)	6 (42.9%)	
Body Weight (Kilograms)	64.71 ± 8.65	66.78 ± 13.00	0.624
Body Height (Centimeter)	152.57 ± 8.73	158.78 ± 7.84	0.058
BMI (kg/m^2)	27.85 ± 2.80	26.30 ± 3.99	0.243
BMI Category			
Normal	2 (14.3%)	3 (21.4%)	
Overweight	4 (28.6%)	4 (28.6%)	0.964
Obese Grade I	7 (50%)	6 (42.9%)	
Obese Grade II	1 (7.1%)	1 (7.1%)	
Affected Knee			
Right	9 (64.3%)	8 (57.1%)	0.699
Left	5 (35.7%)	6 (42.9%)	
Grade OA			
Grade 2	8 (57.1%)	10 (71.4%)	0.430
Grade 3	6 (42.9%)	4 (28.6%)	
IPAQ Pre Intervention			
Low	8 (57.1%)	10 (71.4%)	0.430
Moderate	6 (42.9%)	4 (28.6%)	
Comorbid			
No Comorbid	8 (57.1%)	9 (64.3%)	
Hypertension	5 (35.7%)	3 (21.4%)	0.313
Diabetes Type II	0 (0%)	2 (14.3%)	
Visual Analog Scale (VAS)	53.07 ± 4.44	53.78 ± 5.46	0.708
Isokinetic Pre-Intervention (Newton meter)	17.78 ± 9.05	19 ± 12.22	0.768

Table 2. Isokinetic peak torque comparison for each group

	Control Group (n = 14)			Intervention Group (n = 14)		
	Pre	Post	p-value	Pre	Post	p-value
Isokinetic Peak Torque (Newton meter)	17.78 ± 2.42	24.21 ± 2.52	0.000	19 ± 12.22	34 ± 17.76	0.001

men and women show no difference.[13] Women also have myostatin Lys-153-arg polymorphism in the muscles which functions as an inhibitor of muscle growth so muscle weakness which is also a risk factor for knee OA is greater in women.[7,15]

In this study the age of the subjects included in the inclusion criteria was 50 to 70 years with an average age in the intervention group 57.71 ± 5.25 and in the control group 61.42 ± 5.70. This data is similar to that of Ferraz *et al* with an average age of 50 to 65 years.[3,13] The aging process results in the replacement of skeletal muscles by fat tissue and it will reduce muscle strength. Fat tissue secretes inflammatory cytokines and adipokines which play a role in the pathogenesis of OA. Biomechanically, patients with overweight and even obese will increase the load on the knee joint 3-5 times the body weight during ambulation.[16] Patients with normal weight also could have KOA since it was not affected by BMI only, but also other risk factors as well.[17]

In this study, most subjects are obese grade I followed by overweight, normal weight, and obese grade II based on Asia-Pacific BMI criteria. Pain is supported by pro-inflammatory agents produced from fat tissue that will cause a person to tend to be inactive and further aggravate weight gain and muscle weakness, especially in the quadriceps. These things will continue to influence each other to form a chain with negative effects. This is also consistent with the profile of knee OA patients studied by Zamri *et al* who examined the prevalence and risk factors for OA patients in Asia, one of which is obesity.[18]

Daily physical activity in each subject was assessed with an IPAQ score where the results of low and moderate physical activity were the same for each group. Low physical activity or tending to immobilize will reduce the production of myokines which consist of cytokines, peptides, and growth factors which play a role in metabolic processes. Myokines are regulated by muscle contractions so the lower a person's physical activity, the lower the myokines produced and the weaker the muscles.[16]

The results of this study showed that there was a significant increase in both groups. This is to the results of a study by Tanaka *et al* mentioned that training with low-intensity loads (20% - 40% 1RM) for at least four weeks can increase the muscle strength through neural adaptation.[19] This result is by the study by Ferraz *et al* and Wang *et al* in which this effect is obtained from the mechanism of tissue ischemia which accelerates the recruitment of type II muscle fibers due to fatigue of type I muscle fibers due to the ischemia conditions and the presence of greater metabolic stress that promotes growth hormone production is associated with muscle hypertrophy which was not examined in this study[3,7]. Data from the IPAQ score in this study showed the activity level of both groups including low and moderate activity, this level of activity may be related to the possibility of smaller muscle mass, especially type I muscle fibers which are sensitive to immobilization. The increase in muscle strength in the control group occurred due to the activation of type I muscle fibers, which are abundant in the quadriceps muscles, and have a lower threshold value than type II muscle fibers, so they will be activated even with low loads.[20,21] Another study by Segal *et al* on male subjects over 45 years old with knee OA had different results, where there was no increase in knee extensor muscle strength in the BFR combination group with low-intensity weight training (30% 1-RM) for 4 weeks while there was a significant increase in the group with low-intensity weight training only. According to Segal *et al* duration of exercise with a BFR of more than 4 weeks especially in males is needed to produce an increase in muscle strength.[22]

The delta in isokinetic peak torque before and after exercise between the two

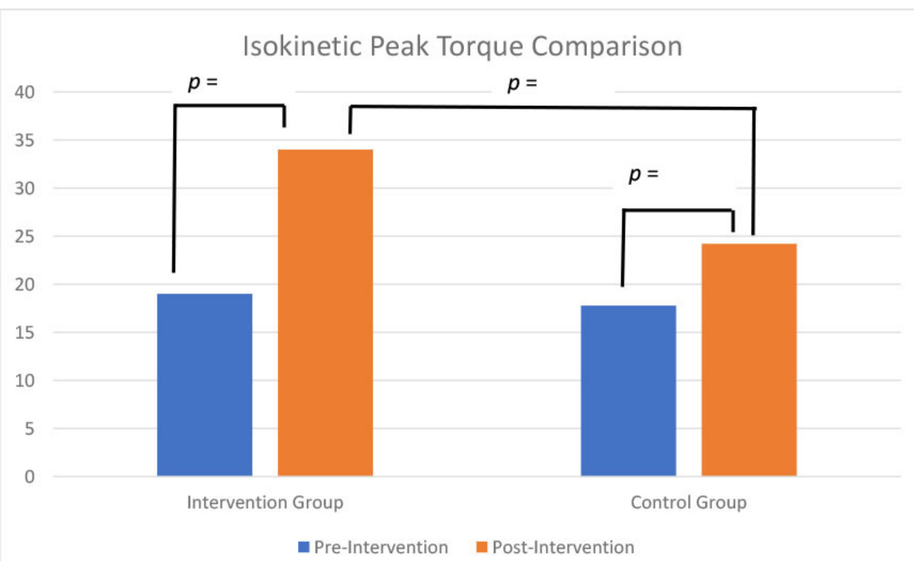

Figure 1. Isokinetic peak torque comparison.

Table 3. Isokinetic peak torque after six weeks of intervention

	Control Group (n = 14)	Intervention Group (n = 14)	*p-value*
Isokinetic Peak Torque (Newton meter)	24.21 ± 9.43	34 ± 17.76	0.044

Table 4. Delta of isokinetic peak torque

	Control Group (n = 14)	Intervention Group (n = 14)	*p-value*
Δ *Isokinetic Peak Torque* (Newton meter)	6.42 ± 3.27	15 ± 12.26	0.018

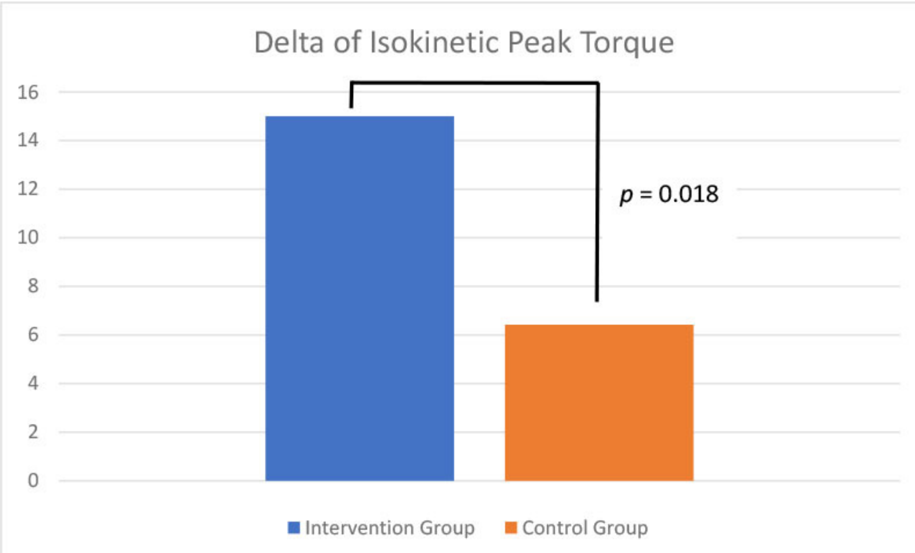

Figure 2. Delta of isokinetic peak torque.

groups showed a significant difference (p-value 0.018), where the delta was greater in the intervention group (15 ± 12.26) compared to the control group (6.42 ± 3.27). A review article by Myers states that the minimum detectable change (MDC) value for the concentric isokinetic peak torque of the knee extensors is 33.9 Newton meters. The results of the difference in muscle strength in the two study groups did not reach the MDC value however, the values in the intervention group were closer than the control group.[23] Segal *et al* mentioned there was a significant increase in isokinetic knee extensor muscle strength in a female who received BFR while there was no significant difference in males.[22] This could be caused by the duration of the study which only lasted 4 weeks, where the effect of increasing muscle strength through neural adaptation only started after 4 weeks.[24] Men are considered to have a higher level of physical activity than women so they have better isokinetic peak torque at baseline, so the changes that occur after 4 weeks do not show a significant increase in men.[25]

The Isokinetic Peak Torque after six weeks of intervention between the two groups showed a significant difference (p-value 0.044). Myers states that the minimum detectable change (MDC) value for the concentric isokinetic peak torque of the knee extensors is 33.9 Newton meters[23], so the results of the intervention group have reached the MDC value, while not in the control group. The effect size in the intervention group is also very large (Cohen's d 1.22). These results are slightly different from the study by Segal *et al* that showed there was a significant difference in the isokinetic of the knee extensor muscles in the BFR group but with a smaller increase of 0.07 ± 0.03 Newton meters. The smaller increase in muscle strength in the study by Segal *et al* could be due to the shorter training duration, which was 4 weeks, whereas in this study, the training was given for 6 weeks. The use of 200 mmHg pressure in the study of Segal *et al* can also trigger discomfort during exercise so that it can inhibit maximum muscle contraction during exercise.[22]

To the best of our knowledge, there were no studies that combined low-intensity weight training and BFR of 50 mmHg in patients with knee OA. A meta-analysis study by Pitsillides uses varying BFR pressures (200 mmHg; 70% total arterial pressure; BFR pressure formula = 0.5 (systolic blood pressure) + 2 (thigh circumference) + 5), but these studies use Kaatsu as a standardized tool for BFR training and Doppler ultrasound to monitor blood flow.[22] Another study by Sumide *et al* showed that a pressure of 50 mmHg can provide a significant increase in isokinetic peak torque in the knee extensor muscles, but the subjects of this study were healthy people. The pressure of 50 mmHg is already greater than the venous pressure so that the venous flow can be dammed and causes ischemia. In this study, there is a significant increase in the isokinetic peak torque of the quadriceps muscles in patients with knee OA with the addition of 50 mmHg in low-intensity weight training (30% 1-RM), 2 sessions per week for 6 weeks without any side effects.[26] The result of this study could be explained due to muscle ischemia and metabolic accumulation that promoted the recruitment of type II muscle fiber, an increase of nitric oxide, and activation of mammalian target of rapamycin (mTOR) that will increase protein synthesis. Greater metabolic stress and cell swelling due to blood restriction also promote growth hormone production to persist in the membrane cell. Growth hormone increases insulin-like growth factor 1 (IGF-1) to activate satellite cell and caused protein synthesis which mean there were more actin and myosin that will be activated in muscle contraction so muscle strength also increases.[27]

This study has several limitations. First, this study does not evaluate markers such as growth factors, muscle mass and fat tissue before intervention which can affect muscle strength. This study also did not assess thigh circumference which could affect cuff pressure to restrict blood flow.

CONCLUSION

Low-intensity weight training with or without additional blood flow restriction in the quadriceps muscles of knee osteoarthritis patients for six weeks increased the isokinetic strength of the quadriceps muscles. However, the addition of Blood Flow Restriction can increase the isokinetic strength of the quadriceps muscles better than low-intensity weight training alone.

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Conflict of Interest

There is no conflict of interest in writing this research report.

Ethical Statement

Ethical clearance obtained from the Ethics Committee for research and basic/clinical

science at Dr. Soetomo Surabaya Hospital/ Airlangga University number 0554/KEPK/ XII/2022.

Author Contribution

All authors contributed equally to this study.

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