Isotonic and Isometric Muscle Contraction Exercises to Reduce Interleukin-6 and Enzyme Cox-2 in Post-Exercise Muscle Injury

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Abstract

Exercise, besides the health benefits, also comes with risks. One risk that commonly occurs is muscle injury, either in the form of lacerations, bruises, or sprains. The acute phase is characterized by inflammation with the emergence of inflammatory markers, including the enzyme Cox-2 and pro-inflammatory cytokines such as Interleukin-6 (IL-6), and pain. The latest approach to the initial treatment of muscle injuries utilizes the PEACE (Protection, Elevation, Avoid Anti-Inflammatory Drugs, Compression, and Education) and LOVE (Load, Optimism, Vascularization, and Exercise) methods. Exercise is believed to reduce inflammation, thus accelerating tissue regeneration. There are two types of muscle contraction that can be used in exercise, including isometric muscle contraction and isotonic muscle contraction. This research is conducted to determine which type of muscle contraction is better in reducing enzyme Cox-2 and IL-6 in post-exercise muscle injuries.

Methods: This research was conducted on 21 members of the sports club who experienced grade I muscle injuries. They were divided into three groups by consecutive random sampling. Group I was given an isometric contraction exercise intervention, group II was given an isotonic contraction exercise intervention, and group III as the control group was not given any intervention. Each group was given soft taping action with the lymphatic method. Blood plasma examination was carried out on each sample to measure the enzyme Cox-2 and IL-6 pre- and post-intervention using ELISA. The intervention was conducted with a dose of progressive continuous exercise with a frequency of once a day for 7 days.

Results: The calculation results of the enzyme Cox-2's average decrease in group II amounted to 2,877 ± 2.4 compared to group I by 1,454 ± 1.5, while the control group increased by 3,377 ± 2.8. The calculation results of the IL-6's average decrease in group II amounted to 11,299 ± 6.9, experiencing a greater decrease as well, compared to group I of 4,521 ± 4.7 and group III of 6,535 ± 6.2. The statistical difference test for the decrease in enzyme Cox-2 with Kruskal–Wallis showed $p = 0.37$ or $p>0.05$ and the ANOVA test for IL-6 measurement showed $p = 0.25$ or $p>0.05$.

Conclusion: There is no significant difference between isometric contraction exercise and isotonic contraction exercise as well as the control group in reducing enzyme Cox-2 and IL-6 in post-exercise muscle injury.

Keywords: *isometric muscle contraction, isotonic muscle contraction, enzyme Cox-2, Interleukin-6, muscle injury*

I. RESEARCH BACKGROUND

Muscle injuries are the most common injury in sporting activities with 1 in 3 occurrences. The frequency varies between 10-55% in sustained injuries (Järvinen et al., 2013). Research by Gonzales (2021) shows that the average incidence of sports injuries is 2.7 per 1000 hours, whereas football occupies an average of 7.21 per 1000 hours. The most common injuries are lumbar muscle strains (12.4%), ankle sprains (11.98%), bone fractures (9.31%) where 49.28% of injuries occur during training, and 40.72% of injuries occur in the pre-competitions and during competitions (Prieto-González et al., 2021).

The initial response to injured muscle is inflammation in the tissue which is characterized by an increase in several inflammatory proteins in the form of enzymes, such as Cyclooxygenase 2 (Cox-2) and cytokines such as Tumor Necrotic Factor-α (TNF-α) and Interleukin-6 (IL-6) (Leung & Cahill, 2010). Tissue injury causes arachidonic acid to be released from the cell membrane into the cytosol so that it undergoes metabolism and produces inflammatory mediators such as prostaglandin E2, thromboxane A2, and histamine which cause tissue swelling, pain, and movement disorders (Krüger et al., 2016).

Muscle has the ability to regenerate after injury with active satellite cells that are silent under normal conditions (Shadrach & Wagers, 2011). Shortly after injury, satellite cells become active to promote proliferation, differentiation, and regeneration by forming multinucleated myofiber. However, the role of satellite cells is highly dependent on the cell environment. The balance of pro-inflammation and anti-inflammation macrophages produced by myeloid cells will determine the process of muscle cell regeneration. Exercise reduces inflammation as evidenced by an increase in the macropagh marker CD-68 (Abreu & Kowaltowski, 2020). Myeloid cell activation is highly dependent on the role of microRNA (Nie et al., 2016). One microRNA that plays an active role is microRNA-155. The entire process of tissue repair starting from the activation of satellite cells influenced by exercise is mediated by micro RNA (Chen et al., 2022). At the same time, microRNA-155 is a mediator of other biomarkers including Cox-2 and IL-6 as an inflammatory reaction (Mogharehabed et al., 2022).

The most commonly used treatment for sports-related muscle injuries is the RICE (Rest, Ice, Compression, and Elevation) program, given immediately after the injury (Vuurberg et al., 2018). However, currently, the popular approaches used are the principles of PEACE (Protection, Elevation, Avoid Anti-Inflammatory Drugs, Compression, and Education) and LOVE (Load, Optimism, Vascularization, and Exercise). In the two treatments above, there are differences in the use of exercise, the application of ice and painkillers and inflammation. The LOVE principle applies an early exercise intervention that is adjusted to the level of injury as it spurs vascularization through the regenerative angiogenesis process (Liu et al., 2023). However, the choice of exercise with the type of muscle contraction whether isometric or isotonic contraction is important to consider, in addition to the factors, repetitions, and intensity (Rio et al., 2015a). Exercise therapy is aimed at renewing cellular physiological processes to provide therapeutic effects in the form of decreased inflammation, decreased pain, tissue regeneration, and bioplasticity (Huang et al., 2013). Thus, exercise will benefit an individual in preventing diseases and recovering from injuries or diseases that cause impaired movement and function in everyday life (Leelayuwat, 2017). Nonetheless, it is not yet widely known about the effect of exercise between different types of contractions, isometric and isotonic, on post-injury tissue regeneration as seen from changes in interleukin-6 and enzyme Cox-2.

Exercise therapy is aimed at renewing cellular physiological processes to provide therapeutic effects in the form of decreased inflammation, decreased pain, tissue regeneration and bioplasticity (Huang et al., 2013). Thus, exercise will be useful for someone to prevent diseases and recover from injuries or diseases that cause impaired movement and function in everyday life (Leelayuwat, 2017). However, not much is known about the effect of exercise between different types of contractions, isometric and isotonic, on post-injury tissue regeneration seen from changes in interleukin-6 and enzyme Cox-2. This research aims to determine the differences in the effect between isometric and isotonic muscle contraction exercise on post-injury tissue regeneration seen from changes in interleukin-6 and enzyme Cox-2 levels. This research intends to know which type of muscle contraction is better used in the initial treatment of muscle injury, especially seen from IL-6 and enzyme Cox-2 levels.

II. RESEARCH METHOD

This research was an experimental research with a randomized control design consisting of two treatment groups and one control group. The sample size was determined by the Pocock method based on previous similar research, resulting in 7 samples for each group, thus the total sample amounted to 21 people. Treatment group I was given soft taping and isometric contraction exercise, and treatment group II was given soft taping and isotonic contraction exercise, while the control group was only given soft taping intervention. The distribution of samples in each group was carried out by lottery model with consecutive random sampling.

a. Sample

The targeted sample was members of university-level sports clubs in 4 types of sports, including futsal, badminton, volleyball, and running, who experienced injuries both during training and competition. The inclusion criteria set were members of sports clubs, aged 15-20 years, and had injuries to soft tissue or muscles of grade 1 severity. Injury severity was determined using a musculoskeletal ultrasonography (MUS) examination. The determination of grade 1 injury using MUS referred to the minimum provisions, including localized pain, minimal hemorrhage and swelling, with mild ROM loss (Bailowitz et al., 2021).

b. Exercise Dosage

The dose of exercise intervention was determined by the FITT principle (frequency, intensity, type, and time) by considering overload and specificity (Koltyn et al., 2001). The dose utilized a progressive continuous exercise pattern with the following conditions:

Type	1	2	3	4	5	6	7	Description
Isometric	30	40	50	60	70	80	90	1 contraction 50% RM, 40 seconds
Isotonic	30	40	50	60	70	80	90	1 movement in ROM 5 seconds

The dosage of this exercise was progressive, meaning that the repetitions of movements increased every day and were not interspersed with rest at the end of each movement. The exercise was conducted for 7 days, once a day. The strength of isometric contraction in the treatment group I was measured using surface electro myography. Time counting during exercise was carried out using a stopwatch with the Tabata application.

c. Measurement of IL-6 and Enzyme Cox-2

Measurement of IL-6 and enzyme Cox-2 levels was conducted through blood plasma using the ELISA method, which was carried out both pre- and post-intervention. Blood samples used were 5cc per examination.

III. RESULTS

a. Sample Characteristics

Measurement of anthropometric characteristics was conducted through measuring instruments as required and was carried out at the initial examination before the intervention was given. The measurement results are presented in the table below. Measurements were taken on 23 available samples. However, on the way forward only 21 samples were used with 2 dropouts.

Table 1. Description of Anthropometric Measurement Results

Type of Measurement	Group I	Group II	Group III	N total
BW	64,8±9,1	53,7±13,6	60±3,5	21
H	168,4±7,8	169,5±7,1	169,5±7,5	21
BP	122,2/86. ±10,7/5	121,8/84,7±4,8/10,1	120,8/85,6±6,2/11,4	21
AGE	20,2±1,1	19,2± 0,7	20,1±1,5	21
N	7	7	7	21

b. List of Injured Muscles and Injury Grade Measurement

Injury grade was measured using MUS with the results presented in the table below.

Table 2. Injury Grade Examination

No	Injury Location	Injury Grade	Frequency	Percentage
1	ATFL (D)	1	1	4,76%
2	PTFL (D)	1	1	4,76%
3	Vastus Lateralis (D)	1	6	28,57%
4	Vastus Lateralis (S)	1	2	9,52%

5	Rectus Femoris (D)	1	6	28,57%
6	Extensor Carpi (S)	1	5	23,81%
	N	7	7	7

c. Measurement Results of IL-6 and Cox-2

Measurement of IL-6 and Cox-2 levels was carried out 24 hours after the injury occurred before the intervention in the treatment group and the control group. The same was done post-intervention on day 7. It can be seen in Table 3 below.

IL-6 ELISA Examinati on	No	Group 1		Group 2		Group 3	
		Pre	Post	Pre	Post	Pre	Post
	1	54.958	44.987	65.728	59.200	56.113	51.270
	2	67.219	68.152	82.067	70.983	42.093	50.155
	3	65.981	53.528	52.677	46.057	50.602	52.151
	4	57.433	53.896	81.064	56.403	50.602	52.151
	5	56.403	55.823	58.449	75.148	57.862	45.253
	6	50.433	48.774	54.384	47.408	43.137	59.928
	7	49.601	52.112	65.728	59.2	53.806	54.151
MEAN	N = 7	57.4326 ±6.9	53.896 ±7,2	65.7281 ±11.9	59.200 ±10.8	50.602 ±6.0	52.151 ±4.4

Based on the data above, data normality test was carried out through the Shapirowilk test, and data homogeneity test through the Levene's test to determine the required statistical test, with the results showed in the following table:

Table 4. Data Normality Test Results

Examination	Group I	Group II	Group III
	p	p	p
Pre	0.321	0,229	0,408
Post	0,307	0,502	0,639

Table 5. Data Homogeneity Test Results

Examination	Group I, II, III
	p
Pre	0,217
Post	0,209

From the table above, it can be known that all data were normally distributed and homogeneous because p>0.05. Therefore, the difference test utilized for the three different groups was the one-way ANOVA parametric test.

The different test results of those three sample groups conducted through the one-way ANOVA test are presented in the following table:

Table 6. Results of the One-Way ANOVA Difference Test for IL-6

Examination	IL-6	(p)	Detail
		0,25	>0,05

The different test above showed a value of p=0.25 or p>0.05, which means that there was no significant difference between the three groups on IL-6 levels. However, the average difference value of group II was higher.

d. Pre and Post Measurement Results of Enzyme Cox-2

Enzyme Cox-2 levels were measured pre and post-intervention from venous blood using the ELISA technique. The results are presented in the table below:

Table 7. Mean Data of Pre and Post Cox-2 Measurements

Cox-2 ELISA Examination	No	Group 1		Group 2		Group 3	
		Pre	Post	Pre	Post	Pre	
	1	11.678	11.143	14.269	12.761	11.95	
	2	14.594	12.923	18.201	13.929	8.693	
	3	14.297	10.814	11.143	12.782	7.266	
	4	10.233	9.604	17.955	10.361	10.113	
	5	12.018	12.087	12.502	15.654	12.363	
	6	10.618	14.223	11.543	11.077	8.932	
	7	10.425	10.233	14.269	12.761	11.471	
MEAN	N = 7	11.980 ±1.8	11.575 ±1.6	14.268 ±2.8	12.760 ±1.7	10.112 ±1.9	12.862 ±2.2

From the table above, data normality test was carried out through the Shapirowilk test and the homogeneity test through the Levene's test with the results presented in the table below:

Table 8. Data Normality Test Results

Examination	Group I p	Group II p	Group III p
Pre	0,128	0,225	0,619
Post	0,861	0,698	0,416

Table 9. Data Homogeneity Test Results

Examination	Group I, II, III p
Pre	0,466
Post	0,676

From the above results, it can be seen that the distribution of data was not entirely normal because p = 0.04 or p < 0.05, while the data variation was homogeneous because all p-values were > 0.05. Based on these results, the statistical difference test between the three groups used the Kruskal Wallis non-parametric test.

Table 10. The Kruskal Wallis Different Test Results

Examination	Cox-2	(p)	Detail
		0,379	>0,05

The test results above showed a value of p=0.379 or p>0.05, which means that there was no significant difference between the three groups. However, when viewed from the average aspect, group II experienced a decrease in Cox-2 levels.

IV. DISCUSSION

a. Research Sample Description

The sample of this research amounted to 21 people out of 22 people who entered the inclusion criteria for members of various sports with the majority of futsal branches and experienced injuries after matches and training. One sample dropped out because he did not continue the process due to fear of taking blood. Of the 21 samples, consecutive random sampling was carried out because the injury did not occur at the same time and was divided into 3 groups using a lottery. The results of each group amounted to 7 people.

All samples were members of a student sports club with ages between 19.2 - 20.2 years old with normal body mass index. This age range referred to previous research to see the benefits of isometric and isotonic contractions on health (Azeem & Zemková, 2022). Vital signs of blood pressure and pulse were also within the normal range. This shows that the entire sample has a fit body condition and does not experience chronic diseases. Referring to research conducted by Neegaard (2019), IL-6 persistently rises in people who are obese and will appear as an initial reaction to infection (Wedell-Neergaard et al., 2019). Thus, the results of IL-6 measurements taken in the sample were purely from the injury experienced. IL-6 is produced rapidly and transiently as an acute response to infection and tissue injury (Tanaka et al., 2014).

The sports included were football, volleyball, badminton, and basketball, 4 sports that have greater potential to cause injury both during training and competition. Of the 21 samples involved in this research, 12 samples or 57% of them were football players. Injuries to football players have the highest incidence compared to other sports (Santanna et al., 2021). In epidemiological studies conducted on professional and amateur football players, it was found that they have a risk of muscle injury.

The location of the injury experienced by the sample in this research was in the lower limb, especially in the quadriceps muscles, experienced by 16 or 76% of them. This result is aligned with epidemiological studies which indicate that the dominance of injuries in football players is in the hamstring muscles, adductors, quadriceps, and calf muscles (Ekstrand et al., 2011).

To fulfill the inclusion criteria, a grade 1 injury examination using musculoskeletal ultrasonography (MUS) was performed before the intervention. The type of muscle injury that occurs is mostly intrinsic injury caused by excessive muscle contraction or prolonged muscle extension, which causes damage to muscle fibers and the area where tendon and muscle meet. Intrinsic muscle damage is divided into three grades, including grade 1 which involves several muscle fibers in one bundle, grade 2 which involves ¾ of the muscle bundle, and grade 3 which almost all parts of the muscle bundle are damaged (Draghi et al., 2013). In this research, the results of the MUS examination showed that 100% of the samples had grade 1 injuries.

MUS examination is considered to be more advantageous for muscle injury examination than other imaging examinations in terms of cost efficiency, with better resolution space, convenience, portability, and dynamic evaluation. Linear probes that are commonly used have a frequency of 7-9 MHZ (J. C. Lee et al., 2012). In this research, the MUS used had a linear probe frequency of 5MHz, thus having the disadvantage of achieving deeper muscle imaging. However, muscle imaging using

MUS has a good accuracy rate and is recommended to see the spectrum of damage in musculoskeletal organs (Henderson et al., 2015).

The exercise intervention dosage for the isometric contraction group was set using the 50% IRM standard. Measurements were made with surface electromyography on the same muscle on the healthy side by dividing 50% of the maximum contraction of 1 RM. This dose is greater than previous research around 25% of 1RM (Bement et al., 2008). However, this dose is lower than the research conducted on healthy people around 80% of 1RM (Haley et al., 2020). The selection of this dose was also based on the sample injury level according to the inclusion criteria, grade 1 (mild). Furthermore, in its implementation, 50% 1RM was also adjusted to the tolerable pain limit. In the isotonic group, the dose was carried out in accordance with predetermined standards, namely movement in full ROM without external load.

The three groups were given standard intervention with the soft taping lymphatic method. Group I was added with isometric contraction exercise, group II with isotonic contraction exercise, and the soft taping lymphatic method with daily replacement. Likewise, the isometric and isotonic groups were given post-exercise soft taping interventions. The soft taping given used a net-shaped lymphatic method without pulling. The selection of this soft taping method was based on the results of research which states that soft taping can reduce pain with a method without pulling (Alrawaili, 2019). Malhotra (2022) used soft taping with a no-pull technique in research for the effectiveness of reducing pain in DOMS (Malhotra et al., 2022).

b. Exercise with Muscle Contraction Type, IL-6, and Enzyme Cox-2

Pre-intervention data measurement showed that the average levels of Cox-2 and IL-6 in all three groups increased compared to normal conditions, indicating Cox-2 and IL-6 as enzymes and cytokines that are early inflammatory markers in tissue injury. There was a decrease in Cox-2 and IL-6 levels on the seventh day after intervention in both groups I and II and an increase in group III. The average decrease in group II given with isotonic contraction exercise was greater than in group I given with isometric contraction exercise as well as the control group. The results of this research are in line with research conducted by Lee (2015) which stated that exercise suppresses Cox-2 expression in patients with migraine (Y. Y. Lee et al., 2015). Exercise can inhibit Cox-2 activity and suppress pro-inflammatory cytokines including IL-6. However, this is different from the results of research conducted on healthy adults where exercise increases IL-6 (Behrendt et al., 2021), and research conducted on healthy mice where exercise increases Cox-2 in the mouse brain (Krüger et al., 2016) .

However, the statistical test results in the three groups post-intervention found differences indicating a decrease, yet without any significant difference with $p = 0.127$ or $p > 0.05$. This means that both isometric and isotonic muscle contractions can be used as initial therapy in the PEACE and LOVE approach to muscle injury. A decrease in inflammatory mediators, both Cox-2 and IL-6, is beneficial for Macropagh type 2 (M2) to activate stem cells to start the tissue regeneration process. This decrease also appears to be caused by the expression of microRNA-155 in response to exercise

(Mogharehabed et al., 2022). MicroRNA-155 is known to play a role in muscle tissue regeneration after injury.

The explanation of the benefits of exercise therapy on post-injury tissue regeneration is carried out through the process of mechanobiology, hormones, and bioenergetics. Mechanobilogy is an effort to use biophysics and biomechanics to understand and demonstrate the biological and physiological functions of the body in stages, both in its shape changes and protein interactions that control gene transcription at the cellular level, protein complexes, cell migration, focal addition, ion transfer, and intercellular relationships (Lim et al., 2010). Physiotherapy uses mechanotherapy to encourage mechanobiology in human body cells (Ng et al., 2017). Exercise therapy is one type of mechanotherapy.

The results of this research are aligned with research that explains the benefits of exercise on hormones that work due to muscle contractions. Muscle contractions during exercise are believed to be able to reduce inflammation (Clifford et al., 2019), reduce pain (Naugle et al., 2016), and improve function in injured tissue. Similarly, research by (Magliulo et al., 2021) explains that muscles are endocrine organs that when contracted release cytokines called exerkines. Molecules secreted when muscles contract, either in the form of cytokines often called myokines or other peptides, can work as endocrine, paracrine, and autocrine. These cytokines include IL-6, IL-7, IL-8, IL-15, Leukemia inhibitory factor (LIF), Irisin, TNF-α, Fibroblast growth factor (FGF), and BDNF (Ultimo et al., 2018, Tidball, 2011). IL-6 and LIF are thought to influence satellite cell activation through activation of Janus Kinase (JAK)/signal transducer and transcriptional activation 3(STAT3)/cyclin D1 pathways that promote cell cycle activation. Regular exercise stimulates IL-6 as a pro-inflammatory molecule but can also decrease resting systemic levels of pro-inflammatory cytokines and direct the cytokine balance towards anti-inflammatory (Rowe et al., 2022).

Referring to the research by Rowe et al (2022) above, the data of this research also shows that on the 7th day after the intervention, the level of IL-6 in plasma is still above normal caused by exercise which does increase the level of IL-6 in the muscles but with different properties, namely anti-inflammatory (Narazaki & Kishimoto, 2018). In another research, it is stated that IL-6 has 2 roles, both pro-inflammatory and anti-inflammatory. In the innate immune, due to injury, IL-6 is secreted by B-cells which are pro-inflammatory, while in exercise, IL-6 is secreted by myocytes and is anti-inflammatory (Narazaki & Kishimoto, 2018).

In contrast to Cox-1, during muscle injury, the enzyme Cox-2 excessively produces prostaglandin E2 (PGE2) which together with prostaglandins widens blood vessels and blood delivery to injured tissues increasing vascular permeability. This increases peripheral nerve sensitization and pain (Y. Y. Lee et al., 2015). Cox-2 is easily stimulated by inflammatory cytokines such as Interleukin-6, Tumor Necrotic Factor-α, and stress (Attiq et al., 2018). From this research, the decrease in Cox-2 benefits the body to regenerate after injury.

V. CONCLUSION

Exercise is beneficial, not only as part of prevention, treatment, and rehabilitation efforts for chronic diseases but also for post-injury tissue regeneration. The principle of early mobilization with exercise has a strong scientific footing because exercise can reduce inflammatory mediators such as IL-6 and Cox-2. Exercise with isotonic muscle contraction seems to be the main choice compared to isometric muscle contraction.

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