KOMBINASI UPPER LIMB EXERCISE DAN SUPLEMENTASI CREATINE MONOHYDRATE MENINGKATKAN FUNGSI MUSKULOSKELETAL PADA PASIEN KPKBSK

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KOMBINASI *UPPER LIMB EXERCISE* DAN SUPLEMENTASI *CREATINE MONOHYDRATE* MENINGKATKAN FUNGSI MUSKULOSKELETAL PADA PASIEN KPKBSK

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Abstrak

Latar Belakang: *Kanker paru merupakan penyakit saluran pernafasan kronis yang menyebabkan disfungsi otot. Pemberian suplementasi creatine monohydrate yang dikombinasikan dengan olahraga memiliki efikasi dalam meningkatkan lean body mass, kekuatan otot dan fungsi fisik. Penelitian ini bertujuan untuk menganalisis pengaruh pemberian kombinasi suplementasi creatine monohydrate dan upper limb exercise terhadap disfungsi otot muskuloskeletal pada pasien KPKBSK.*

Metode: *Penelitian quasi eksperimental dengan studi pretest posttest pada pasien KPKBSK yang mendapat EGFR TKI dari rawat jalan di RSUD Dr. Moewardi Surakarta pada bulan September - Oktober 2021. Kelompok kombinasi suplementasi creatine monohydrate dengan upper limb exercise (n=15), kelompok dengan suplementasi creatine monohydrate saja (n=16) dan kelompok kontrol (n=15). Lean body mass dalam kilogram dan persentase, 6-minutes walking test, dan kualitas hidup dinilai setelah 8 minggu perlakuan.*

Hasil: *Peningkatan LBM pada kelompok kombinasi sebesar 4,22 ±1,81kg dan 6,38 ±2,48% (p=0,000). Peningkatan yang lebih besar pada 6-minutes walking test pada kelompok kombinasi adalah 104 ± 20,07 meter. Peningkatan kualitas hidup pada kelompok suplementasi creatine monohydrate kombinasi dengan upper limb execise adalah 20,80 ± 10,75. Perubahan nilai LBM, 6-mwt dan QoL pada suplementasi creatine monohydrate dikombinasikan dengan upper limb execise berbeda bermakna dibandingkan dengan kelompok suplementasi creatine monohydrate saja dan kelompok kontrol.*

Kesimpulan: *Ada pengaruh yang lebih besar pemberian kombinasi suplementasi creatine monohydrate dan latihan ekstremitas atas terhadap LBM, 6-MWT, QoL pada pasien NSCLC.*

Kata kunci: *Creatine, olahraga, KPKBSK, LBM, 6-MWT, QoL*

COMBINED UPPER LIMB EXERCISE AND CREATINE MONOHYDRATE SUPPLEMENTATION IMPROVED MUSCULOSKELETAL FUNCTION IN NSCLC PATIENTS

Abstract

Backgrounds: *Lung cancer is a chronic respiratory disease that causes muscle dysfunction. Giving creatine monohydrate supplementation combined with exercise has efficacy in increasing lean body mass, muscle strength, and physical function. This study aims to analyze the effect of a combination of creatine monohydrate supplementation and upper limb exercise on skeletal muscle dysfunction in NSCLC patients.*

Methods: *A quasi-experimental study with a pretest-posttest study on NSCLC patients given EGFR TKI from outpatient at RSUD Dr. Moewardi Surakarta in September - October 2021. The combination group of creatine monohydrate supplementation with upper limb exercise (n=15), the group with creatine monohydrate supplementation only (n=16), and the control group (n=15). Lean body mass in kilograms and percentages, 6-minutes walking test, and quality of life were assessed after 8 weeks of treatment.*

Results: *The increase in LBM in the combination group was 4.22 ±1.81kg and 6.38 ±2.48% (p=0.000). The combination groups have a greater increase in the 6-minutes walking test was 104 ± 20.07 meters. The increase in quality of life in the combined creatine monohydrate supplementation group with upper limb exercise was 20.80 ± 10.75. Changes in the value of LBM, 6-MWT, and QoL in the creatine monohydrate supplementation combined with upper limb exercise were significantly different compared to the creatine monohydrate supplementation only group and the control groups.*

Conclusion: *There is a greater effect of giving a combination of creatine monohydrate supplementation and upper limb exercise on LBM, 6-MWT, and QoL in NSCLC patients.*

Keywords*: Creatine, exercise, NSCLC, LBM, 6-MWT, QoL*

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BACKGROUND

Lung cancer is a malignant originating from the bronchial epithelium or bronchial carcinoma and about 13 percent (%) of all cancer diagnoses and the leading cause of cancer mortalities worldwide. New cases of lung cancer in Indonesia increased more than five times in the last ten years.[1,2] Most patients with NSCLC adenocarcinoma-type have sensitization mutation in exon 19 or 21 (about 45 and 40% of patients, respectively) that activates the tyrosine kinase domain in the EGFR receptor especially among Asians because it has a higher prevalence of EGFR mutations compared to Caucasians. Gefitinib, Erlotinib, and Afatinib are widely prescribed as first-line EGFR tyrosine kinase inhibitors (TKIs) worldwide.[3–5] The use of EGFR-TKI as a first-line treatment has shown a longer progression-free survival (PFS), improved health-related quality of life, and lower side effects treatment-related when compared with standard chemotherapy.[6]

Lung cancer is a chronic respiratory disease that causes impaired ventilation that causes physical inactivation. Cancer patients are exposed to various specific cancer factors that result in the loss of mass and function of muscle, like factor-related to tumor cancer therapy, malnutrition, lack of physical activity, age, and comorbidities. Compensation to reduce symptoms of shortness of breath and fatigue by reducing activity resulting in muscle atrophy so that the vicious cycle keeps going in progress and explains the connection between physical inactivation and worsening of symptoms.[7,8] Loss of skeletal muscle mass is a key manifestation of cancer, associated with decreased quality of life, progressive functional impairment, and a worsened prognosis. Muscle atrophy contributes to weakness, decreased mobility, and fatigue in cachectic patients and could increase the risk of respiratory failure as a common cause of death from cancer.

Cancer-related muscle dysfunction is defined as a measurable disturbance in muscle strength or muscle composition that is independent of the underlying cause in patients diagnosed with cancer. The degree of muscle dysfunction can be measured from muscle strength and muscle composition in the form of lean body mass.[9,10] Upper extremity muscles are very important for manipulating objects and for personal care and affect the quality of life. Peripheral muscle is easily accessible for tissue sampling in changes associated with muscle dysfunction.[11,12] Muscle strength also depends on muscle mass, length, innervation, size, and fiber type.[11]

Walking is a usual activity for all patients except for those with severe disorders. The American thoracic society (2002) recommends the 6-minute walking test to measure the response of therapeutic interventions for cardiorespiratory disease.[13]

Abnormalities of body composition affect all chronic lung diseases. Weight loss of 10% in the last 6 months or 5% in the past month is an important independent predictor of morbidity and mortality in chronic lung disease. Measuring body mass index (BMI) does not accurately reflect body composition changes. Weight is divided into fat mass and fat-free mass (FFM). Fat-free mass (FFM) consists of bone, muscle, vital organs, and extracellular fluid. Lean body mass (LBM) differs from FFM in the form of lipid in the cellular membranes that are included in the LBM but only a small fraction or as much as 3-5% of the total body weight.[14,15]

Muscle mass is maintained by the balance between protein synthesis and breakdown, called protein turnover. Impaired ventilation due to lung cancer causes hypoxemia resulting in anaerobic metabolism. Lactate from anaerobic metabolism is increased and partially converted into glucose through the Cori cycle which requires ATP, causing a decrease in energy which results in muscle dysfunction. Muscle atrophy due to cancer

occurs as a result of an increased inactivation of protein breakdown and suppression of protein synthesis.[19] Data on muscle mass were assessed by dual-energy X-ray absorptiometry (DXA) scan and bioelectrical impedance.

Nutritional supplements have been widely used to increase muscle mass and increase performance. Creatine monohydrate (Cr) is one of the most researched supplements that has efficacy in increasing lean body mass, muscle strength, and physical function. Red meat and fish contain 1–5 grams of creatine addition per day. In sports, creatine has been recognized as the most effective nutritional supplement to increase exercise tolerance, muscle strength, and lean body mass.[16,17]

Creatine monohydrate is distributed to the whole body in tissue such as the brain, eyes, heart muscle, testes, and kidneys. The main site of 95% distribution of creatine monohydrate is skeletal muscle. Muscles are organsclearance for creatine but because creatine istrapped and used inhealthy individual skeletons muscle and patients with muscle dysfunction.[18,19]

Creatine clearance by muscles is affected by creatine transporters such as insulin, catecholamines, IGF-1, and muscle creatine levels. Greater muscle mass will correlate with more transporters and a bigger storage area for creatine. The second elimination track for creatine is through the kidney. A study by Poortmans (2000) reported no renal dysfunction obtained on 9 weeks-supplementation creatine monohydrate.[18–20]

Creatine plays an important role to supply rapid energy during muscle contraction which involves the transfer of a phosphoryl group from *phosphocreatine* (PCr) to adenosine diphosphate (ADP) for regeneration of adenosine triphosphate (ATP) through a reversible reaction catalyzed by *phosphocreatine* kinase (PCK). Creatine is responsible for the transfer of energy from the mitochondria to the cytosol. *Phosphorylcreatine* provides the energy required for muscle contraction to initiate activity and during explosive, short, and high-intensity exercise.[17,21,22]

The study of Roger Harris (1992) showed that oral creatine intake can increase intramuscular creatine content to increase exercise capacity.[22] Study by Buford (2007) reported that creatine as supplement nutrition is most effective to increase exercise tolerance, muscle strength, and LBM.[23] Study by Greenhalf (1995) reported that consumption of creatine 20 grams/day for 5 days can increase more than 20% of muscle creatine in the form of PCr.[17] Study by Hultman (1996) used tissue biopsy to determine total muscle creatine levels showed that there was a decrease in total creatine levels of 6 mmol/kg dm at 14 days after creatine monohydrate supplementation was discontinued.[24]

Cr supplementation in patients with muscle inactivation did not show the expected effect. Olsen (2006) reported that in healthy people, Cr supplementation in combination with progressive resistance training (PRT) strengthened the increasing number of satellite cells and concentration of *myonuclei* in skeletal muscle fibers, thereby facilitating muscle growth and hypertrophy.[25] Creatine monohydrate has also been shown to increase the expression of *myogenin* and other myogenic regulatory factors that regulate the expression of the myosin heavy chain, which affects the content of contractile proteins like actin and myosin.[16,17,26]

Exercise training is widely used as the cornerstone of pulmonary rehabilitation. The goal of the exercise program in chronic respiratory conditions is to optimize lung function in daily activities. The standard pulmonary rehabilitation protocol consists of three sessions of 30 to 90 minutes per week for 6 to 8 weeks consisting of individual aerobic exercise and strength training.[27,28]

Muscle strength resistance training involves specific muscle groups by lifting or pushing weights repeatedly. Endurance training can improve weakness and peripheral muscle

dysfunction in a form of systemic manifestation of CRD. Guidelines by the American Thoracic Society/European Respiratory Society (ATS/ERS) for lungs rehabilitation recommend two tours set with 6-12 reps, the intensity from 50% to 85% is gradually increased, a maximum of two to three times per week.[14,27,29]

Upper and lower extremity flexibility exercises are the most frequently exercised. Flexibility exercises include stretching several major muscle groups such as the calves, hamstrings, quadriceps, biceps, neck, and shoulders. Clinical trials that show the effectiveness of exercise flexibility are still rare. Repair mobility and chest posture in CRD patients are expected to increase vital capacity.[27,30]

Adaptation occurs when a person is following a programming exercise for 2 days or more per week. Anatomical and physiological changes depend on the person's initial level of fitness, the individual's genetic potential for improvement, the chosen exercise, the intensity of the exercise, the duration of the exercise period, and the frequency of exercise. The respiratory system also responds to the stress of exercise. Pulmonary ventilation increases almost instantaneously large through stimulation of the respiratory center in the brainstem.[31–33]

Non-pharmacological modalities of therapy in lung cancer patients are still not widely studied. This study aims to determine the effect of the combination of creatine monohydrate supplementation and upper limb exercise in improving skeletal muscle dysfunction and improving the quality of life in NSCLC patients.

METHOD

Quasi-experiment studies with pretest and post-test control group designs were done to evaluate the lean body mass (kg), lean body mass (%), 6-minutes walking test, and quality of life. The study was carried out at Dr. Moewardi Surakarta from September 2021 to November 2021. The study population was NSCLC patients with EGFR TKI at RSUD Dr. Moewardi Surakarta. The sampling of this research used consecutive sampling. The research subjects were grouped into the treatment group with the combination of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation only, and the control group. Subjects measured the lean body mass with a bioelectrical impedance scale, 6-minutes walking test, and quality of life using a Fact-L questionnaire.

The combination group received an education on how to give creatine monohydrate supplementation and was taught about upper limb exercise. Creatine supplementation monohydrate as much as 5 grams (1 teaspoon) dissolved in 250 ml drinking water and consumed 1x a day. The upper limb exercise is carried out in a sitting position by holding a bottle filled with 600 ml of water then performing elbow flexion and extension movements to train the biceps and triceps muscles, abduction and adduction movements of the upper arms to train the deltoids. The movement is continued by bending the body slightly then raising both hands and bringing them together behind the neck. The next movement is in a lying position and moving both hands ahead. Each set of movements is done for 12 repetitions and repeated up to 5 sets. Upper limb exercise sessions are carried out every day. The supplementation group only received education on how to give the same amount of creatine monohydrate supplementation without giving upper limb exercise treatment. The control group was not given any treatment. All forms of treatment are given every day for 8 weeks. Evaluation of lean body mass, 6-minutes walking test, and quality of life were measured again after 8 weeks. The number of samples required is 15 samples per group.

Inclusion criteria of this study are NSCLC stadium IV patients in hospital Dr. Moewardi Surakarta with targeted therapy for TKI EGFR at least on the second month, shows a minimum

performance status (PS) of 70-80, the patient is willing to take part in the study by signing the informed consent, the patient's age is minimum 18 years, as well as patient, could read and write. The exclusion criteria of this study are patients with impaired consciousness, walking disorders, upper extremity activity disorders, and patients with pneumonia. The criteria for the discontinuity of the study were the subjects did not perform the procedure for 14 days consecutive.

This research was approved by the Ethics Worthiness Committee of the RSDM/Faculty of Medicine, Sebelas Maret University, Surakarta in October 2021. All research data were carried out by the normality test of the distribution of research data. All research data were tested for the normality of research data using the normality Kolmogorov-Smirnov test. The p-value> 0.05 means that the subjects in the study are homogeneous. A difference test is a statistical technique test used to see the difference between treatment samples. Statistical tests on the pre and post-test independent samples were tested using a paired t-test if the data distribution was normal. If the data distribution is not normal then the Mann-Whitney test is used. The next difference test is ANOVA to see the difference among the three groups if the data distribution is normal. If the data distribution is not normal then used the Kruskal-Wallis test. The difference test among the 3 groups was continued with the Bonferroni post hoc test if the data were homogeneous and Games-Howell if the data are non-homogeneous. The limit of the mean if the value of p≤0.05 means significant statistically.

RESULTS

This study was conducted on patients with NSCLC in Dr. Moewardi hospital Surakarta from September 2021 to October 2021. The research subjects were divided into three groups by consecutive sampling which is combination group with creatine monohydrate supplementation with upper limb exercise, the group of creatine monohydrate supplementation only, and the control.

The number of subjects until the end of the study counted 46 subjects, from the total number of samples taken as many as 49 samples were. Three samples were discontinued in the study because the patient passed away. The samples were then divided into 3 groups. The first group consisted of 15 NSCLC patients who received targeted therapy and creatine monohydrate supplementation combined with upper limb exercise. The second group consisted of 16 NSCLC patients who received targeted therapy and creatine monohydrate supplementation only. The third group was the control group, which consisted of 15 NSCLC patients who received targeted therapy. The research data collected were tabulated and then analyzed as follows.

Patients

The research subjects are 46 NSCLC patients consisting of 15 men and 31 women (p-=0.990). The average age in the combination group is 60.7 ± 7.43 years, in the creatine monohydrate supplementation-only group is 58.1 ± 8.16 years and in the control group 53.1 ± 14.17 years (p = 0.135).

The subject consists of 32 people (69,5%) with mutation exon 19 and 14 people (30,5%) with exon 21 mutations (p=0.213). The targeted therapy regimen with Afatinib was 27 people (58.6%), Erlotinib 9 people (19.5%) received Erlotinib and 10 people (21.7%) received Gefitinib with p-value =0.611. The average of EGFR TKI therapy that has been obtained in the combination group is 10.4 ± 9.62 months, in the creatine monohydrate supplementation group only is 11.06 ± 6.77 months and in the control group 13.27 ± 9.03 months (p=0.631).

In the combination group, there were 3 people (6.5%) who had a history of smoking and 12 people (26.1%) without a history of smoking. In the creatine monohydrate supplementation group, 5 people (10.9%) had a history of smoking, and 11

people (23.9%) had no history of smoking. In the control group, there were 4 people (8.7%) who had a history of smoking and 11 people (23.9%) without a history of smoking (p=0.774). All of the subjects have no different statistically p>0.005. The basic characteristics of the research subjects can be seen in table 1.

Table 1. Characteristics of Subjects.

Characteristics	Group			p
	Creatine monohydrate + upper limb exercise	*Creatine monohydrate only*	Control	
Sex				0,99
Men	5 (10,9%)	5 (10,9%)	5 (10,9%)	
Women	10 (21,7%)	11 (34,8%)	10 (21,7%)	
Age	60.7 ±7,43	58,1 ±8,16	53,1 ±14,17	0,135
Exon				0,213
19	9 (19,6%)	10 (21,7%)	13 (28,3%)	
21	6 (13%)	6 (13%)	2 (4,3%)	
Regimen targeted therapy				0,611
Afatinib	11 (23,9%)	8 (17,4%)	8 (17,4%)	
Erlotinib	2 (4,3%)	3 (6,5%)	4 (8,7%)	
Gefitinib	2 (4,3%)	5 (10,9%)	3 (6,5%)	
Duration therapy	10,4 ±9,62	11,06 ±6,77	13,27 ±9,03	0.631
Smoking history				0,774
Smoker	3 (6,5%)	5 (10,9%)	4 (8,7%)	
Non Smoker	12 (26,1%)	11 (23,9%)	11 (23,9%)	

Variables

The variable analyzed in this study is lean body mass, 6-minutes walking test, and quality of life in patients with NSCLC. Lean body mass is assessed in kilograms (kg) and percent (%), a 6-minutes walking test is assessed in meters, and quality of life is assessed by a FACT-L questionnaire in the form of total scores. The results of the different tests using one-way ANOVA on each variable showed that lean body mass and 6-minutes walking test after treatment had significant differences in all three groups, whereas the other variable showed no statistically significant difference (p>0.005). The characteristics of the variables can be seen in table 2.

Table 2. Characteristics of Variables

Variable	Group			p
	Creatine monohydrate + upper limb exercise	*Creatine monohydrate only*	Control	
Lean body mass (pre) [kg]	34,01 ±7,16	32,23 ±6,33	36,53 ±9,55	0,313
Lean body mass (pre) [%]	74,24 ±5,19	72,15 ±8,76	69,17 ±8,11	0,192
Lean body mass (post) [kg]	38,24 ±7,40	33,41 ±6,88	36,29 ±9,15	0,236
Lean body mass (post) [%]	80,63 ±5,57	74,61 ±10,07	68,93 ±8,98	0,002*
6-minutes walking test (pre)	225 ±72,39	206 ±69,23	223 ±76,69	0,729
6-minutes walking test (post)	329 ±70,42	268 ±65,31	268 ±79,38	0,033*
Quality of life (pre)	86 ±20,7	85 ±20,9	96 ±14,6	0,199
Quality of life (post)	107 ±15,89	96 ±20,32	104 ±14,58	0,200

Lean Body Mass

The average value of lean body mass in kg before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 34.01kg ± 7.16; the creatine

monohydrate supplementation group only was 32.23kg ± 6.33; and the control group was 36.53kg ±9.55. Lean body mass average score after treatment on the combination of supplementation creatine monohydrate with upper limb exercise group was 38.24kg ± 7.40; in the group supplementation creatine monohydrate only was 33.41kg ±6.88; and in the control group was 36.29kg ± 9.15. There is an increase in lean body mass in the combination group of creatine monohydrate supplementation with upper limb exercise and creatine monohydrate supplementation 4.22kg ±1.81 (p=0.000), 1.17kg ± 3.45 (p=0.192). The decrease in lean body mass occurred in the control group -0.24kg ± 1.87 (p=0.623). Change in lean body mass is statistically significant if p<0.005 occurred in the combination group of creatine monohydrate supplementation with upper limb exercise.

Another assessment for lean body mass (%) was obtained from the total body weight. The average value of lean body mass (%) before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 74.24% ± 5.19; in the supplementation group creatine monohydrate is 72.15% ±8.76, and in the control group is 69.17% ± 8.11. The average value of lean body mass after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise obtained 80.63% ± 5.57; in the creatine monohydrate supplementation only group it was 74.61% ± 10.07 and in the control group was 68.93% ± 8.98.

The difference in the addition of lean body mass in the combination group of creatine monohydrate supplementation with upper limb exercise and creatine monohydrate supplementation only was 6.38% ± 2.48 (p=0.000), 2.46% ± 7.34 (p=0.200), and there is the decrease of lean body mass on group control -0.23% ± 2.32 (p=0.699). Changes were statistically significant if p<0.005 occurred in the combination group of creatine monohydrate supplementation with upper limb exercise. The differences can be seen in table 3.

Table 3. Lean body mass difference pair-test among groups

Groups	*Lean body mass*			
	Pre	Post	Difference	*p-value*
Creatine monohydrate + upper limb exercise	34,01kg ±7,16	38,24kg ±7,40	4,22kg ±1,81	0.000*
	74,24% ±5,19	80,63% ±5,57	6,38% ±2,48	0.000*
Creatine monohydrate only	32,23kg ±6,33	33,41kg ±6,88	1,17kg ±3,45	0.192
	72,15% ±8,76	74,61% ±10,07	2,46% ±7,34	0.200*
Control	36,53kg ±9,55	36,29kg ±9,15	-0,24kg ±1,87	0.623
	69,17% ±8,11	68,93% ±8,98	-0,23% ±2,32	0.699

The multivariate test showed p<0.005 means there was a significant difference between the three groups. The homogeneity test on lean body mass in kg (p=0.084) was obtained at p>0.05, which means the data was homogeneous so it continued with the post hoc Bonferroni test. The post hoc test results for lean body mass (kg) stated that the combination of creatine monohydrate supplementation with upper limb exercise was significantly different compared to the creatine monohydrate supplementation group and the control group.

Homogeneity test on lean body mass in % (p=0.01) obtained p<0.05, meaning that the data was not homogeneous it continued with the Games-Howell post hoc test. The post hoc test results stated that the combination of creatine monohydrate supplementation with upper limb exercise was not significantly different compared to the creatine monohydrate supplementation group only but significantly different from the control.

Table 4. Post hoc test results on changes in lean body mass

				Mean Difference	Sig.
Lean Body Mass (kg)	Bonferroni	Creatine monohydrate + upper limb exercise	Creatine monohydrate only	3,057	0,005*
			Control	4,494	0,000*
		Creatine monohydrate only	Creatine monohydrate + upper limb exercise	-3,057	0,005*
			Control	1,436	0,364
		Control	Creatine monohydrate + upper limb exercise	-4,494	0,000*
			Creatine monohydrate only	-1,436	0,364
Lean Body Mass (%)	Games-Howell	Creatine monohydrate + upper limb exercise	Creatine monohydrate only	3,9220	0,136
			Control	6,621	0,000*
		Creatine monohydrate only	Creatine monohydrate + upper limb exercise	-3,9220	0,136
			Control	2,699	0,363
		Control	Creatine monohydrate + upper limb exercise	-6,621	0,000*
			Creatine	-2,699	0,363

monohydrate only

6-Minutes Walking Test and Quality of Life

The average value of the 6-minutes walking test before treatment in the combined creatine monohydrate supplementation group with upper limb exercise was 225 meters ± 72.39, in the creatine monohydrate supplementation group, only 206 meters ± 69.23, and in group control is 223 meters ± 76.69. The average value of the 6-minutes walking test after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 329 meters ± 70.42, in the creatine monohydrate supplementation group only was 268 meters ± 65.31, and in the control group is 268 meters ± 79.38. The increase of the 6-minutes walking test in the combination group of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation-only group, and control is 104 meters ± 20.07 (p=0.000), 62 meters ± 28.69 (p=0.000), and 45 meters ± 19.89 (p=0.000) respectively.

The mean score of the quality of life before treatment in the combination group of creatine monohydrate supplementation with upper limb exercise obtained 86 ± 20.7; in the creatine monohydrate supplementation group only was 85 ± 20.9, and in the control group was 96 ± 14.6. The average value of quality of life after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 107 ± 15.89; in the creatine monohydrate supplementation-only group was 96 ± 20.32, and in the group control was 104 ± 14.58. The difference in the addition of quality of life in the combination group of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation-only group, and control group each 20.80 ± 10.75; 10.62 ± 7.30; and 7.26 ± 4.81 respectively in the three groups p=0.000, which mean that there was a statistically significant change in the quality of life score. Both of 6-minutes walking test and quality of life have larger additions in the combination of creatine monohydrate supplementation with the upper limb exercise group compared to the creatine monohydrate supplementation-only group, and the control group. The change is statistically significant if $p < 0.005$ occurred in the three groups. The differences can be seen in table 5.

Table 5. Paired test of 6-minutes walking test and Quality of Life

	6-minutes walking test			
	Pre	Post	Diff	*p-value*
Creatine monohydrate + upper limb exercise	225 ±72,39	329 ±70,42	104 ±20,07	0.000
Creatine monohydrate only	206 ±69,23	268 ±65,31	62 ±28,69	0.000
Control	223 ±76,69	268 ±79,38	45 ±19,89	0.000
	Quality of life			
	Pre	Post	Diff	*p-value*
Creatine monohydrate + upper limb exercise	86 ±20,7	107 ±15,89	20,80 ±10,75	0,000
Creatine monohydrate only	85 ±20,9	96 ±20,32	10,62 ±7,30	0,000
Control	96 ±14,6	104 ±14,58	7,26 ±4,81	0,000

The statistical test for changes in the 6-minutes walking test and quality of life score was followed by the Kolmogorov-Smirnov test and continued with the homogeneity test. The homogeneity test on the 6-minute walking test was found p>0.05 (p=0.173) means that the data was homogeneous. The value of quality of life (p= 0.01) obtained p <0.05 means that the data was not

homogeneous. Both data followed by a multivariate test showed the value of p <0.005 meaning there was a significant difference in the three groups and followed by a post hoc test Bonferroni for the 6-minutes walking test and Games-Howell for quality of life. The post hoc test results stated that the combination of creatine monohydrate supplementation with upper limb exercise was significantly different compared to the creatine monohydrate supplementation group and the control group. The creatine monohydrate supplementation group only was not significantly different from the control group. It means combination groups have a superior effect on the 6-minutes walking test and quality of life. The results can be seen in table 6.

Table 6. Post hoc test results on changes in 6-minutes walking test and Quality of life

				Mean Difference	Sig
6-minutes walking test	Bonferroni	Creatine monohydrate + upper limb exercise	Creatine monohydrate	42,396	0,000*
			Control	58,533	0,000*
		Creatine monohydrate only	Creatine monohydrate + upper limb exercise	-42,396	0,000*
			Control	16,138	0,185
		Control	Creatine monohydrate + upper limb exercise	-58,533	0,000*
			Creatine monohydrate only	-16,138	0,185
				Mean Difference	Sig
Quality of life	Games-Howell	Creatine monohydrate + upper limb exercise	Creatine monohydrate	10,175	0,014*
			Control	13,533	0,001*
		Creatine monohydrate only	Creatine monohydrate + upper limb exercise	-10,175	0,014*
			Control	3,358	0,298
		Control	Creatine monohydrate + upper limb exercise	-13,533	0,001*
			Creatine monohydrate only	-3,358	0,298

DISCUSSION

This research is a quasi-experimental study to determine the effect of the combination of creatine monohydrate supplementation and upper limb exercise on muscle dysfunction and quality of life in patients with NSCLC. Muscle dysfunction assessment covers lean body mass and a 6-minutes walking test. NSCLC patients that met the inclusion criteria from September 2020 – to November 2020 count 49 patients. 3 patients discontinued the study post-treatment because of passed away and statistical analysis was carried out on 46 research subjects. A total of 3 patients died, namely 2 patients from the combination group of creatine monohydrate supplementation and upper limb exercise and 1 patient from the control group.

Analysis of Subject Characteristics Study

The research subjects were 46 patients with NSCLC consisting of 15 (32.6%) males and 31 (67.4%) females. These data are similar to several studies including studies by Zhang in the year 2016 stated that EGFR mutation is higher in a woman (43.7%) compared to men (24%).[4] Average age of subjects in creatine monohydrate supplementation combined with upper limb exercise group was 60.7 ± 7.43 years, the creatine monohydrate supplementation-only group was 58.1 ± 8.16 and in the control group 53.1 ± 14.17. A study by Devi in 2021 showed that NSCLC patients at dr. Moewardi is mostly 60-70 years.[34]

There are 12 subjects (26.1%) who have a smoking history and 34 subjects (73.9%) have no smoking history. Other criteria with exon 19 mutation happened in 32 people (69.6%) and exon 21 mutations in 14 people (30.4%). These data are similar to the study by Zhang (2016) that patients with NSCLC without a smoking history were 49.3% compared to those with no smoking history by 21.5%. Most of the research subjects with exon 19 mutations were 75.21%.[4] The study by Hsu et al (2018) reported that EGFR mutations occur at some point between exons 18 and 21. Exon 19 deletions and mutations point L858R on exon 21 is a general detected type mutation and accounted for 50% and 40% of all patients, respectively. The two types of mutations are sensitization mutations and tumors with these mutations are sensitive to EGFR tyrosine kinase inhibitors (TKI).[6]

Research subjects received Afatinib as many as 27 people (23.9%), Erlotinib as many as 9 people, and Gefitinib as many as 10 people (4.3%). Gefitinib and erlotinib are reversible EGFR TKIs. Both drugs are quinazoline-based derivatives and act as ATP competitive inhibitors which tied tyrosine kinase EGFR. Both drugs show activity in inhibition against EGFR wildtype and EGFR mutation sensitivity. Afatinib is a second-generation EGFR TKI which is an irreversible EGFR TKI. Its structure is similar to that of Gefitinib or Erlotinib with a quinazoline backbone. The use of EGFR TKI as a first-line treatment show progression-free survival (PFS), longer health-related quality of life improvements, and lower treatment-related side effects when compared with standard chemotherapy. Many clinical guidelines recommend that all patients with EGFR mutations causing sensitization receive first-line treatment with this drug, in addition to all patients with advanced or metastatic CPCBS.[6] Although different EGFR TKIs have different efficacy or toxicity profiles in NSCLC patients with EGFR mutations, it is still uncertain. A recent meta-analysis showed that Erlotinib, Gefitinib, Afatinib, and Icotinib had equivalent efficacy with different toxicity profiles for NSCLC patients with EGFR mutations.[35]

Analysis of the effect of creatine monohydrate supplementation combined with upper limb exercise and creatine monohydrate supplementation-only on lean body mass

The average value of initial lean body mass in the combination group of creatine monohydrate supplementation with upper limb exercise was 34.01kg ± 7.16 and 74.24% ± 5.19, respectively.

The average baseline lean body mass in the creatine monohydrate supplementation-only group was 32.23kg ± 6.33 and 72.15% ± 8.76. The average initial lean body mass in the control group was 36.53kg ± 9.55 and 69.17% ± 8.11, respectively. There was no significant difference in the average lean body mass value in kg or percentage (p=0.313 and 0.192). The average value of lean body mass after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 38.24kg ± 7.40 and 80.63% ± 5.57. The average lean body mass after treatment in the creatine monohydrate supplementation group was 33.41kg ± 6.88 and 74.61% ± 10.07, respectively. The average lean body mass after treatment in group control was 36.29kg ±9.15 and 68.93% ± 8.98.

No significant difference mean in kg lean body mass (p=0.236) but there is a significant difference in means in the lean body mass percentage (p=0.002).

The difference in the addition of lean body mass in the combination group of creatine monohydrate supplementation with upper limb exercise was 4.22kg ± 1.81 and 6.38% ± 2.48, respectively. In the creatine monohydrate supplementation-only group 1.17kg ± 3.45 and 2.46% ± 7.34. There was a decrease in lean body mass in the control group -0.24kg ± 1.87 and -0.23% ± 2.32. The different values of lean body mass in the combination group of creatine monohydrate supplementation with upper limb exercise in kg and the percentage obtained the value of p <0.05 (p = 0.000) mean change in lean body mass significant. Additional value of lean body mass on creatine monohydrate supplementation-only group no significant with p = 0.192 and p = 0.200. The addition was greater in the combination group of creatine monohydrate supplementation with upper limb exercise and was statistically significant. The decrease in the control group was not statistically significant in kg and percentage with p = 0.623 and p = 0.699. There is a significant effect of the combination of creatine monohydrate supplementation with upper limb exercise on lean body mass.

A study by Xiao et al (2017) based on the National data Health and Nutrition Examination Survey (NHANES) III obtained the median value of % body fat is 24% in men and 40% in women aged less than 40 years with body mass index normal, as well as 28% for men and 45% for women aged >70 years. The normal value for lean body mass is 70-90% of total body weight.[36] Additional lean body mass on a combination of creatine monohydrate supplementation with upper limb exercise group and creatine monohydrate supplementation-only showed a normal value so that supplementation with creatine monohydrate can help improve lean body mass clinically assisted by a combination of upper limb exercise so that the addition of lean body mass increased.

The research data according to a study by Olsen in 2006 reported that in healthy humans, creatine monohydrate supplementation in combination with progressive resistance training (PRT) strengthened the increase in satellite myocytes and concentration of myonuclei in skeletal muscle fibers, thereby facilitating muscle growth and hypertrophy.[25] Other studies by Sakkas in 2009 demonstrated that creatine monohydrate supplementation augmented the effects of PRT on muscle strength, energy, and body composition in 27 immunocompromised patients.[37] Studies related to supplementation of creatine monohydrate by Jatoi (2017) failed to show the benefit which can be demonstrated in lean body mass, muscle strength or function. Inactive muscle conditions can cause decreased absorption of creatine monohydrate thereby interfering with the effects of creatine supplementation on lean body mass and muscle strength.[38]

Analysis of the effect of creatine monohydrate supplementation combined with upper limb exercise and creatine monohydrate supplementation-only on a 6-minutes walking test

Measurements of the 6-minutes walking test were carried out in the three study groups. The mean score of the initial 6-minute walking test in the combination group of creatine monohydrate supplementation with upper limb exercise obtained 225 ± 72.39, the average 6-minutes walking test in the creatine monohydrate supplementation-only group is 206 ± 69.23, and the average 6-minutes walking test in the control group was 223 ± 76.69 with p = 0.729 after the one-way ANOVA test showed no significant difference between groups. The average value of the 6-minutes walking test after treatment in the combination group of creatine monohydrate supplementation with upper limb exercise was 329

± 70.42, the average 6-minutes walking test after treatment in the group of creatine monohydrate supplementation-only was 268 ± 65.31 and the average 6-minutes walking test after treatment in the control group was 268 ± 79.38 with p = 0.033 after one-way ANOVA test showed there was difference mean among groups. The difference in the addition of a 6-minutes walking test in the combination group of creatine monohydrate supplementation with upper limb exercise, creatine monohydrate supplementation-only group, and control group each 104 ±20.07, 62 ± 28.69, and 45 ± 19.89 respectively with each group conducted paired t-test and obtained p = 0.000 indicates there is a significant change.

The measurement of the 6-minute walking test was carried out by the recommendations of the American thoracic society in 2002 as a measure of response to therapeutic interventions for cardiorespiratory disease.[13] The research data is similar to a study by Peddle-McIntyre in 2019 stated that patients who exercised a 6-minute walking test were 63 meters higher than 122 meters.[9] Another study by Edbrooke 2019 showed a change in the 6- minute walking test after the first 8 weeks of the intervention there was a difference between the control and intervention groups of 48 m.[29]

Analysis of the effect of creatine monohydrate supplementation combined with upper limb exercise and creatine monohydrate supplementation only on quality life

The average value of initial quality of life in the combination group of creatine monohydrate supplementation with upper limb exercise was 86 ± 20.7, and the average quality of life was 86 ± 20.7. The initial on the creatine monohydrate supplementation-only group was 85 ± 20.9 and the average initial quality of life in the control group was 96 ± 14.6. all three groups showed no significant difference p=0.199. The average quality of life after treatment in the combination of creatine monohydrate supplementation with upper limb exercise group obtained 107 ± 15.89, the average quality of life after treatment in the creatine monohydrate supplementation group was 96 ±20.32 and the average quality of life after treatment in the control group was 104 ±14.58. There was no significant difference between the three groups, p=0,200.

The different quality of life in creatine monohydrate supplementation with upper limb exercise, the creatine monohydrate supplementation-only group, and the control group was 20.8 ± 10.75; 10.62 ± 7.30; and 7.26 ± 4.81 respectively. The three groups showed different significant mean p=0.000. The data was similar to a study by Peddle-McIntyre in 2019 that reported that exercise in advanced lung cancer patients increased health-related quality of life (HRQoL) by 13.0 (p = 0.005).[9] Another study by Gerritsen in 2016 reported that exercise intervention improved the quality of life in cancer patients significantly by 5.55 (SD 3.19-7.90) with p<0.001.[39]

Comparative analysis of the effect of creatine monohydrate supplementation combined with upper limb exercise, creatine monohydrate supplementation-only, and control on lean body mass, 6-minutes walking test, and quality life

Research data in the form of changes in lean body mass, 6-minutes walking test, and quality of life in the combination group of creatine monohydrate supplementation and upper limb exercise, creatine monohydrate supplementation-only, and the control group were tested for normality with the Kolmogorov-Smirnov test, and obtained lean data body mass and 6- minutes walking test distributed normally each p-value = 0.200 and p = 0.071 while the quality of life was not normally distributed (p = 0.000). The homogeneity test showed that the lean body mass and 6-minute walking test data were homogeneous with p-value = 0.084 and p = 0.173, respectively. Quality of life data in the study showed that the data was not homogeneous with

a p-value = 0.001. Homogeneity test affected post hoc test after one-way test ANOVA.

Lean body mass, 6-minute walking test, and quality of life of research subjects showed significant numbers after the one-way ANOVA test with a p-value = 0.000 at that three variables. Post hoc test on the lean body mass and 6- minutes walking test data using Bonferroni. The results of the Bonferroni test on lean body mass data showed significantly different results between the combination group of creatine monohydrate supplementation with upper limb exercise, compared to the creatine monohydrate supplementation-only group (p=0.005) and the control group (p=0.000). There was no significant difference between the creatine monohydrate supplementation-only group with the control group (p=0.364). Bonferroni test results on 6-minutes walking test data obtained different means between a combination of creatine monohydrate supplementation with upper limb exercise group, compared to the creatine monohydrate supplementation-only group (p=0.000) and the control group (p=0.000). There was no significant difference between the creatine monohydrate supplementation group and the control group (p=0.185). Post hoc test on the quality of life data used the Games-Howell test and obtained significantly different results among the combination of creatine monohydrate supplementation with the upper limb exercise group, compared with the creatine monohydrate supplementation-only group (p=0.014) and with the control group (p=0.001). There was no significant difference between the creatine monohydrate supplementation group and the control group (p=0.298). The results were consistent with a study by Sakkas (2009) showed that supplementation of creatine monohydrate augmented the effects of PRT on muscle strength, energy, and body composition in 27 immunocompromised patients, and the Jatoi study (2017) that supplementation with creatine monohydrate only failed to show any demonstrable benefit in lean body mass, strength or muscle function.[37,38]

CONCLUSION

Creatine monohydrate supplementation and upper limb exercise affect the lean body mass, 6-minutes walking test, and quality of life in NSCLC patients. A combination of creatine monohydrate supplementation and upper limb exercise has superior effects compared to creatine monohydrate only and control.

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