Original Research

The Effect of Combination of Calcium Supplement and Physical Exercise on Increasing Muscle Strength in Chronic Ischemic Stroke Patients

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Introduction: Stroke causes muscle weakness which results in limitations in daily activities such as self-care, eating, walking, etc. This study aims to evaluate the effect of calcium supplement and physical exercise on increasing muscle strength in chronic ischemic stroke patients.

Methods: This research was conducted at Dadi Makassar Hospital and Haji Hospital from March to May 2023. The sample obtained was 37 subjects based on purposive sampling with an unpaired numerical comparative formula for two sample groups consisting of 18 people in the treatment group and 19 people in the control group. The research was carried out for 6 weeks using a Manual Muscle Testing (MMT) measuring instrument for muscle strength.

Results: There is a significant increase in lower extremity muscle strength between the pre-test and post-test in the treatment group and control group (p=0.001; p=0.014, p<0.05), There is an increase in the upper extremity muscle strength between the pre-test and post-test in the treatment group and control group (p=0.001; p=0.025). There is no significant difference in the increase in muscle strength in the upper and lower limbs between the two groups (p=0.051).

Conclusion: Physical exercise with calcium supplements are not more significant in increasing muscle strength than physical exercise alone in chronic ischemic stroke patients.

Keywords: Tuberculosis, family centered nursing, motivation, behavior

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INTRODUCTION

Stroke is an acute neurological disorder of the blood vessels in the brain due to the blood supply to an area of the brain stopping, causing tissue cells to lack oxygen [1]. Chronic ischemic stroke sufferers will experience problems in the form of muscle weakness which results in impaired ADL. This decrease in muscle strength is due, in part, to increased levels of calcium (Ca²⁺) in the blood [2] which plays a role in the signal transduction pathway to carry messages in the release of neurotransmitters from neurons [3] and contraction of muscle cells. This metabolic disorder will cause subsequent injury to neurons which will trigger rapid translocation of Ca²⁺ ions from the extracellular space to the intracellular tissue [4]. After a chronic ischemic stroke, pathological disturbances occur in the tissue, namely a leak in the Ca²⁺ channel signaling pathway which causes an increase in Ca²⁺ levels at the cytosolic level which results in disruption of protease activation which is highly dependent on Ca²⁺ ions [5].

The calpain in the protease will degrade myofilaments so that it can cause muscle weakness and Acute Respiratory Failure (AFR). The decrease in Ca²⁺ ions also causes an increase in the concentration of 1,25-dihydroxyvitamin D (1,25(OH)₂D) and Parathyroid Hormone (PTH) which affects intracellular calcium concentrations. Disruption of Ca²⁺ signaling will affect the regulation of muscle contractile strength in muscle fibers as well as disruption of Ca²⁺ ion homeostasis which results in muscle weakness [6].

Muscle weakness will have an impact on disrupting daily activities in chronic ischemic stroke patients, which can be minimized by providing physical exercise and taking calcium supplements. Calcium can maintain sodium permeability in cells, as an intracellular messenger, regulate excitation-contraction coupling (ECC) in muscles, and help release acetylcholine in the neuromuscular junction [7]. Calcium supplements are one mineral of the universal intracellular messengers that controls a variety of cellular processes such as gene transcription, muscle contraction, cell proliferation, programmed cell death, and neurotransmission, and are also considered as an important contributor in regulating skeletal muscle plasticity [8]. Calcium supplements can be divided into either an organic or inorganic group, which differ in their chelating capability. Organic calcium supplements include negatively charged organic molecules, such as malate, citrate, fumarate, and gluconate, while inorganic calcium supplements include carbonates, phosphates, and chlorides [9].

Calcium is needed to activate intramuscular calcium which will activate calcium calmodulin kinase, convert Adenosine Triphosphate kinase, convert Adenosine Triphosphate (ATP) into Adenosine Monophosphate (AMP) to then activate Adenosine Monophosphate Kinase (AMPK). In the ECC mechanism, acetylcholine will bind to a receptor which will open the sodium ATPase channel (Na⁺ ATPase Pump) in the sarcolemma and down the T tubules into the myofibrils. Physical exercise is given when there is excess Ca²⁺ in the cytosol due to pathological disorders will increase and
restore Ca²⁺ osmolarity due to increased blood flow, increasing the number and cross-sectional area of muscle capillaries due to increasing sensitivity of Ca²⁺ channels so that it will restore the balance of Ca²⁺ homeostasis in extracellular and intracellular[8]. In addition, giving calcium supplements will metabolize excess fat mass. Calcium intake is a mediator in fatty acid synthesis when muscles contract.

Providing physical exercise also improves muscle function, increases muscle strength, reduces the risk of muscle weakness due to lack of use of weak extremities, increases respiratory fitness, and increases protein synthesis [3]. The previous research shows that active and passive training will increase muscle strength and mass, provide stimulus to muscle fibers, and increase proprioception when muscle contractions occur. During intensive physical exercise, it causes an increase in plasma insulin, which functions to replenish muscle glycogen which is reduced during physical exercise [10].

METHODS

Design

This research used a quasi-experimental pretest-posttest design with two groups, namely a treatment group and a control group. The treatment group was given calcium supplements (Cal-95) combined with physical exercise and the control group was given physical exercise only.

Population, Sample, Sampling

The population of this study was 108 patients with chronic ischemic stroke at Dadi Hospital & Haji Hospital Makassar from March to May 2023. The sample size was calculated using the paired numerical comparative formula with two measurements.

The research sampling technique uses the following formula [11]:

\[ n_1 = n_2 = \left( \frac{Z_\alpha + Z_\beta S}{\mu_1 - \mu_2} \right)^2 \]

The research sample is 37 chronic ischemic stroke patients at the physiotherapy department at Dadi Hospital and Haji Hospital, who were divided into 2 groups (treatment group=18, control group=19). Eight samples were obtained from the Haji Hospital (treatment group = 4; control group = 4), and the remaining 29 were obtained at Dadi Hospital (treatment group =17; control group = 17). The samples were selected using a purposive sampling technique gradually until the number of targeted samples was achieved. The inclusion criteria were chronic ischemic stroke patients with an attack period of 2 weeks to 6 months, experienced muscle weakness, and had muscle scores above 1 according to MMT. The exclusion criteria were the stroke patients who took supplements other than calcium or had gastrointestinal disorders or kidney failure. The dropout criteria are if the patient dies or stop taking calcium supplement before the intervention is completed.

Instrument

MMT forms are a measurement of the patient’s ability to contract a muscle or group of muscles voluntarily to determine muscle
strength. As for the implementation, the sample will be instructed to move the upper and lower extremities according to the patient’s ability. The MMT assessment consists of 6 degrees ranging from 0 to 5. Value 0 is no visible or palpable contractions, value 1 is visible or palpable contractions but without movement, value 2 is Range of Motion (ROM) full but not against gravity, value 3 is full ROM and against gravity, value 4 is full ROM and against gravity with moderate resistance, and value 5 is full ROM and against gravity with maximum resistance, with a level of reliability and validity 95%, r=0.768 with p-value = 0.001 [12].

Data collection

Data collection in the study began by selecting the patients according to the inclusion criteria. If the sample meets the criteria, the researcher asked for informed consent to the patients by explaining the purpose of this research as well as indications and contraindications for giving calcium supplements and physical exercise. After obtaining approval from the patients, the researcher checked the MMT (pre-test) on the upper and lower extremities in the first week, then the patients received a calcium supplement of 500 mg/day every morning before training and physical exercise “bobath exercises” 3 times a week for 6 weeks, while the control group received physical exercise only 3 times a week for 6 weeks. The Muscle strength will be measured again using Manual Muscle Testing (MMT) [13] at week six (post-test). Proprioceptive Neuromuscular Facilitation (PNF) and stretching were done by a physiotherapist at the hospital. The researchers only measure and observe the patient’s development during therapy. Measurements of the muscle strength of the patients were taken by the researchers to avoid measurement errors.

Analysis

The data analysis began with Lavene’s test to determine the similarity of the two groups of data (p=0.26 or p > 0.05), which means the two groups were similar. The Shapiro-Wilk test result shows that p-value = 0.001 (p<0.05), which means the data distribution wasn’t normal. Then the data was tested by the Wilcoxon test to check the differences of muscle strength in pre-test and post-test in group and the Mann-Whitney test to determine the comparison of muscle strength between the intervention group and the control group with a significant level is α<0.05.

Research Ethics

Before conducting research, this research received ethical approval from the Ethics Commission of the Faculty of Medicine, Hasanuddin University, Makassar, on March 13th, 2023 with No.166/JN4.6.5.31/PP36/2023.

RESULTS

The final total number of samples was 37 patients (treatment group=18, control group=19). Five patients dropped out because they did not continue therapy or stop taking calcium supplements, 3 patients in the
treatment group dropped out due to stopping consuming calcium supplements, and 2 patients in the control group dropped out due to refusing to continue the treatment.

Based on the data in Table 1, 42.1% of stroke patients 46-59 years old and 60-74 years old were 46-59 years old in treatment group. Meanwhile, 57.9% of stroke patients in the control group were female, whereas in the treatment group, 77.8% of stroke patients were male.

This research shows that there was an increase in muscle strength in both pre-test and post-test group. The Wilcoxon test result shows that $p=0.025$ ($p<0.05$), which means there is a significant difference in the increase of the superior extremity muscle strength between pre-test and post-test of MMT in the control group. The Wilcoxon test result in the treatment group shows that $p=0.001$ ($p<0.05$), which means there is a significant difference in the increase of the superior extremity muscle strength between the pre-test and post-test of MMT. Based on Figure 1, the median score in the control group increased by 1 point and the pre-test score of MMT is lower than the post-test with a median difference of 1. Meanwhile, the median score of the superior extremity in the treatment group was 3 (2-4) which is lower than the post-test value of 4 (3-5) with a delta difference of 1.

Based on Figure 2, the Wilcoxon test result shows there is a significant increase in lower extremity muscle strength between the pre-test and post-test on in the control group ($p=0.014$, $p<0.05$). with a median score of MMT of 2 (2-4) which is lower than the post-test of 3 (2-4) with a delta difference of 1. Meanwhile, the Wilcoxon test result in the treatment group shows that there is also significant increase in lower extremity muscle strength between the pre-test and post-test ($p=0.001$, $p<0.05$), with the median score of MMT of 3.00 (2-4) which is lower than the post-test of 4.00 (3-5) with a delta difference of 1.

Based on Table 2, the Mann-Whitney result shows that there is no difference in muscle strength in the superior dan inferior limb in chronic ischemic stroke patients in both groups ($p=0.051$, $p>0.05$). The muscle strength of the superior limb has same score as the muscle strength in the inferior limb. From these data, it can be concluded that the effect of providing calcium supplements and physical exercise did not provide a significant difference in muscle strength in both superior and inferior limb in chronic ischemic stroke patients.
### Table 1
Respondent Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group</th>
<th>Treatment Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Age (y/o)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 – 45</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>46 – 59</td>
<td>8</td>
<td>42.1</td>
<td>14</td>
</tr>
<tr>
<td>60 – 74</td>
<td>8</td>
<td>42.1</td>
<td>3</td>
</tr>
<tr>
<td>75 – 90</td>
<td>3</td>
<td>15.8</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>42.1</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>57.9</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>100</td>
<td>18</td>
</tr>
</tbody>
</table>

*Age Classification according to the World Health Organization (WHO)

**Fig. 1.** Comparison of Superior Extremity Muscle Strength Between Two Groups

**Fig. 2.** Comparison of Inferior Extremity Muscle Strength Between Two Groups
Table 2
Comparison of Superior and Inferior Extremity Muscle Strength

<table>
<thead>
<tr>
<th>Group</th>
<th>MMT Superior Limb</th>
<th>MMT Inferior Limb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Min-Max)</td>
<td>Median (Min-Max)</td>
</tr>
<tr>
<td></td>
<td>Pretest</td>
<td>Posttest</td>
</tr>
<tr>
<td>Control Group</td>
<td>2 (2–4)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>Treatment</td>
<td>3 (2–4)</td>
<td>4 (3–5)</td>
</tr>
</tbody>
</table>

DISCUSSION

The results of this study show that giving calcium supplements followed by physical exercise had a more significant effect on increasing muscle strength (MMT) in chronic ischemic stroke patients before and after intervention than giving physical exercise only. However, after comparing both groups (intervention and control group), it was found that giving calcium supplements and physical exercise did not have a significant difference in increasing muscle strength in both the upper and lower extremities compared to those who were given physical exercise only. This may be because the duration of calcium supplementation in this study was only 6 weeks and it is possible that it has not yet produced results due to the adaptation process of the action of calcium on muscle and nerve working mechanisms to improve the working mechanism of excitation-contraction coupling in increasing muscle strength so it is possible that a longer duration of time is needed. It will take a long time to find out the maximum effect of giving calcium supplements with the aim of increasing muscle strength.

The treatment group that was given calcium supplements and physical exercise and the control group that was given physical exercise only showed an increase in muscle strength in both superior and inferior extremities. Initially, the samples were only able to move the extremities with full ROM but not against gravity and those who were able to resist gravity experienced an increase in muscle strength. It is increasing very significantly, where the sample can move the superior and inferior extremities with full ROM and fight gravity with minimal and maximum resistance. Increased muscle strength when given calcium supplements and physical exercise is mainly related to increased muscle endurance due to increased energy resulting from calcium metabolism which plays a role in the formation of ATP from glucose. When physical exercise is carried out [14], there is an increase in insulin secretion which increases systolic calcium by regulating the activation of calcium channels and the lysis process. The transport of glucose in muscles requires the help of GLUT4 to the membranes in muscle fibers to be converted into ATP [15]. The increase in calcium concentration that enters...
intracellularly during muscle contraction will activate AMP kinase (AMPK), which is the fuel that will be used in physical exercise [16].

Age can affect changes in muscle strength capabilities caused by changes in the composition of fat-free mass (FFM) which is used as a source of energy reserves needed for muscle contraction. According to the previous research, after the age of 45 years, there is a decrease in FFM from 62 kg to 55 kg in men and from 48 kg to 39 kg in women so women allow less ATP to be produced for use in muscle contraction. Likewise, women and men also contribute to this change, where women have more fat deposits compared to men who have more muscle tissue [17].

At the CNS level, when there is a lack of calcium levels in the cells (hypocalcemia) it causes motor damage due to a decrease in dopamine concentrations in the nigrostriatal pathway which plays a role in nerve transmission [18], so when calcium levels in the cells are met, the dopamine substantia nigra will release dopamine from the presynaptic axonal to the striatum and from the dendritic soma area to the midbrain [6] which will mediate the physiological function of dopamine neurons in nerve synapse transmission which will reduce the conductivity of peripheral motor neurons thereby reducing the tingling feeling, especially in the arms and legs [19].

In the muscle, there is an increase in calcium concentration of around 100 to 200 mmol/l which will penetrate the intracellular membrane against the cell gradient of the endoplasmic and sarcoplasmic reticulum. However, only a portion of the calcium concentration can penetrate the permeability of Ca2+ channels to enter intracellularly, where most cells that can be excited at rest permeability to calcium are only in low amounts [20]. In contrast, when muscle contraction occurs, the intracellular calcium concentration will also increase, which will increase the ability of the actin folds and also the myosin cross bridges in the ECC mechanism. It is the molecular capabilities of proteins involved in calcium signaling that can determine the specific interactions between stimulation and changes in organelle state [21]. Because most of the cellular calcium is in a bound state, an increase in calcium in the cells will trigger secretion in the sarcoplasmic and endoplasmic reticulum as a calcium storage place to release the bound calcium. The stimulation of the secretion process in the glands can occur by changing the state of bound calcium. This is related to the action of pituitary hormones on the adrenal cortex and thyroid gland to secrete calcium which will be used in the muscle contraction mechanism. The stimulation of the secretion process in the glands can occur by changing the state of bound calcium [6].

Providing calcium supplements during physical exercise will help restore energy deficits so that it can increase training sessions that initially could only be done one training session but can now be done two or three training sessions. This is due to a decrease in the rate of fat oxidation which will increase Non-esterified Fatty Acid (NEFA). When physical exercise is carried out there is an increase in NEFA and calcium intake will increase the level of fat oxidation [20]. Apart from that, in this study it was found that there was a decrease in fatigue during and after
training, especially training with medium and high intensity, which allows the frequency and intensity of training to be increased to maximize muscle work. This fatigue occurs due to changes in ion concentration in the form of an excessive increase in extracellular calcium concentration which will affect the slowing of relaxation in muscle fibers which occurs due to repeated contractile activation, so reducing calcium concentration during physical exercise will reduce fatigue. The previous study shows that reducing the calcium concentration of myoplasm will reduce fatigue. However, there is another opinion that says that increased calcium concentrations can be normalized or reduced by reducing calcium sensitivity in muscle cells, but this still needs to be proven [3]. Other research states that reducing calcium absorption by the sarcoplasmic reticulum, reducing extracellular calcium concentrations, and inhibiting the calcium entry pathway will increase fatigue [18]. Calcium intake will help utilize fat as the main energy source during exercise which will increase the availability of NEFA so that it can help increase fat oxidation during certain physical exercises. This can help reserve glycogen for certain exercises which will improve muscle contraction performance and delay fatigue [21].

The amount of calcium taken up during muscle contraction is related to the extracellular calcium concentration and increased calcium uptake cannot be maintained during sustained stimulation during physical exercise but may decrease over time. Due to the inactivation of the calcium concentration, the intracellular calcium concentration increases to the point where it will damage cells and reduce the muscle contraction response, so when there is an excess increase in calcium concentration, it must be balanced and reduced by physical exercise which will be used in the ECC mechanism during muscle contraction [23]. The more calcium that can be used in this mechanism, the stronger and longer the intensity of the ECC action during contraction, so that the muscle work adaptation mechanism will increase muscle strength [22].

Giving calcium supplements increases tissue and muscle mass, especially in men, when followed by physical exercise. This allows performance related to daily activities such as eating, bathing, toileting, ambulances, walking, and so on. The decrease in activity for women is also influenced by hormonal factors such as the hormone estrogen which will increase fat stores in subcutaneous tissue, allowing muscle performance to decrease further. In addition, the risk of experiencing osteoporosis is greater which will affect bone density when doing activities. According to research, after the age of 45 years, there is a decrease in FFM from 62 kg to 55 kg in men and from 48 kg to 39 kg in women so women allow less ATP to be produced for use in muscle contraction. In this study, it was stated that changes in FFM in the upper and lower legs were associated with a sedentary lifestyle so the legs had the ability to protect against insulin resistance and dyslipidemia apart from total fat mass [3]. Other research also states that FFM in the legs is a determinant of cardiometabolic risk after menopause which results in bone loss, so that bones become
brittle due to reduced estrogen hormones in women and testosterone in men which affects calcium transport and reabsorption [24]. Apart from that, stroke recovery in old age is more focused on improving cardiorespiration, namely in the form of increasing fitness reserves, increasing Vo2Max and increasing walking ability [25].

**LIMITATIONS**

This study has a small sample size because some patients were dropped out. Likewise, additional doses of calcium supplements also need to be taken into account, namely 1000 - 2000 mg with the consideration of further improving the ECC mechanism in muscles. Apart from that, psychological disorders in the form of depression can also cause problems to influence the patient's motivation to exercise, thereby impacting recovery.

**NURSING IMPLICATION**

This research can be used as complementary therapy in nursing in treating chronic ischemic stroke patients by combining drugs such as supplements and physical exercise so that it will further increase the ability of muscle strength that experiences post-stroke weakness.

**CONCLUSION**

Providing calcium supplements and physical exercise have a more significant effect on increasing muscle strength, but statistically when comparing the two interventions, it shows that there is no specific difference between the two treatments in increasing muscle strength in chronic ischemic stroke patients. It is hoped that there will be further research regarding the effect of calcium supplements and physical exercise on increasing muscle strength in chronic ischemic stroke patients by paying attention to aspects of checking calcium and hormonal levels, psychological influences, training doses, and appropriate techniques.

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