



Physical Therapy (13:30 ~16:00 Lecture Room 3)

Chaired by the academic adviser of each presenter

DEVELOPMENT OF AN INSTRUMENT FOR MEASURING PATELLAR MOBILITY AND ITS CLINICAL APPLICATION

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Introduction

Passive patellar mobility was believed to be one of the important forms of assessment for patient with patellofemoral pain (PFP) and the decreased range of motion (ROM) at the knee joint. Moreover, it shows the laxity of the knee joint which could also contribute to sports knee injuries.

However, there is no methods to assess the quantitative measurement of patellar mobility in clinical situation. Given the need for objective measurements of patellofemoral (PF) joint impairments, we have developed a clinical device (patellofemoral joint arthrometer [PFA]) to quantify medio-lateral patellar displacement.

The purposes of this research were 1) to assess the validity of prototype PFA, 2) to apply PFA to the person with PF and to compare with the healthy subjects, 3) to investigate the relationship of patellar mobility and knee ROM after total knee arthroplasty (TKA).

Materials and Methods

Study 1¹⁾

Subjects: A total of 26 individuals (24 females and 2 males) participated, and 14 were asymptomatic with PFP. The average \pm SD age, height and body mass of the participants was 27 ± 4 years, 164 ± 5 cm, and 59 ± 8 kg, respectively. Twelve of the participants had a current history of patellofemoral pain at the time of testing, while 14 were asymptomatic.

Methods: A custom designed prototype PFA was used to assess the amount of lateral patellar displacement. PFA was secured to the femoral condyle, and the femur was refer to this measurement. The adjustable arm allowed the medial border of the patella to be localized in the frontal plane with respect to the fixed ruler. Subjects were measure the displacement of lateral patella between quadriceps relaxed and isometric contracted by PFA. Following assessment of lateral patellar displacement using the PFA, participants underwent MRI of the patellofemoral joint. The same procedures of using PFA was performed on using MRI. Bisect offset index and patellar tilt angle was measured the true lateral patellar displacement. The comparison of these patellar mobilities using both methods was performed as the validity study.

Study 2²⁾

Subjects: The study comprised 22 females with PFP (PFP group) and 22 females who had no knee pain (control group) who were matched to the subjects with PFP based on age, height, and body mass index.

Methods: Patellar mobility was measured objectively using PFA. Measurements of lateral and medial patellar displacement, patellar mobility balance (lateral minus medial patellar displacement), lateral patellar mobility index (LPMI: lateral patellar displacement/ patellar width), and medial

patellar mobility index (MPMI: medial patellar displacement/ patellar width) were used.



Figure 1. Patellofemoral arthrometer



Figure 2. Initial position of the patellar mobility (set 0 mm of the digital caliper)

The PFA was clamped to the femoral condyles aligned parallel to the table. The digital caliper was positioned at an angle of 90 degrees to the line between the center of the patella and the ASIS using the plane adjuster. Before each subject was measured, the amount of force (approximately 80N) to be used to move the patella for testing was practiced using a hand-held dynamometer, MicroFET2 (Hoggan Health Industries Inc., West Jordan, UT) to enable the examiner "to feel" what it was like to apply an 80N force. For testing, relaxation of the musculature was confirmed by palpation of the quadriceps and passively moving the patella in the lateral and medial directions.¹⁷ To measure lateral patellar mobility, the lateral border of the patella was palpated and located with a laser using the adjustable laser module arm, and the digital caliper was zeroed, setting this point as the initial position. Lateral displacement of the patella was then achieved by manually pushing the patella laterally (applying approximately 80N of force), at which point the lateral border of the patella was again

located by sliding the laser module arm on the caliper and reading the measurement. Medial passive patellar mobility was assessed in the same manner except for the force application being applying toward the medial direction. All of these procedures for passive patellar mobility were performed by the same tester for all subjects.

Study 3³⁾

Subjects: Fifty-one patients [osteoarthritis (OA) group: 34 knees; rheumatoid arthritis (RA) group: 22 knees] were examined after TKA.

Methods: Patellar mobility was measured preoperatively and 1, 2, and 6 months postoperatively using a patellofemoral arthrometer (PFA) fixed to the femoral condyles to measure medial and lateral patella displacement at 30 degrees of knee joint. Knee joint ROM was also measured in each of these 4 sessions.

All participates in these studies were approved by each Ethics Committee of the University of Southern California and the school of Health Sciences, Nagoya University.

Data analysis: Patellar mobility was measured three times, and the averages of the displacements were used in these studies.

For the validity study was used intra-class correlation (ICC2,k), and t test was performed to compare the displacements between PFP group and control group in study 2. For the analysis of the relationship between patellar mobility and ROM in the study 3 were used the Pearson correlation. The differences between each session was using ANOVA and Tukey's procedure. Significance was set at $P < 0.05$.

Results

Study 1: The ICC assessing the level agreement between the MRI and PFA measures of lateral patellar displacement was good (0.86). Excellent intratester (ICCs of 0.96 and 0.97) and intertester reliability (ICC 0.92) was demonstrated.

Study 2: Lateral and medial patellar mobility values were not significantly different between the individuals in the PFP and control groups. When normal patellar mobility was arbitrarily defined as the average \pm 2SD based on the data from the control group, normal lateral patellar displacement was within a range of 7.2 to 17.6 mm and normal medial patellar displacement was within a range of 6.8 to 14.0 mm.

Study 3: In the OA group, lateral patellar mobility was positively correlated with knee flexion angle, while there was no correlation between medial patellar mobility and knee flexion angle. Knee joint extension was not correlated with either lateral or medial patellar mobility. In the RA group, both lateral and medial patellar mobility were positively correlated with knee joint flexion/extension 1 and 2 months after TKA.

Although, knee ROM were significantly improved from 1 month to 6 months after TKA, medial and lateral patellar mobility were not improved.

Discussion

From the study 1, the validity of the prototype PFA compared to MRI method was acceptable range in the clinical application. This prototype was made of polyethylene for using in side of MR imaging.

Study 2 was introduced to PFA to apply the clinical evaluation. PFA was adjusted the patellar mobility using equipped the adjustable lever, lever joints and laser. Based on

an arbitrarily defined normal range of values calculated using the mean \pm 2SD of the patellar displacements measured for the individuals in the control group, we note that the distribution of the data points are very similar between the 2 groups, with only few subjects with PFP falling outside what we considered a normal range of scores. From the results of this study, abnormal patellar mobility might not be a factor in female adults with mild symptoms of PFP.

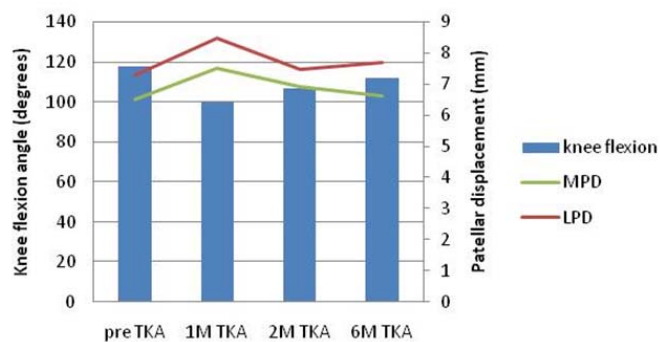


Figure 3. Changes of knee flexion angle and patellar mobility in OA group

In the study 3, although patellar mobility was shown to be related to knee ROM after TKA, there were differences in the relationship between OA and RA groups. In both groups, lateral patellar mobility was positively related to knee flexion angle 1 and 2 months after TKA. In the OA group, knee extension was not associated with patellar mobility, while lateral and medial patellar mobility were related to knee ROM (flexion and extension) after TKA in the RA group. Although these features should be taken into consideration in planning of physical therapy treatment regimens to improve patellar mobility after TKA, the relations identified in the present study represent only cross-sectional findings. However, our findings demonstrated that medial and lateral patellar mobility had no sufficient longitudinal relationship with knee ROM after TKA.

Conclusions

We have developed PFA to assess the patellar mobility quantitatively, and we applied it to patients with PFP and after TKA. The patellar mobility might not be a factor in this research subjects with PFP (mild symptom). The knee ROM after TKA could not be related to medial and lateral patellar displacement. This study would be a framework for a future clinical trial on patellar mobility in patient with knee disorder.

References

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CD105 POSITIVE MESENCHYMAL STEM CELLS FROM MOUSE ES CELLS SHOW HIGH POTENTIAL FOR DIFFERENTIATION

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Introduction

Mesenchymal stem cells (MSCs) have a potential to differentiate into any mesenchymal cell type such as osteocytes, chondrocytes, adipocytes and muscular cells. Recently, adipose tissues are indicated as a useful and rich source of adipose tissue-derived mesenchymal stem cells (ADSCs). Although ADSCs have therapeutic efficiency in repairing damaged mesenchymal tissues, isolation and purification of ADSCs from adult adipose tissue still requires complicated and troublesome processes[1,2]. Mouse embryonic stem cells (ES cells) are pluripotent, and their induction to adipogenesis has been well described[3,4]. We initially supposed that MSCs would differentiate through the process of adipogenesis from undifferentiated ES cells (Figure 1). The aim of this study was to establish a method for the induction and collection of MSCs using a typical cell surface marker CD105 through adipogenesis from ES cells without genetic manipulation.

Materials and Methods

ES cells (G4-2; kind gifts from Dr. Niwa) carrying the enhanced green fluorescent protein —EGFP— gene under the control of cytomegalovirus/chicken β -actin promoter were expanded their population and embryoid bodies (EBs) were formed in hanging drops. EBs were cultured in a retinoic acid containing medium. After washing, they were settled on culture dishes and maintained with adipogenesis medium (insulin / triiodo-thyronine). After the increase of CD105+ cells, we isolated and sorted them by a magnetic cell sorter (MACS; Miltenyi). Purification of CD105+ cells using MACS was confirmed by flow cytometry (FACS). CD105+ cells were then differentiated into mesenchymal cells such as adipocytes, osteocytes, chondrocytes, and skeletal muscles. Differentiation was examined by oil red O, alizarin red, alcian blue, and M-cadherin and/or skeletal muscle myosin heavy-chain (MHC) immuno-staining, respectively. Expression of each cell type-specific mRNA was analyzed by RT-PCR. Obtained CD105+ cells were then injected into tibialis anterior muscles of immunodeficient (SCID) mice to demonstrate their potential for differentiation in vivo.

Results

Appearance and Sorting of CD105+ Cells

After 10 days of induction to adipogenesis, small, round CD105+ cells appeared, began to increase, and reached their maximum population on day 14. After that adipocytes then increased and CD105+ cells alternately decreased. Since double staining with CD105 and BODIPY demonstrated that adipocytes did not express CD105, sorting by MACS was usually carried out on day 14. The efficiency of sorting by MACS was confirmed by FACS analysis, and more than 91% of cells were CD105+ after MACS separation. Sorted CD105+ cells were uniformly bipolar in a shape similar to that of the ADSCs previously reported.

Differentiation Potential of CD105+ cells to Mesenchymal lineages in vitro

CD105+ cells showed a high potential for differentiation into mesenchymal cells in vitro, when both CD105+ and CD105- cells were induced to mesenchymal cells and compared with each other. After induction of adipogenesis, almost all CD105+ cells differentiated into adipocytes. CD105- cells, however, did not produce large Oil Red O-positive oil droplets. CD105+ cells turned Alizarin Red-positive after induction of osteogenesis. The CD105- cells did not survive under the condition of osteogenesis and disappeared. Under the pellet culture for chondrogenesis, the CD105+ cells formed small ball like-aggregations. When a cryo-section of the aggregations was stained with Alcian blue, the matrix surrounding the chondrocytes turned blue. The matrix produced by CD105+ cells also expressed collagen type II immunoreactivity, while the CD105- cells did not form cell aggregations and were not stained with either Alcian blue or anti-collagen type II antibody. When CD105+ cells differentiated into skeletal muscle cells, they became thin and fibrous, and began to express M-cadherin. They ran in the same direction and distributed parallel to each other. They finally constructed sarcomeres exhibiting bands with myosin and actin filaments regularly arrayed. A few CD105- cells expressed M-cadherin immunoreactivity, but they did not form myotubes under the same condition.

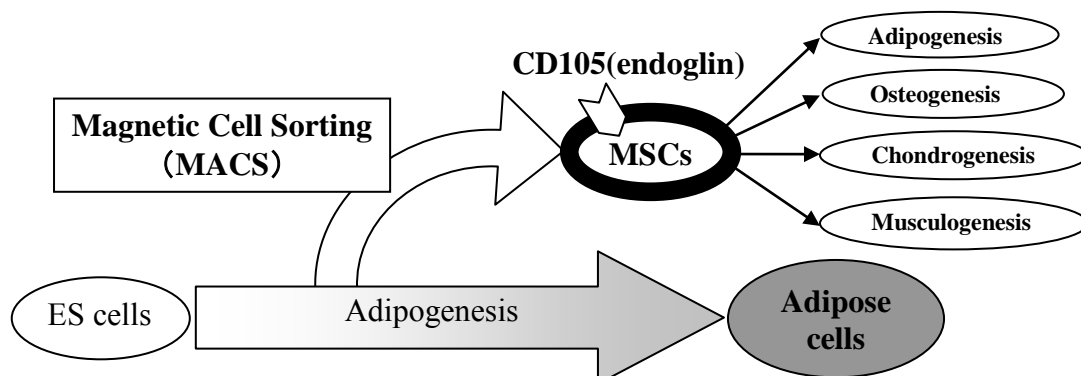


Fig. 1 Schematic view of the induction and isolation of MSCs from ES cells

Potential of CD105+ cells for differentiation into mesenchymal cells was confirmed as well by the expression of their specific mRNAs detected by RT-PCR.

After the induction of adipocytes and the formation of lipid droplets, CD105+ cells expressed *PPAR-γ* and *LPL* mRNAs. Following the formation of osteogenic cells, they displayed both *Runx-2* and *Osterix* mRNAs. The small ball-like structures observed after the induction of chondrogenesis expressed *Collagen2* and *agglycan* mRNAs. Skeletal muscle cells differentiating from CD105+ cells expressed *Myogenin*, *M-cadherin*, *MyoD* and *Myf5* mRNAs.

Differentiation Potential in vivo; Transplantation to Immunodeficient (SCID) Mice

Potential for differentiation into mesenchymal cells in vivo was examined by transplantation to SCID mice. CD105+ cells were transplanted into injured tibialis anterior muscles 24 hours after clamping. Transplanted cells located at the injected area were clearly distinguished from host cells by their EGFP immunoreactivity. After 1 week of transplantation, EGFP-positive cells showed M-cadherin immunoreactivity. Some of them express MHC immunoreactivity. Their nuclei were located at the center of the cells and occasionally appeared as multinuclear cells in the cross section. After 2 weeks of transplantation, EGFP and MHC-double positive cells increased and became large enough to involve several nuclei in the cross section. From the HE staining, many blood vessels invaded the colony of transplanted cells. Flk1-positive cells indicated angiogenesis.

Discussion

Expression and Specificity of CD105

CD105, also known as endoglin, is a homodimeric type transmembrane glycoprotein that binds to TGF-β1 and TGF-β3 to form a receptor complex comprised of TGF-β receptors I and II. TGF signaling plays important roles in cell growth, differentiation and migration, and is also known as a functional marker for the isolation of mesenchymal stem cells including ADSCs. Almost all reports describing mesenchymal stem cells have demonstrated the expression of CD105 on the cell surface, further gene expression profiles of mesenchymal stem cells have involved CD105 [2,5]. After the completion of adipogenesis, mature adipocytes did not express CD105. This indicates that only stem cells or progenitor cells express CD105, whereas mature mesenchymal cells themselves lose the expression. Therefore, CD105 was confirmed as a useful marker to separate and collect mesenchymal cells in our system. The isolation efficiency rate by MACS was more than 91%. This was further enhanced using a technique of adhesion separation after sorting by MACS.

Potential of Differentiation into Mesenchymal Cells in vitro and in vivo Indicates MSCs

CD105+ cells demonstrated a high potential for differentiation into mesenchymal-type cells, i.e., adipocytes, chondrocytes, osteogenic cells and skeletal muscles in vitro and in vivo. Their differentiation potential indicates that CD105+ cells were mesenchymal stem cells (MSCs). Our MSCs were easily differentiated into skeletal muscles, though ADSCs have been described as hardly differentiating into muscles [6]. In general, the requirement of the provision for specific ADSCs does not in fact involve the potential for skeletal muscle differentiation [2]. The prominent potential of our MSCs to differentiate into skeletal muscle probably depends on the medium containing insulin and T3 for

adipogenesis before sorting by MACS. Skeletal muscle cells are sensitive to insulin and the IGF family as growth factors. IGF-II promotes myogenesis through Rho-ROCK activity and induces myoD1 [7]. The receptors of insulin and/or IGFs may be highly expressed before induction of myogenesis in our MSCs. Culture conditions generating our MSCs showed advantages over myogenesis in our method.

Transplantation to the injured tibialis anterior muscles differentiated MSCs into skeletal muscles in vivo. This suggests that the fate of MSCs ultimately depends on their micro-environments as already described [2]. Induction factors from host tissues surrounding MSCs regulate their differentiation into a certain mesenchymal cell type. Further studies of the molecular mechanisms of differentiation into specific mesenchymal cell type by MSCs should advance the MSC cell therapies.

Conclusions

We developed MSCs with a high potential for differentiation into mesenchymal cell lineages, including skeletal muscles in vitro from ES cells using CD105 as a cell surface marker without gene manipulation. Depending on their surrounding micro-environments in vivo, MSCs differentiated into skeletal muscles of injured tibialis anterior muscles. All properties of our MSCs proved very beneficial to cell-derived regeneration and therapeutic usage.

References

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EFFECTS OF FORCED IMPAIRED FORELIMB USE ON CENTRAL NERVOUS SYSTEM AFTER SMALL INTERNAL CAPSULE HEMORRHAGE IN RATS

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Introduction

Forced impaired forelimb use (FLU) is known as an effective method to promote functional recovery of the affected forelimb after hemiplegic stroke (e.g., constraint-induced movement therapy) [1,2]. However, the detailed mechanism of FLU effect on the brain was still unclear. In this study, we investigated whether FLU induces functional recovery after small intracerebral hemorrhage (ICH) and how the dominant use induces improvement of motor functions.

Materials and Methods

Experimental setup: Adult male Wistar rats (250-300g) were housed at a 12 h light/dark cycle with food and water ad libitum. Rats were randomly assigned to four groups: ICH (n=8), ICH-FLU (n=9), Sham (n=5) and Sham-FLU (forced-preferred limb use: n=6). All experimental procedures were performed in accordance with the animal care guidelines of the Nagoya University. Figure 1 shows a timeline of the performed experiments.

Intracerebral hemorrhage: In the present study, we used internal capsule hemorrhage model [3]. Under deep anesthesia, 1.4 μ l Collagenase (15 Units/ml, Type IV; Sigma-Aldrich, St. Louis, MO, USA) were injected into the internal capsule contralateral to the preferred forepaw. Figure 2 shows a typical histological appearance of hemorrhage.

Forced-impaired limb use: FLU-treated animals were fitted with a 1-sleeve plaster cast 24hrs after ICH surgery. The upper torso and the unimpaired/unpreferred forelimb were wrapped in soft felt and Plaster of Paris strips. Rats were forced to completely rely on either their impaired/preferred forelimb for 1 week.

Behavioral assessment: After restraint, rats were assessed various forelimb motor functions, such as skilled reaching (assessed by single pellet reaching test), coordinated forelimb stepping (by ladder test), spontaneous use of the impaired forepaw (by cylinder test), and tactile-evoked forelimb placing (contact placing response). Figure 3 shows the appearances of these tests. Assessment was carried out at postoperative day 10-12 and 26-28. Before ICH, single pellet reaching test and ladder test were pre-trained and determined baseline performance.

Lesion volume: After the completion of behavioral testing, all animals were deeply anesthetized and perfused transcardially with 0.9% saline followed by 4% phosphate-buffered paraformaldehyde (pH 7.4). The brains were removed and postfixed, and then 40 μ m thick coronal sections were obtained using a cryostat. These sections were processed with hematoxyline-eosin staining and volume of lesion was determined.

Retrograde labeling of corticospinal tract: An additional group of rats (ICH; n=6, ICH-FLU; n=6, Sham; n=9) was used for quantification of the remaining corticospinal tract. After same FLU treatment, animals were anesthetized and their spinal cords were exposed at the C6-C8 level using laminectomy. 4% fluorogold (FG; Biotium, Hayward, CA) was injected into the spinal cord with a glass micropipette.

Each animal had four injections of 250 nl of FG spaced at 0.5 mm, along the spinal cord (0.75 mm lateral from the midline and 1.2 mm below the spinal cord surface). Seven days after injection, animals were perfused and processed for cryosectioning. Series of 30 μ m brain cross sections (with 180 μ m gaps) were used for quantification of labeled cells.

Real-time PCR: Separate cohorts of animals exposed to the same FLU treatment were used for quantitative transcription polymerase reaction (PCR) analysis (ICH; n=6, ICH-FLU; n=6, Sham; n=6, Sham-FLU; n=6). Sensorimotor cortex forelimb region harvested at the end of the FLU period was analyzed by real-time PCR of brain-derived neurotrophic factor (BDNF) and growth-associated protein 43 (GAP43).

Statistical analyses: One-way ANOVA followed by a Tukey post hoc test was used for statistical analyses of behavioral tests, FG-positive cell number, and real-time PCR assay. Student's t-test was used for lesion volume. All statistical analyses were conducted using the statistical software SPSS (release 12.0). Data are presented as means \pm SEM.

Results

Behavioral assessment: After FLU treatment, improvement of the skilled reaching task in single pellet reaching test was found in the ICH-FLU in comparison with ICH rats. Additionally, the reaching style of ICH-FLU group was more normally than ICH group. Better performance of skilled stepping in ladder test was also shown in the ICH-FLU group than ICH group. However, no significant differences were found in cylinder test and contact placing response among experimental groups.

Lesion volume and remaining corticospinal tract: Injection of low-dose collagenase caused small hemorrhage localized the internal capsule (see figure 2). However, lesion volume was not difference between ICH and ICH-FLU group. In parallel, the number of FG-positive neurons in sensorimotor cortex decreased significantly after ICH, but FG-positive neuron number was similar between ICH and ICH-FLU group.

Real-time PCR: BDNF and GAP43 are known as growth-promoting factor and involved plastic change of central nervous system. After FLU treatment, mRNA expression of BDNF and GAP43 was significantly enhanced in ICH-FLU animals compared with ICH and Sham animals. These changes were found in the sensorimotor cortex contralateral side to the forced-use side forelimb (ipsilateral side to collagenase injection), but not in ipsilateral side (contralateral to injection).

Discussion

In this study, we demonstrated early FLU promote functional recovery of the skilled movement of forelimb (reaching, ladder stepping). Furthermore, upregulation of BDNF and GAP43 was shown in the sensorimotor cortex contralateral to the forced-use forelimb. These data suggested that use-dependent plastic alterations in the forelimb sensorimotor area would be induced by FLU after ICH, causing skilled functional recovery with relation to enhanced expressions of BDNF and GAP-43.

In addition, brain lesion volume and damage of corticospinal tract were mostly unchanged by early FLU. Some previous research has reported immediate FLU after cortical insult enlarged lesion volume and exaggerated functional recovery [4,5]. In this study we used subcortical lesion model, therefore these discrepancy might be related to pathological conditions (cortical vs. subcortical lesion).

Conclusions

Forced-use of impaired forelimb after capsular hemorrhage induced better recovery of skilled reaching and stepping of the impaired limb. This functional recovery might be related use-dependent alterations of the growth-promoting factors expression in the sensorimotor cortex.

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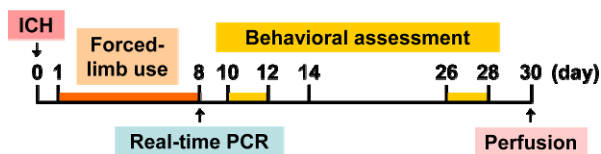


Figure 1. Timeline of the experiments

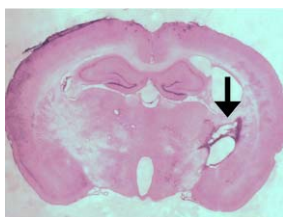


Figure 2. Typical photograph of internal capsule hemorrhage

Hematoxylin and eosin staining 30 days after ICH shows small hemorrhage localized the internal capsule (arrow).

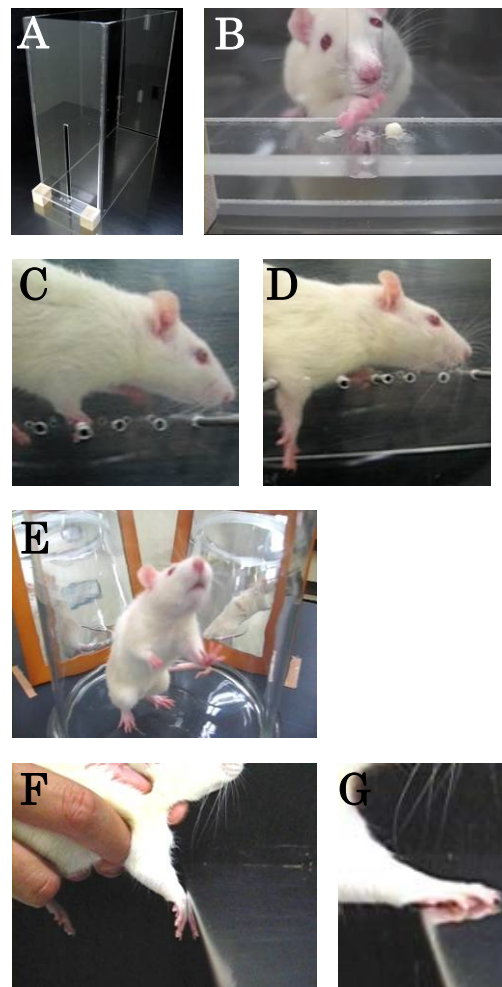


Figure 3. Behavioral tests

(A-B) Single pellet reaching test: A shows the apparatus of single pellet reaching test. Reaching to retrieve pellets through a narrow slit by their impaired forelimb was analyzed (B). (C-D) Ladder test: Crossing the 1-m long ladder was videotaped and assessed the rate of correct step and fall. C demonstrated correct step (midportion of limb placed on rung) and D showed fall. (E) Cylinder test: Rats were placed in a plexiglas cylinder 5min, and the percentage of the impaired limb use when touching the cylinder wall was analyzed. (F-G) Contact placing response: Rats were held with the forelimb suspended, and advanced until the dorsum of the forepaw touched the edge of a table (F). Normally, rats show a placing response by extending the forepaw digits and putting them on the table (G).

RECURRENT RISKS AFTER MILD ISCHEMIC STROKE IN A JAPANESE POPULATION

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Introduction

The high rate of stroke recurrence during several years after first ever stroke has suggested in Hisayama study in Japan. Furthermore, the 70% of ischemic stroke patients have mild motor paresis. However, stroke recurrence has not studied depends on the severity of the paresis, so precise data in the recurrence rate and predictive variables for stroke recurrence in mild stroke remained unknown. Therefore, This study aimed to estimate 3 year cumulative recurrence rates and identified independent predictors of vascular events after TIA and mild ischemic stroke (IS).

Materials and Methods

Subjects: From December 2005 to September 2006, patients with acute TIA or IS who met criteria of modified Rankin Scale 0-2, no communication disability and emergent admission to a sophisticated acute hospital in Nagoya city district were consecutively enrolled in this study. Patients with age over 80 years old, cardiogenic stroke, severe dementia, psychiatry disorder and extracorporeal dialysis were excluded. During hospitalization, we assessed sex, family history, age, height, weight, stroke subtype, blood pressure, lipid profile, fasting glucose, HbA1c, smoking, alcohol consumption, exercise habits, waist circumference, and ankle-brachial pressure index (ABI). And we also assessed physical activity and salt-intake at 3 month after discharge. We divided into 4 groups followed by physical activity and salt intake. Primary outcome was recurrence of stroke or other vascular events such as myocardial infarction, angina pectoris, and peripheral artery disease during 3 years.

Statistical analysis: Continuous variables are expressed as mean standard deviation (SD). Univariate associations between pathophysiological / lifestyle factors and recurrence were assessed using Kaplan–Meier survival analysis, and significance was determined using the log rank test with continuous variables analyzed as median value. Hazard ratios (HRs) for recurrence were determined by univariate Cox proportional hazards regression analyses and variables with a P value of <0.1 at univariate analysis were entered into a multivariate Cox model to determine HRs. All statistical analyses were performed with the SPSS 16.0 software package (SPSS Japan, Tokyo, Japan), and a P value of <0.05 was considered significant.

Results

• Study population

A total of 102 patients (78 men and 24 women) were successfully followed for 3 years. The mean follow-up period was 1134 ± 80 day. The mean age at study entry was 65.0 ± 10.5 years.

• Outcome at 3 years

Figure 1 shows the Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects. Twenty-five out of 102 patients (24.5%) had stroke recurrence, 4 (3.9%) had a coronary event, 2 (2%) died due to cancer, and 1 (1%) had no fixed residence. Eight patients of the 25 who had recurrent strokes had a severe stroke (mRS ≥ 3).

• Pathophysiological factors

In univariate analyses in patients with LVD, abnormal ABI and MetS were significantly associated with higher recurrence rates. In multivariate Cox regression analyses, LVD (HR:2.81, CI:1.13-6.96, $P=0.025$), abnormal ABI (HR:3.30, CI:1.33-8.20, $P=0.009$) and MetS (HR:2.67, CI:1.23-5.80, $P=0.013$) were selected as significant independent predictors for stroke recurrence or cardiovascular events.

• Lifestyle factors

In univariate analyses, higher salt intake was associated with higher recurrence (HR: 2.43, CI:1.04-5.68, $P=0.040$) and lower physical activity tended to be associated with higher recurrence (HR: 1.10, CI: 0.36 - 3.33, $P=0.076$). When divided into four groups, the poor lifestyle management group was associated with higher stroke recurrence (HR:1.62, CI:1.10-2.39, $P=0.013$). In multivariate Cox regression analyses, the poor lifestyle management group remained associated with recurrence. Kaplan–Meier survival curves for lifestyle management are presented in Figure 2.

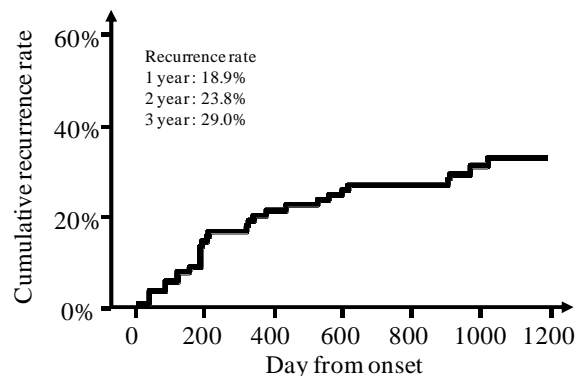


Figure 1. Kaplan–Meier estimates of cumulative recurrence rates of stroke. Deaths without stroke recurrence were censored.

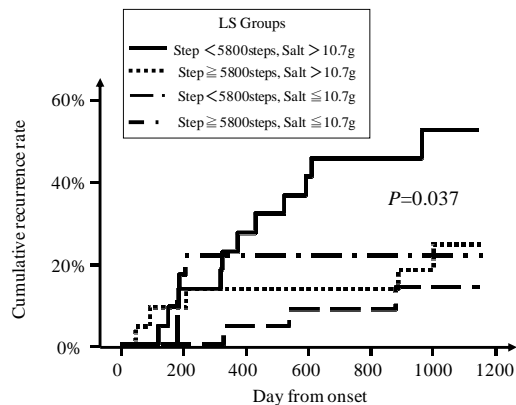


Figure 2.
Kaplan–Meier estimates of cumulative recurrence rates of stroke according to lifestyle management.

Discussion

The results of the present study showed that approximately 30% of mild ischemic stroke patients experienced vascular events during the 3 years after onset. To our knowledge, this report is the first study to demonstrate the high recurrence rate in Japanese patients with mild strokes. Moreover, the findings of this study provide several predictive risk factors which include not only pathophysiological factors but lifestyle factors for vascular events.

In the present study, the 3-year risk of recurrence after mild stroke was approximately 30%, exceeding the 10% to 20% rates reported in previous community-based studies which included mild to severe stroke. There might be several reasons for this discrepancy. First, a high proportion of LVD in the present study might have influenced the recurrence rate. For the background behind this higher recurrence rate, increasing prevalence of recurrent risk factors may raise the rate of recurrence. These risk factors have gradually increased during the past decade in Japanese population. Secondly, race may be a possible reason for high stroke recurrence. High stroke recurrence results in increase of severity of the effects of stroke. Indeed, approximately 30% of cases of stroke recurrence in the present study resulted in severe disability.

Pathophysiological factors for recurrent predictors

The results of the present study indicated that abnormal ABI, MetS and LVD were independent predictive factors for 3-year vascular events. This suggests that advances of atherosclerosis or complexity of traditional risk factors are essential for moderate-term vascular events in mild stroke.

Low ABI, a subclinical marker for lower extremity arterial disease. Previous study showed that ABI is inversely related to traditional risk factors for vascular disease and represents a marker for atherosclerotic changes in other vascular beds. Thus the etiology of abnormal ABI is atherothrombosis. Prevalence of abnormal ABI with other atherothrombosis like stroke in this study has reported to result in poor prognosis. The findings of this study are in line with these previous reports, suggesting abnormal ABI can be

a powerful prognostic factor for stroke recurrence in mild stroke.

MetS shows that obesity with visceral fat accumulation closely associates with atherosclerotic vascular events. Moreover visceral fat obesity is closely related to adipose tissue. Several studies have demonstrated that adipose tissue actively produces a variety of locally and systemically functioning bioactive molecules, including tumour necrosis factor- α , plasminogen-activator inhibitor type-1 and adipocytokine, that also interact in cardiovascular diseases. Especially, adiponectin and leptin effect on increase blood pressure, sympathetic nervous system activity, and expressed within atherosclerotic plaques.[1]

Lifestyle factors for recurrent predictors

High salt intake and lower physical activity were also indicated as independent predictive factors for stroke recurrence. This result highlights that lifestyle modification can help to prevent vascular events. Results from Japanese population-based prospective cohort studies have showed significant associations between salt intake and stroke incidence[2]. As reported in a previous study, stroke mortality has a strong relationship to dietary salt intake independent of blood pressure. The mechanism responsible for the association between salt intake and strokes is still unknown, but may be related to artery thickness, stiffness and platelet reactivity.

Physical activity also tended to be associated with stroke recurrence. In a meta-analysis, lower physical activity had a 33% higher risk of stroke incidence compared with more active individuals[3]. Although the association between physical activity and strokes has not been well established, it has been clearly demonstrated that insulin resistance and HDL-cholesterol, which contribute to prevent the progression of atherosclerosis, are related to higher physical activity. Improvement of endothelial dysfunction by exercise is also other possible mechanism for the prevention of stroke recurrence.

Conclusions

The findings of the present study suggest that the recurrence rate in mild strokes has increased in conjunction with increased prevalence of cardiovascular risk factors. The results also suggest that risk reduction through a combination of medication and lifestyle intervention will improve this higher recurrence rate.

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LOCOMOTOR IMAGERY TRAINING IMPROVES GAIT PERFORMANCE IN PEOPLE WITH CHRONIC HEMIPARETIC STROKE

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Introduction

Motor imagery practice is an active practice in which the patient imagines or visualizes the performance of a function, a movement, or a task without overt physical therapy.¹¹ Beneficial effects of motor imagery practice have been supported through studies of brain-imaging. The same areas of the central nervous system are activated during real performances and during motor imagery practice of the equivalent tasks.^{12,13} Neuroplasticity of motor activity arising from physical therapy is also reproduced on the neural substrate in the brain involving motor imagery practice of the same activity.^{12,14} Recently, motor imagery of gait training for individuals with stroke has been introduced by some researchers.⁵⁻⁷ Most studies on motor imagery practice are focused on treating loss of upper extremity function¹¹ and on improving performance in activities of daily living.¹⁵ There are not full studies of intervening in lower extremity and gait dysfunction^{5-7,11}

Dickstein et al. (2004) reported remarkable improvement in spatiotemporal parameters after gait-focused motor imagery practice. Locomotor imagery training (LIT) for persons with hemiparetic stroke is a motor imagery training technique that improves gait performance without requiring actual movements by paretic or less paretic limbs. LIT may be beneficial for patients who unable to participate in physical gait training secondary to fatigue, severe paralysis, or improper balance.

The purpose of this study was to evaluate whether motor imagery for gait training improves spatiotemporal parameters on gait, related kinematic gait variables and clinical measures for gait in individuals with hemiparetic stroke.

Materials and Methods

Participants: Thirteen hemiparetic hemiparetic subjects were experimental group. Then we recruited same number of age, lesion, sex, post-stroke duration matched control group subjects. However, two subjects in the control group were drop out before completing post-test. The study was approved by the human research ethics committee of all participating institutions, and all subjects signed an informed consent form after they received information about the study's purpose, procedure, possible benefits and risks, privacy and use of data.

The inclusion criteria were (1) six months or more since stroke onset, (2) ability to walk independently over-ground for at least 10 m with or without use of an ankle foot orthosis or assistive device, (3) absence of any cognitive impairment (scores above 24 on the Mini Mental State Examination),¹⁶ (4) ability to understand verbal instructions, (5) no cerebellar lesion, (6) no significant body or visuospatial hemineglect, and (7) a good ability for imagery functioning (a score of 32 or higher on the revision of movement imagery questionnaire).¹⁷ Table 1 explains the general characteristics of the LIT and control groups

Interventions: The subjects in the LIT group participated in four weeks of LIT five-times weekly, with each session lasting 25 to 30 minutes. Subjects in the control group watched documentary television programs for the same period of time.

The first week of the four-week training focused on familiarizing patients with normal gait sequences and

identifying their own problems in gait by studying the differences between the first knowledge of performance of the subject's gait and that of the normal gait. Normal gait sequences were described on the eight phases of gait cycle including initial contact, loading response, midstance, terminal stance, preswing, initial swing, midswing, and terminal swing. The therapist explained the kinematic changes in each phase hip, knee, ankle, and foot. During the last three weeks, the LIT group performed motor imagery practice according to a five-stage protocol: progressive relaxation, external imagery (analysis of task sequences), problem identification, internal imagery, and mental rehearsal. This protocol was developed based on the "active relaxation, imagery, and mental rehearsal (AIM)" strategy, which is commonly used in studies of motor imagery practice for sports.¹⁸ A detail description of the five-stage protocol is shown in Appendix 1.

Outcome Measures and Analysis: 3-dimensional motion analysis system and workstation software, Activities-specific balance confidence scale, Berg balance scale, Dynamic gait index.

Statistics: Pre-treatment demographic data of the subjects were compared between the LIT and control groups using independent t-tests and chi-square (χ^2) tests. Independent t-tests were used to determine whether the changes from the pretest to the posttest of the spatiotemporal, kinematic, clinical parameters significantly differed between the two groups. An alpha level of $P < .05$ was used as statistical significance. All statistical analyses were performed using the SPSS statistical package 12.0¹.

Results

Spatiotemporal parameters

The increase of walking velocity from the pretest to posttest was significantly greater in the LIT group than in the control group ($P=0.034$) (Figure 2). However, the changes between the pretest and posttest for cadence were not significantly different between the two groups ($P=0.722$). The changes of affected and less affected limbs stride length between the pretest and posttest were significantly greater in the locomotor imagery training group (Figure 3). Spatiotemporal parameters except for walking velocity and stride length of both limbs were not significantly different between the groups.

Kinematic data

In the affected hip joint, the peak-to-peak extension-to-flexion angular displacement increased from $31.95 \pm 9.68^\circ$ during the pretest to $38.08 \pm 5.51^\circ$ after the locomotor imagery training. However, the peak-to-peak joint angular displacement of hip extension-to-flexion in the control group decreased $1.46 \pm 4.30^\circ$. In the affected knee joint, the peak-to-peak extension-to-flexion angular displacement increased from $30.25 \pm 14.27^\circ$ during the pretest to $41.20 \pm 12.37^\circ$ after the locomotor imagery training. However, the peak-to-peak joint angular displacement of knee extension-to-flexion in the control group decreased by $3.73 \pm 6.26^\circ$. This change was significantly greater in the locomotor imagery training group compared with the control group ($P=0.001$). However, the test

¹ SPSS Inc, 233 S Wacker Dr, Chicago, IL, USA 60606

changes of other joint motions were not significantly different between the two groups ($P>0.05$).

In less affected hip joint, the peak-to-peak angular displacement of rotation decreased by $8.77\pm 10.57^\circ$, from $22.18\pm 11.63^\circ$ during the pretest to $13.41\pm 5.15^\circ$ at the posttest, in the locomotor imagery training group. However, the peak-to-peak joint angular displacement of hip rotation in the control group decreased by $0.21\pm 9.17^\circ$. This change was significantly greater in the locomotor imagery training group compared with the control group ($P=0.048$). However, the test changes of other joint motions were not significantly different between the two groups ($P>0.05$).

Clinical measures

The changes in the scores of ACTIVITIES-SPECIFIC BALANCE CONFIDENCE scale BBT, and DGI were significantly greater in the locomotor imagery training group compared with the control group (Table 2) ($P=0.000$). The total mEFAP time scores was more decrease in the locomotor imagery training group than in the control group. The change of time scores was significantly greater decreased in locomotor imagery training group compared with control group ($P=0.035$). The performance time in performing all mEFAP (floor, carpet, up & go, obstacles, and stairs) decreased upon termination of the experiment in both the groups. The change of time scores in locomotor imagery training group were significantly greater in all subtests except for up & go compared with those of the control group.

Conclusion

The LIP is a cost effective and relatively safe motor rehabilitation intervention for individuals with stroke.⁹ Locomotor imagery training maximizes practice opportunities for individuals with stroke with hemiakinesia, low-level functional ability, and little or no movement in the paralyzed limb. locomotor imagery training is possible form of early gait training despite focusing cognitive stage in motor learning without overt motor output.

Key Words

Gait, Locomotor imagery training, Motion analysis, Stroke

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Memo

The effects of an isometric knee extension with hip adduction (KEWHA) exercise on selective VMO muscle strengthening

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Introduction

In general, patellofemoral rehabilitation involves maximizing quadriceps strength while minimizing the patellofemoral joint reaction forces and stress (Tang et al., 2001). There are many types of quadriceps strengthening exercises. Traditionally, quad sets (Cerny, 1995) and knee-extension exercises have been used (Hanten and Schulthies, 1990). However, these are designed to strengthen the whole quadriceps femoris. The VL muscle is naturally stronger than the VMO muscle; therefore, sustained exercise of both facilitates further strengthening of the VL muscle. In addition, during these exercises, lateral and medial forces are not adequately balanced, and increased lateral displacement of the patella into the trochlear groove occurs (Grabiner et al., 1994). This continued imbalance between the VMO and VL muscles accentuates PFPS (Hanten and Schulthies, 1990).

In this study, we investigated the 4-week training effects of knee extension with hip adduction on onset timing of EMG activity for the VL muscle and VMO muscle in asymptomatic participants. We also compared different methods for the determination of EMG onset times.

Methods

Design: The training effect was evaluated using a one-group pretest–posttest study design. We measured EMG onset times during pre- and post-stair ascending tasks. We determined whether VMO muscle onsets were earlier than those of the VL muscle and whether the times of EMG onset changed after training.

Participants: Thirty-three participants with no known lower extremity surgical, musculoskeletal, or neurological history participated in the pretest session of this study. Participants showed faster VL muscle than VMO muscle EMG onset times when they ascended stairs, were selected as participants for the 4-week training using the knee extension with hip adduction (KEWHA) exercise.

Equipment: Muscle EMG activities were recorded using a Noraxon Telemyo 2400T (Noraxon Inc., Scottsdale, AZ, USA) with two bipolar Ag–AgCl surface electrodes (Blue sensor, Olystyke, Denmark) during a stair-ascending task. Custom-made stairs were used in this study and consisted of two steps, 20 cm in height, leading to a 60-cm-long platform. The first stair had a run of 28 cm, and the second stair had a run of 90cm. **The stair ascending task:** During the pre-test, the stair-ascending task was used to identify subjects with earlier VL muscle onsets, as described previously (Cowan et al., 2001; Crossley et al., 2004; Hinman et al., 2002). Participants placed the non-dominant foot on the floor, 20 cm away from the dominant foot which was on top of the first step, with the hip and knee joints at approximately 45°; their arms were relaxed by their sides. Both feet were parallel and shoulder-width apart, with no hip rotation and no pelvic rotation. Weight-bearing was mainly on the non-dominant foot, with minimal weight-bearing on the dominant foot where it was in contact with the stair (controlled by an EMG biofeedback program, threshold 1.0–2.0 μ V). The participants were instructed to ascend with their

non-dominant foot, to keep their trunk in an upright position, and to maintain a steady gaze to the front. Ascending speed was at a rate of 96 steps per min, as paced by a metronome, because it is not known if onset time is affected by different walking speeds. Ascending began randomly when the examiner sounded a bell. Prior to the examination, participants practiced ascending the stairs to ensure they were able to step in time to the metronome. The EMG onsets for the VMO and VL muscles in the stair-ascending task during the pre-test were used to select participants with a 10-ms later onset for the VMO muscle than for the VL muscle (Cowan et al., 2002).

Intervention: Subjects were selected on the basis of the pretest participated in the 4-week KEWHA exercise. Participants sat on the Noland–Kickoff table (N-K table) and performed isometric knee extension exercises with 15° hip adduction, as described by Monteiro-Pedro et al. (1999). The subjects performed the exercise 3 days a week with a trainer and 2 days a week at home for a total of 4 weeks. Each session consisted of five trials of 10 repetitions (resting for 5 s between repetitions). One trial involved alternating legs to prevent asymmetry between the strength of the right and left quadriceps muscles. Subjects were seated with their arms folded across their chests and used a back-rest set at a hip angle of 130°. A belt was attached to both the pelvis (from the anterior superior iliac spine [ASIS] line to the chair) and the trunk (under the inferior angle of the scapula to the chair) to prevent motion of the pelvis and the trunk. The chair height was adjusted so that both feet were off the floor.

Results

Effect of the knee extension with hip adduction (KEWHA) exercise on VMO and VL muscles onset time differences

The means \pm SDs of the EMG onset time differences in the pre- and post-tests are shown in Figure 1. There was no significant difference among the EMG onset time differences for the VMO muscle compared with the VL muscle between the pre- (-7.72 ± 95.88) and post-tests (-4.22 ± 40.98) ($p = 0.63$) when data at two SDs of the mean baseline activity were analyzed. Very large variations in individual onset times were observed. When data at three SDs of the mean baseline activity were analyzed, less variation in individual onset times was found, and there was a significant difference in the onset time differences for the VMO muscle compared to the VL muscle between the pre- (23.78 ± 13.61) and post-tests (-15.44 ± 34.70) ($p = 0.00$).

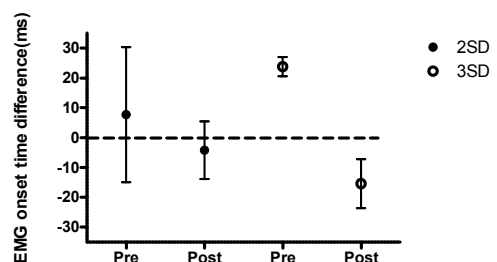


Figure 1. Mean EMG onset time differences (OTD) between VMO and VL during ascending stair task. The dot indicates the mean EMG OTD and the each line indicates the standard deviation (SD). Two and three standard deviations of the mean baseline activity; (2SD, 3SD), VL onset time faster than VMO onset time; (VMO < VL), VMO onset time faster than VL onset time; (VMO > VL).

Discussion

The results of this study indicate that participants with a delayed onset time for the VMO muscle showed a decreased difference between VMO and VL muscles onset time after performing the KEWHA exercise for 4 weeks. These results are in accordance with those of Cowan et al. (2002), who conducted studies during a McConnell-based rehabilitation program. However, their study focused on the effects of the position of hip adduction on VMO muscle onset time during the knee-extension exercise, not on a complex exercise program. In addition, our investigations showed that when the threshold for activity was set at two SDs of the mean baseline activity, the results were more variable than those using a threshold of three SDs.

Knee extension with hip-adduction (KEWHA) exercise

Hip adduction exercises can be used to selectively strengthen the VMO muscle (Coqueiro et al., 2005). Previous studies combined hip adduction and open- or closed-chain exercises performed by asymptomatic subjects. The VMO muscle exhibited a significantly greater amount of activity than the VL muscle during open chain hip-adduction exercises (Hanten and Schulthies, 1990). No change in the activity of the VMO muscle was found during a combination of isometric hip adduction and open-chain knee extension, although VL muscle activity was significantly less than that of the VMO muscle. These data indicate that extensor mechanisms can reinforce decreased VL muscle activity (Rice et al., 1995). Earl et al. (2001) produced more overall activity in the quadriceps by combining isometric hip adduction with a closed-chain mini-squat. However, this exercise did not specifically support the activity of the VMO muscle, as VMO and VL muscles activity increased by the same amount. Reports on the activation of the VMO and VL muscles during open- or closed-chain exercises cannot be applied to our study, as they are not directly related to it. We did not consider open- or closed-chain exercises, as we modified the methods of traditional quadriceps strengthening exercises that use extension of the knee joint from 90° flexion to full extension on the N-K table. Furthermore, the purpose of our study was to investigate the differences in onset times that arise from changes in motor control as well as the differences in quadriceps activation after exercise. Herrington and Pearson (2006) found no significant differences in onset times between open- and closed-chain knee extension exercises. This suggests that the interactions between the VMO and VL muscles remain fairly constant irrespective of the type of exercise.

Conclusion

The knee extension exercise is an established 'self-exercise' used for knee pathology treatment and strengthening exercises. However, if therapists do not adequately instruct the subject on proper positioning, the patella will receive a negative impact due to an imbalance in the activation of the VMO muscle and VL muscles. This study describes the 4-week training effects of the KEWHA exercise, which was used in an attempt to decrease the onset-time difference between the VMO muscle and VL muscles. This is one factor that influences the lateral tracking of the patella. As a result of the 4-week training period, the onset time difference between the VMO and VL muscles was decreased. In our study, the KEWHA exercise removed

one of the PFPS risk factors that reduced the onset time difference between the VMO muscle and VL muscle. Furthermore, we suggest that the use of a correct KEWHA exercise may reduce the risk of lateral tracking of the patella.

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