Curcumin: A compound in turmeric that has the potential to reduce Nuclear Factor-Kappa Beta (NF-kB), Tumor Necrosis Factor-Alpha (TNF-a) levels, and pain intensity after high-intensity physical exercise

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Abstract

Purpose The purpose of this study was to analyze and prove the effect of curcumin on NF-kB, TNF-a levels, and pain intensity after high-intensity physical exercise.

Method This experimental study used a pre and post-control group design. Research subjects were selected using a purposive sampling technique and then the subjects were divided into 2 groups, namely group (K1) with placebo administration and group (K2) with 400 mg dose of curcumin. A total of 20 healthy men aged between 20-30 years participated in this study. On the first day, all subjects took data on the characteristics of research subjects, then warmed up, and then the subjects did a high-intensity physical exercise in the form of squad and leg press exercises with an intensity of 80-90% of maximum abilities. The exercise was carried out in 4 sets for each form of exercise and rest between sets for about 1 minute. On the second day, after 24 hours, all subjects measured pain intensity and took pre-test blood samples, then were given interventions based on their respective groups. On the third day, after 24 hours, all subjects took pain intensity measurements and took post-test blood samples. Measurement of pain intensity using the Visual Analytical Scale (VAS) and blood samples were analyzed in the laboratory using the ELISA method to examine levels of NF-kB and TNF-a. After the data was obtained, the data were analyzed using the IBM SPSS version 26 application.

Results The results of this study reported that the group that was given curcumin after high-intensity physical exercise was able to significantly reduce levels of NF-kB, TNF-a, and pain intensity (*$p<0.05$) compared to the placebo group.

Conclusions We believe that the main cause of muscle soreness is the uncontrolled increase of pro-inflammatory cytokines after high-intensity physical exercise. Since the reduction in pain intensity after high-intensity exercise is necessary to support bodily functions, we highly recommend the use of curcumin which has many positive benefits for exercisers.

Introduction

High-intensity physical exercise such as resistance training is an important component of an overall fitness regimen for athletes and recreationally active people [1]–[3]. High-intensity physical exercise is good for increasing lean muscle mass, but Exercise Induced Muscle Damage (EIMD), Delayed Onset Muscle Soreness (DOMS), can limit performance after a training session [4]–[7].

Several studies have reported that muscle pain reaches its peak 24 hours after exercise [8]–[11]. In connection with this phenomenon, currently, around 30 million people worldwide who experience DOMS are usually treated with non-steroidal anti-inflammatory drugs (NSAIDs) [12], [13]. Giving NSAIDs after exercise has the effect of inhibiting hypertrophy and muscle strength. resulting in giving NSAIDs will actually negate the results of the exercise performed [14].

High-intensity physical exercise will increase Nuclear Factor-kappa Betta (NF-κB) signaling so that it will trigger inflammation [15]. Meanwhile, muscle pain is caused by increased levels of pro-inflammatory cytokines, namely Tumor Necrosis Factor Alpha (TNF-a) in the blood in response to muscle damage [16]. TNF-α at the correct levels will provide protection and healing, but at excessive levels, it will cause tissue damage [17].

Other alternative solutions need to be sought to reduce complaints of muscle pain, but still not interfere with the response of muscle growth after exercise. One of the natural ingredients contained in turmeric is curcumin. Curcumin is known for its active compounds that have anti-inflammatory activity [18]. Curcumin is able to inhibit inflammation by modulating NF-κB signals and blocking TNF-α signals by activating protein responses in muscles [19], [20]. The anti-inflammatory activity of curcumin also inhibits the production of pro-inflammatory eicosanoids which include prostaglandins and leukotrienes [21]–[23].. Curcumin has been widely used to increase endurance and VO2 max [24]. In addition, curcumin has been widely used in the medical world to accelerate wound healing [25]. Until now, curcumin has never been reported to cause post-exercise side effects, but the effect of curcumin on reducing muscle pain is unknown by reducing NF-κB and TNF-α signals due to inflammation after high-intensity physical exercise in untrained people.

The purpose of this study was to analyze and prove the effect of curcumin on NF-κB levels, TNF-α levels, and pain intensity after high-intensity physical exercise.

Methods

Study Design

This experimental study used a pre and post-control group design. The research subjects were selected using a purposive sampling technique and then the subjects were divided into 2 groups, namely group (K1) with placebo administration and group (K2) with curcumin administration.

Subjects

A total of 20 healthy men participated in this study (subject characteristics are shown in table 1). The inclusion criteria in this study were men aged 20 to 30 years, with normal BMI, and not trained in sports. Exclusion criteria in this study were subjects under 20 years of age and abnormal blood pressure before physical exercise. The criteria for dropping out in this study were consuming coffee, consuming foods containing turmeric, consuming non-steroidal anti-inflammatory drugs (NSAIDs), and doing massage. research subjects received instructions about research procedures and signed a written consent willing to become research subjects.

Procedure

1. In the beginning, we prepared administration such as ethical eligibility permits and permits for borrowing facilities and infrastructure

2. We screened respondents who were used as research subjects based on inclusion and exclusion criteria and filled out the form willing to become research subjects (Informed Consent) by research subjects.
3. Subjects were divided into two groups, namely the group receiving a placebo and the group receiving curcumin. Placebo was given in the form of empty capsules and curcumin was given at a dose of 400 mg.
4. On the first day, all subjects collected data on the characteristics of the research subjects, then did a warm-up, and then the subjects did physical exercises in the form of squad exercises and leg presses with an intensity of 80-90% of their maximum ability. Exercise is done 4 sets of each form of exercise and rest between sets of about 1 minute.
5. The second day, after 24 hours, all subjects measured pain intensity and took pre-test blood samples to measure NF-kB levels, TNF-a levels, then administer interventions based on each group.
6. On the third day, after 24 hours, all subjects measured pain intensity and took post-test blood samples to measure NF-kB levels, and TNF-a levels..
7. Blood samples were analyzed in the laboratory using the ELISA method with catalog numbers Human NF-kB ELISA kit E0690Hu and Human TNF-a ELISA kit E0082Hu.

Statistical analysis

Statistical analysis in this study used the IBM SPSS version 26 application, a descriptive test was performed to obtain the mean, standard deviation and standard error. Furthermore, the normality test was carried out using the Shapiro-Wilk method, if the data were normally distributed the different test was carried out using the paired t-test and independent t-test, but if the data was not normally distributed, the difference was carried out using the Wilcoxon signed rank test..

Ethics

This research protocol has been declared ethical in accordance with 7 (seven) WHO 2011 standards, namely 1) social value, 2) scientific value, 3) distribution of burdens and benefits, 4) risk, 5) seduction / exploitation, 6) confidentiality and privacy 7) Approval after explanation, which refers to the 2016 CIOMS guidelines. This is shown by the fulfillment of indicators for each standard. Declaration of ethics was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga with registration number (No.118/EC/KEPK/FKUA/2022).

Results

Data on the characteristics of the research subjects are shown in Table 1.

Table 1
Characteristics of research subjects

Data	Group	N	$\bar{x}$±SD	Shapiro-Wilk	p-value
Age	K1	10	22.60±1.83	0.149	0.389
	K2	10	23.30±1.70	0.850	
Height	K1	10	166.95±4.46	0.891	0.179
	K2	10	169.80±4.64	0.243	
Weight	K1	10	63.55±9.11	0.823	0.938
	K2	10	63.20±10.68	0.386	
BMI	K1	10	23.13±4.20	0.046	0.173
	K2	10	21.70±3.17	0.477	
Body temperature	K1	10	36.56±0.26	0.184	0.619
	K2	10	36.47±0.49	0.523	
systolic	K1	10	123.00±6.27	0.475	0.355
	K2	10	119.80±8.62	0.987	
Diastolic	K1	10	75.30±6.66	0.100	0.385
	K2	10	71.60±11.31	0.385	
Pulse	K1	10	84.70±5.45	0.053	0.165
	K2	10	88.70±6.83	0.779	

In the table above, only BMI K1 data is not normally distributed, so the Wilcoxon Signed Ranks Test is used for different tests. All data from the table above did not differ significantly in each group.

Curcumin lowers NF-kB Levels

Table 2
Results of the Normality Test for NF-kB Levels

Data	Group	Shapiro-Wilk	
		n	p-value
NF-kB Levels (Pre-test)	K1	10	0.461
	K2	10	0.988
NF-kB levels (Post-test)	K1	10	0.272
	K2	10	0.990
delta_ NF-kB	K2	10	0.988
	K2	10	0.990
Information:			
P > 0.05 = Data is normally distributed			

The results of the analysis of NF-kB levels between the pre-test and post-test in each group are presented in Fig. 1.

Table 4.5
NF-kB Level Different Test Results

Metode Uji Beda	**Group**	**P**
Paired t-test	K1 (pre-test and post-test)	0.593
	K2 (pre-test and post-test)	0,030*
Independent t-test	Delta K1 and K2	0,387
Information		
*There is a significant difference in the Paired test (p < 0.05)		

Curcumin lowers TNF-a levels

Table 4.2
Normality Test Results for TNF-a Levels

Data	Group	Shapiro-Wilk	
		n	p-value
TNF-a levels (Pre-test)	K1	10	0.159
	K2	10	0.737
TNF-a levels (Post-test)	K1	10	0.060
	K2	10	0.477
delta_TNF-a	K2	10	0.737
	K2	10	0.477
Information:			
P > 0.05 = Data is normally distributed			

The results of the analysis of TNF-a levels between the pre-test and post-test in each group are presented in Fig. 2.

Table 4.3
TNF-a Levels Different Test Results

Difference Test Method	**Group**	**P**
Paired t-test	K1 (pre-test and post-test)	0.089
	K2 (pre-test and post-test)	0,016*
Independent t-test	Delta K1 and K2	0,007**
Information		
*There is a significant difference in the Paired test (p < 0.05)		
** There is a significant difference in the Independent t-test (p < 0.05)		

Curcumin reduces Pain Intensity

Table 4.6
Pain Intensity Normality Test Results

Data	Group	Shapiro-Wilk	
		n	p-value
Pain Intensity (Pre-test)	K1	10	0.478
	K2	10	0.051
Pain Intensity (Post-test)	K1	10	0.140
	K2	10	0.426
delta_ Pain Intensity	K2	10	0.051
	K2	10	0.426
Information:			
P > 0.05 = Data is normally distributed			

The results of the analysis of pain intensity between the pre-test and post-test in each group are presented in Fig. 4.3.

Table 4.7
Pain Intensity Different Test Results

Difference Test Method	**Group**	**P**
Paired t-test	K1 (pre-test and post-test)	0.454
	K2 (pre-test and post-test)	0,000*
Independent t-test	Delta K1 and K2	0,000**
Information		
*There is a significant difference in the Paired test (p < 0.05)		
** There is a significant difference Independent t-test (p < 0.05)		

Discussion

This study was conducted to analyze the effect of curcumin on levels of NF-kB, TNF-a, and pain intensity after high-intensity physical exercise..

We observed that the placebo group did not significantly decrease NF-kB, TNF-a levels and pain intensity after high-intensity physical exercise, while the 400 mg curcumin group significantly reduced NF-kB, TNF-a levels, and pain intensity. painful. Our research answer and confirm a literature study reported findings that curcumin has a positive effect on inflammatory responses [16], [26]. High-intensity physical exercise,

especially with eccentric movements, will result in muscle damage and inflammatory response [27], [28].. Eccentric movements contribute to high mechanical stress and produce bone extracellular matrix fragments that are recognized by receptors expressed by innate immune cells [27]. Cell activation mediated by this process stimulates NF-kB activation [29].

A theory reports that NF-kB plays a role in controlling inflammation, especially in the secretion of pro-inflammatory cytokines such as TNF-a and IL-6 [27]. In this regard, we believe that the main cause of muscle pain is due to an uncontrolled increase in pro-inflammatory cytokines such as TNF-a for several days after high-intensity physical exercise. In the case of exercise-induced muscle damage, a histological study showed that neutrophils enter the muscles and accumulate in the damaged area from 1 to 24 hours after exercise [30]. In addition, muscle damage is characterized by ultrastructural disturbances of the muscles which increase the release of inflammatory cytokines by macrophages [27]. Neutrophils and pro-inflammatory cytokines that interact with each other aim to control the pro-inflammatory response when muscle damage occurs [31]. On the other hand, while pro-inflammatory cytokines increase, macrophages also release anti-inflammatory cytokines that contribute to muscle recovery and regeneration [32].

We believe the role of NF-kB is the therapeutic goal of curcumin in inflammation because of the importance of NF-kB in the regulation and expression of TNF-a which is a cause of muscle pain. Our research findings are supported by an experimental study on the effect of curcumin on NF-kB expression in rats induced by drinking ethanol (Fatolahi et al. 2020). In that study, curcumin can significantly reduce NF-kB levels. In addition, a study reported that curcumin is able to attenuate osteoarthritis through the NF-kB pathway [33]. Curcumin is one of the natural ingredients that have anti-inflammatory activity [26], [34]. A recent literature study reported that curcumin works by suppressing the secretion of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-17, and TNF-a [35]. Research on the effect of curcumin on TNF-a levels after exercise is perhaps limited. However, on the other hand, we found a study that reported that there was no significant reduction in TNF-a levels given curcumin at a dose of 1500 mg/day for 28 days after aerobic exercise in trained men [36]. We analyzed from this study that the ineffective effect of curcumin is probably due to aerobic exercise which is classified as moderate exercise intensity so it does not trigger post-exercise inflammation. In this regard, what distinguishes this research is that the subjects involved are people who are not trained and the exercises are carried out with high intensity. This is a strong foundation that physical exercise performed at high-intensity results in muscle damage and triggers an increase in pro-inflammatory cytokines such as TNF-a and IL-6 in the blood [16], [26]. On the other hand, at the right levels, TNF-a will provide protection and healing, but at excessive levels, TNF-a will cause tissue damage and trigger muscle pain [11].

In summary, interesting new findings in this study reported that curcumin given at a dose of 400 mg/day was able to reduce NF-kB levels, TNF-a, and pain intensity after high-intensity physical exercise. Based on laboratory tests that we have done, we believe the reduction in pain intensity occurs due to the anti-inflammatory effect of curcumin which is able to modulate NF-kB signals and blockade TNF-a signals. Meanwhile, we carefully all aspects of research and measurement during the research. We believe that

the strengths of these findings outweigh our shortcomings in the study. In future studies, we hope to examine the effects of curcumin on other inflammatory biomarkers.

Conclusion

Giving curcumin at a dose of 400 mg after high-intensity physical exercise was able to reduce levels of NF-kB, TNF-a and pain intensity after high-intensity physical exercise. Since reducing pain intensity after high-intensity exercise is necessary to support bodily functions, we highly recommend using curcumin which has many positive benefits for sports enthusiasts.

Declarations

Conflict of interest The authors declare no conflict of interest

Ethical approval This research protocol has been declared ethical in accordance with 7 (seven) WHO 2011 standards, namely 1) social value, 2) scientific value, 3) distribution of burdens and benefits, 4) risk, 5) seduction / exploitation, 6) confidentiality and privacy 7) Approval after explanation, which refers to the 2016 CIOMS guidelines. This is shown by the fulfillment of indicators for each standard. Declaration of ethics was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga with registration number (No.118/EC/KEPK/FKUA/2022).

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Figures

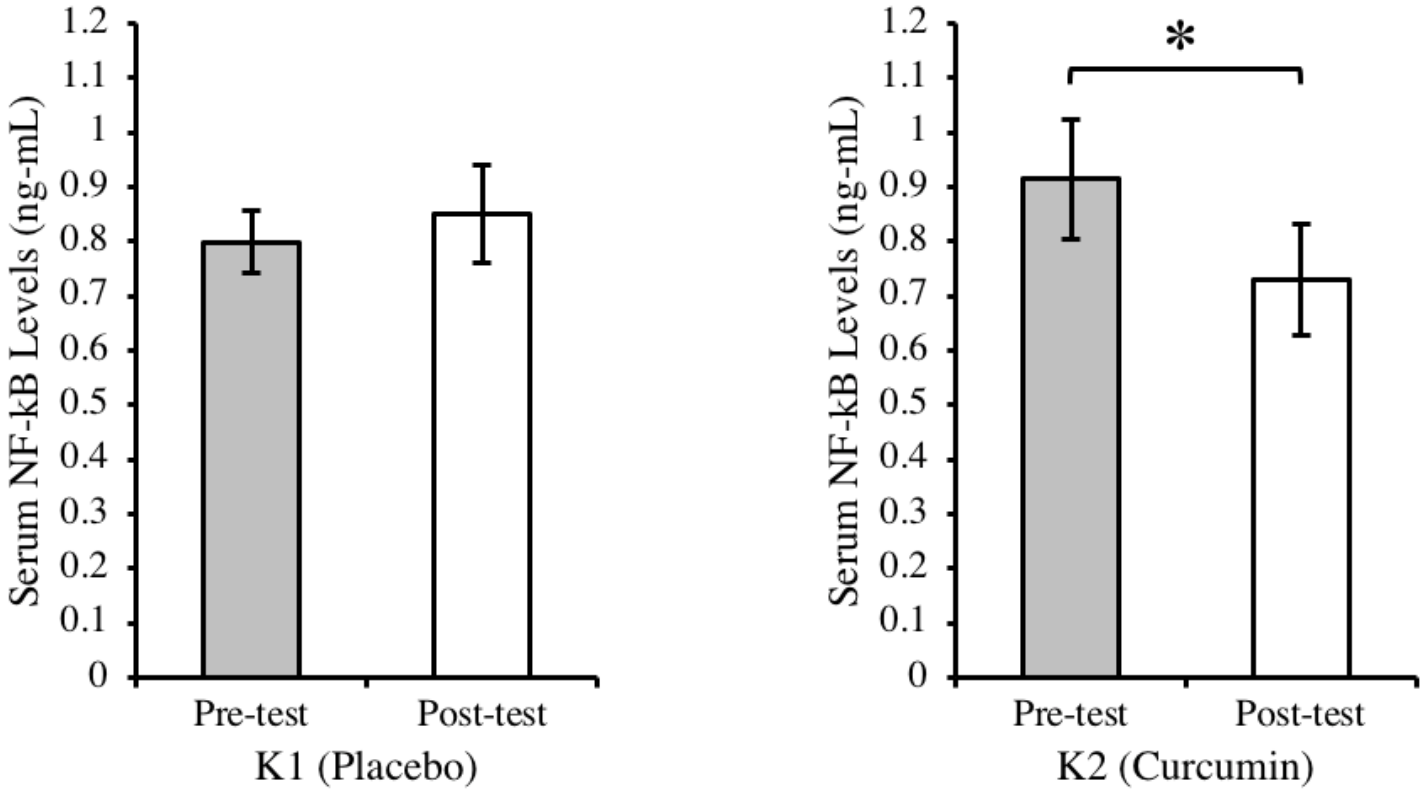

Figure 1

Group (K2) that was given curcumin after high-intensity physical exercise was able to reduce NF-κB levels significantly (*p<0.05) compared to group (K1) that was given placebo. Data presented as Mean ± Std Error.

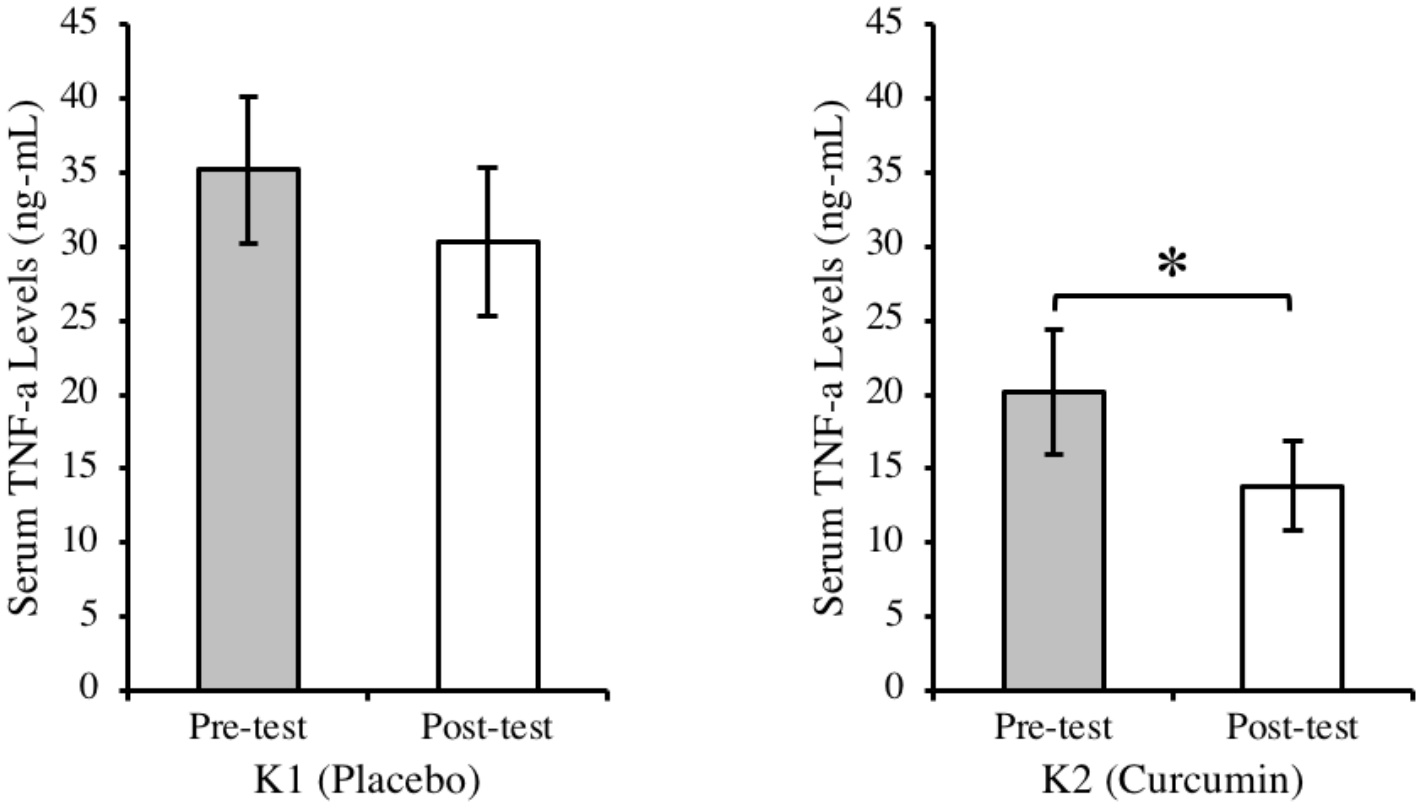

Figure 2

Group (K2) which was given curcumin after high-intensity physical exercise was able to reduce TNF-a levels significantly (*p<0.05) compared to group (K1) which was given a placebo. Data presented as Mean ± Std Error. The P-value was obtained using a paired t-test to compare the pre-test and post-test of each group.

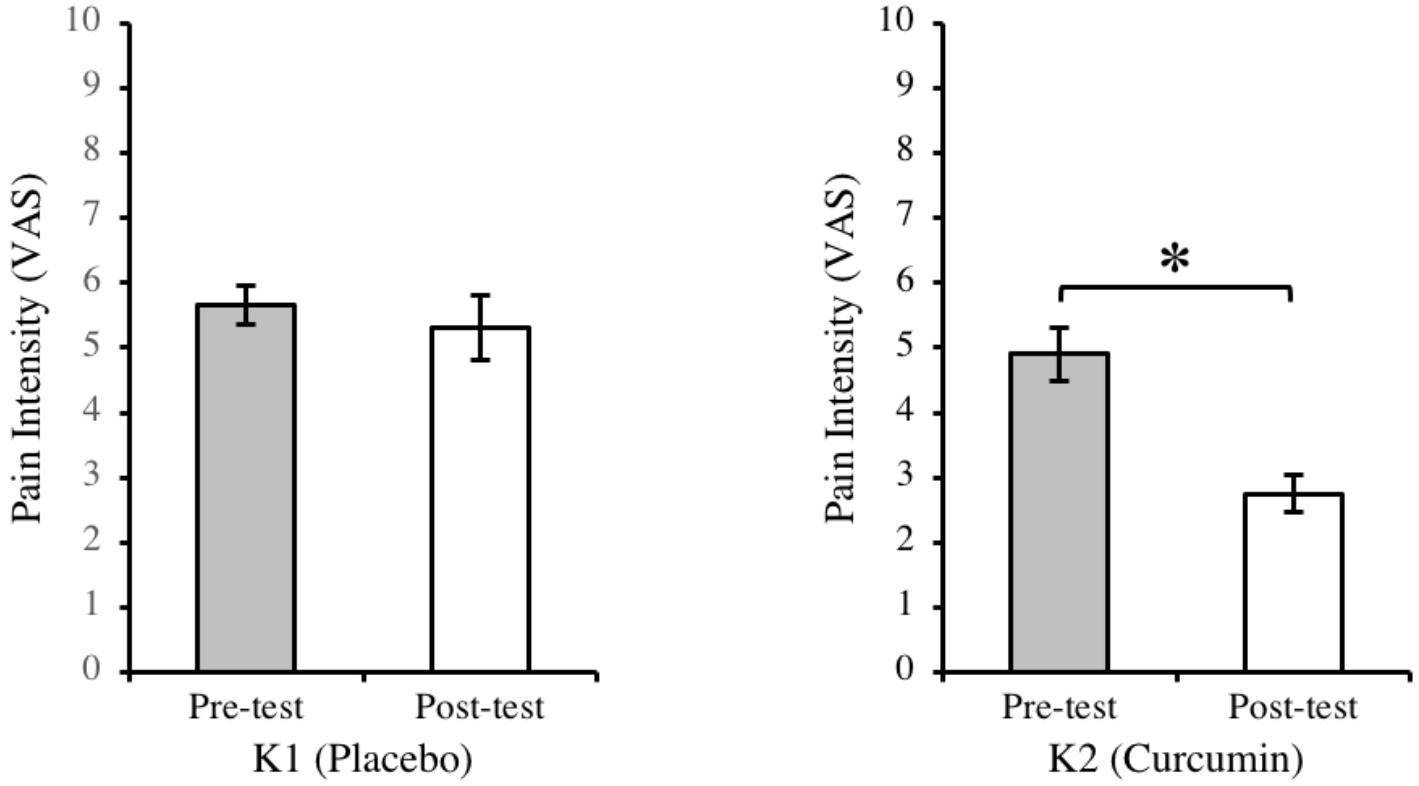

Figure 3

Group (K2) which was given curcumin after high-intensity physical exercise was able to reduce pain intensity significantly (*$p<0.05$) compared to group (K1) which was given a placebo. The data presented is in the form of mean, std error, and p-value.