Robotic Training for Stroke Neurorehabilitation

NCT02639390

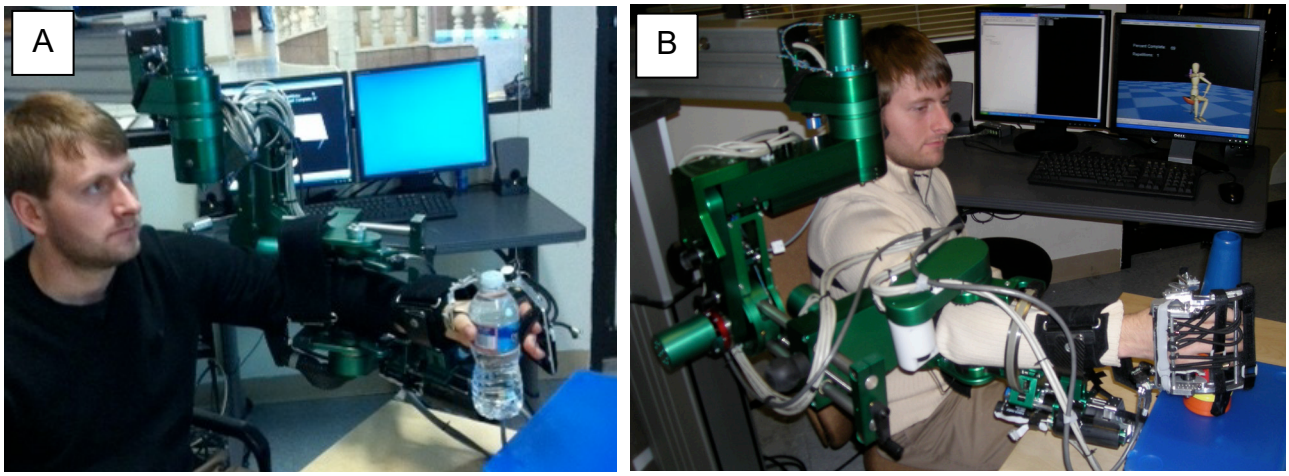
10/1/2017

1. Title

Task-specific upper-extremity robotic training for stroke neurorehabilitation

2. Objective

Our long term objective is to improve the lives of veterans and civilians with impaired upper extremity (UE) function after stoke. We previously developed a novel training protocol that combined the ARMin and HandSOME exoskeletons (Fig. 1). This is one of only a few arm exoskeletons that allow coordinated whole limb training in reach and grasp tasks with both virtual and real objects. A pilot clinical trial using this robotic device with stroke subjects was funded by the Department of Veterans Affairs and performed at the DC VAMC under protocol# 01103: "Use of an innovative robotic system for upper limb rehabilitation following stroke". We found that this robotic exoskeleton elicited improvements in arm function that can potentially supplement conventional methods to improve outcomes (Brokaw 2014). In this study, a clinical trial will be performed to evaluate this robotic therapy against conventional treatment.



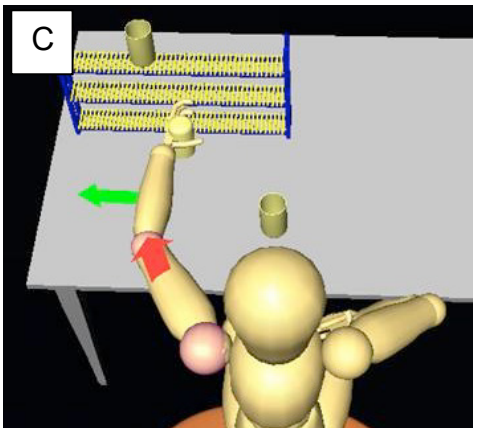


Figure 1. (A & B) ARMin and HandSOME devices. (C) Visual feedback user interface during the shelf task. Virtual cups are grasped and placed on a high shelf. Arrows indicate the direction of joint rotation needed to complete the task. The arrow colors indicate if a joint is not rotating in the correct direction and preventing advancement in the trajectory. During training with real objects, the subjects focus on the object to be moved and refer to the visual interface only when they get stuck and need guidance.

3. Aims / Hypotheses

Specific AIM: We will perform a clinical trial to compare the effectiveness of robotic training to conventional therapy from an occupational therapist. To take advantage of the facilitatory effect of robot therapy on subsequent conventional therapy, the experimental treatment will be 12 hours of robot therapy followed by 12 hours of conventional therapy. Chronic stroke

subjects (N=46) will be randomly assigned to receive this experimental treatment or 24 hours of conventional therapy from an occupational therapist.

Hypothesis I: Gains from the initial 12 hours of robotic therapy will be significant ($p<0.05$) in the domains of impairment (Fugl-Meyer), function (Action Research Arm Test) and amount of arm use (Motor Activity Log).

Hypothesis II: Gains in impairment, function and arm use in the experimental group (robot + conventional therapy) will be significant ($p<0.05$) and clinically important (defined as greater than 10% gain) immediately after all treatments and also at the 6-month follow-up.

Hypothesis III: Gains in impairment, function and arm use will be significantly greater in the experimental group (robot + conventional therapy) than the conventional therapy control group immediately after the end of all treatments and also at the 6-month follow-up.

4. Background

Approximately 795,000 individuals in the United States have a stroke each year (Go 2014). Approximately 15,000 veterans are hospitalized for stroke each year (http://www.queri.research.va.gov/str/), with costs of $75 million for post-acute inpatient care and $88 million annually for follow-up care (http://www.queri.research.va.gov/about/factsheets/stroke_factsheet.pdf). Fifty percent of stroke survivors older than 64 have persistent hemiparesis at six months post-stroke and 26% are dependent in activities of daily living (ADL)(Roger 2012). In the upper extremity, reaching and grasping movements are often impaired and a focus of rehabilitation. Impairments include decreased muscle activation and weakness (Zackowsky 2004, Gowland 1992), disrupted interjoint coordination (Cirstea 2003, Beer 2000), decreased smoothness of movement (Rohrer 2002, Krebs 1999), and dyscoordination between reach and grasp movements (van Vliet 2007). Limitations in ADL ability and decreased quality of life can result from even mild impairments in upper-limb function (Nichols-Larsen 2005, Dromerick 2006).

In a pilot clinical trial funded by the Department of Veterans affairs, we found that the robotic exoskeleton elicited improvements in arm function that can potentially supplement conventional methods to improve outcomes (Brokaw 2014). The robot has 5 active motors that assist with 3 shoulder DOF, elbow flexion/extension and supination/pronation (Fig. 1). A passive hand orthosis (HandSOME) is worn to assist with opening the hand. Twelve chronic stroke subjects were randomized to 12 hours of robotic or conventional therapy and then crossed over to the other therapy type after a 1 month washout period. Across the 3 month study period, subjects showed significant improvements in the Fugl-Meyer Test of Motor Function ($p=0.013$) and Box and Blocks tests ($p=0.028$). The Fugl-Meyer (Fugl-Meyer 1975) tests impairment throughout the upper extremity, while the Box and Blocks (Platz 2005) scores the number of one-inch blocks that can be moved from one box to another over a partition in one minute. In the Action Research Arm Test (ARAT, Lang 2006), a measure of function, the robotic intervention produced significantly greater improvements than conventional therapy ($p=0.033$).

Interestingly the robotic training appeared to facilitate the effects of conventional therapy. There were significant gains in the Box and Blocks after conventional therapy only if it was preceded by a period of robotic training ($p=0.044$). Clinically significant gains were present in the Fugl-Meyer when robot therapy was given first and followed by conventional therapy. The mean gain was 7±2.2 points, which was statistically significant ($p=0.034$). This gain was larger than 10% of full scale (6.6 points), which is considered the minimally clinically important difference (MCID) on this scale (Gladstone 2002, Lo 2010, Page 2012). In the ARAT, the gains at the end of treatment (robot + conventional) did not reach the MCID threshold of 10% or 5.7

points (van der Lee 1999, van der Lee 2001). However, gains following the first period of robot treatment did approach the MCID threshold (gain=5.6±2.1; p=.057).

5. Study Design

Overview

The robotic system will be used in a clinical trial with chronic stroke subjects with impaired upper extremity function. 46 subjects will be randomly assigned to an experimental or control group. The experimental group will receive 1-hour robotic training sessions, 3 times per week for a total of 12 sessions supervised by a research assistant. Immediately following this robot training, these subjects will receive the same dosage and schedule (1-hour sessions, 3 times/week, 12 total sessions) of conventional one-on-one therapy from an occupational therapist. The control group will receive 24 hours of conventional one-on-one therapy on the same schedule (1-hour sessions, 3 times/week). Clinical and biomechanical evaluations will be performed before treatment, after 12 hours of treatment, after 24 hours of treatment and at a 6-month follow-up.

Recruitment

Subjects will be recruited from the outpatient clinics at the Washington DC VAMC. The DC VAMC annually has over 100 admissions for stroke. Co-investigator Dromerick, MD, has WOC status at the DC VAMC and will confirm that patients meet study criteria. Additionally, veterans will be recruited from nearby MedStar National Rehabilitation Hospital (NRH), Washington Hospital Center (WHC), and Medstar Health outpatient clinics.

The inclusion criteria are: 1) Age 21 or older; 2) ischemic or hemorrhagic stroke (with confirmatory neuroimaging) that occurred more than 6 months before entering the study; 3) presence of voluntary hand activity indicated by a score of at least 1 on the finger mass extension/grasp release item of the Fugl-Meyer Test of Motor Function; 4) adequate cognitive status, as determined by Mini-Mental Status Examination (Bleecker 1988) score >24; 5) no upper extremity injury or conditions that limited use prior to the stroke. Subjects will be excluded if they: 1) cannot give informed consent; 2) have clinically significant fluctuations in mental status within a month of enrollment; 3) were not independent prior to the stroke as measured by scores <95 on the Barthel Index (de Morton 2008) or >1 on the Modified Rankin Scale (Quinn 2009); 4) have hemispatial neglect as determined by >3 errors on the Star Cancellation Test (Manly 2009); 5) have severe sensory loss as determined by a score of 2 on the sensory item of the NIHSS (Lai 1988); 6) receiving oral or injected antispasticity medications during study treatment; 7) pain that interferes with daily activities; 8) history of prior stroke.

In a previous study in chronic stroke, we found that the dropout rate was 16.7%, so we will plan to **recruit 46 subjects**. Subjects who drop out of the study will be replaced until a total of **38 subjects complete the protocols**. All therapy will be in addition to the regular PT and OT subjects may be receiving as part of their outpatient treatment. The amount of outside PT or OT targeting arm or hand function received by subjects while enrolled in the study will be logged and used as a potential covariate in the analysis.

Experimental group treatments

Subjects will come to the clinic 3 times/week for 1-hour sessions until 12 hours of robotic treatment are received. All robot therapy sessions will be run by a research assistant trained in use of the robot. The treatment Occupational Therapist (Rahsaan Holley) will be available during robot training should an issue arise requiring his guidance. The training will be similar to that used in our pilot study. Tasks will include a Shelf Task, where subjects grasp objects and place them on a shelf using simultaneous shoulder elevation and elbow extension. In a Pouring Task, subjects grasp and pour from a pitcher using shoulder internal/external rotation and

simultaneous wrist pronation/supination. In Sorting, subjects grasp and move objects from one location to another using shoulder elevation and simultaneous shoulder horizontal abduction. An automatic algorithm grades the level of arm gravity compensation and assistance torques at the joints. Subjects practice first with virtual objects and then physical objects are added to increase difficulty.

Following the robotic training, subjects will undergo one-on-one therapy sessions from a Occupational Therapist with 14+ years of experience (Rahsaan Holley). Subjects will come to the clinic 3 times/week for 1-hour sessions until 12 hours of treatment are received. Individualized programs focusing on arm function are established at the initial training session based on assessment and patient goals. Treatment will focus on practice of specific tasks, such as reach, grasp, transport and release of various objects between different targets. Progression is done by varying the shape, size and weight of objects, altering the end range of the target or increasing the speed of movement. In weak muscles, manual therapy techniques are used to obtain isometric contractions in the shortened range. Subjects receive mobilization to restricted joints as needed and stretching exercises to increase range-of-motion. Higher functioning subjects select from isolated hand movements (typing, 'playing the piano', molding putty) and whole body activities such as swinging a tennis racquet or carrying a tray on an open hand.

Control group treatments

Subjects will receive 24 hours of one-on-one treatment from the same therapist (Rahsaan Holley) that performed the conventional therapy for the experimental group. The treatment sessions will be identical to the conventional therapy provided to the experimental group. The treatment schedule will parallel that given to the experimental group (1-hour sessions, 3 times/week).

Clinical evaluations

Clinical evaluations will be performed before training, after 12 hours of treatment, after 24 hours of treatment and again at the 6-month followup. All clinical testing will be performed by an Occupational or Physical Therapist (TBN), who has extensive experience in performing these tests. He/she will be blinded to the study design and unaware of the sequence or content of training that subjects receive. The Fugl-Meyer Test of Motor Function will be used to assess motor impairments at the shoulder, elbow, wrist and fingers (Fugl-Meyer 1975). The Fugl-Meyer test scores reflexes and the ability to perform several movements and tasks on a 3-point scale. The Fugl-Meyer was designed for the recovery patterns observed after stroke and is very responsive to change in severe and moderately impaired subjects, but is less responsive in mildly impaired subjects (van der Lee 2001). The Action Research Arm Test (ARAT) (Lang 2006) is an impairment level measurement tool that assesses the functional limitations of the upper extremities. It is one of the most frequently used primary endpoints in UE training trials in stroke. The assessment incorporates 19 items that are divided into four subscales: Grasp, Grip, Pinch, and Gross movement. Item scores are summed to form a subtest score, and then a full-scale score. The ARAT has established reliability, responsiveness and validity in stroke subjects (Platz 2005). The Motor Activity Log (MAL) will be used to assess use of the limb at home (Uswatte 2006). It is a structured interview during which respondents are asked to rate how they use their more-impaired arm for 28 ADL in the home over a specified period. The MAL is administered independently to the patient and an informant. Activities include brushing teeth, buttoning a shirt or blouse, and eating with a fork or spoon. For each item the participant must report how well (6-point, Quality of Movement or QOM scale) and how often (6-point, Amount of Use scale) each activity was performed during a specified period. The MAL has high internal consistency, test-retest reliability, and high convergent validity (Uswatte 2005).

Secondary outcome variables

We will also perform the Box and Blocks test as a secondary measure of function. The Box and Blocks (Platz 2005) scores the number of one-inch blocks that can be moved from one box to another over a partition in one minute. We did not include Box and Blocks as a primary outcome because we are unaware of any studies that have estimated MCID for this test in chronic stroke. However, we include this as a secondary measure because of our pilot study results, which showed that conventional therapy was especially effective in affecting performance gains in this outcome if preceded by a period of robotic therapy.

To assess the movement strategies used by the upper limb, three dimensional motion analyses will be performed pre-treatment, post-treatment and at the 6-month followup. We will use a protocol for data collection currently being used as part of an ongoing VA Merit Review Project. We will measure the three dimensional movements of the arm and trunk during the performance of standardized versions of common everyday tasks. These tasks include placing a nut on a bolt, shelving boxes, taking a drink from a water bottle, opening a jar, etc. We will use an electromagnetic motion capture system, the MiniBirds® (Ascension Technologies) controlled by the Motion Monitor® Software (Innovative Sports Technology). The electromagnetic markers will be placed at the first thoracic vertebrae spinous process, acromion, the lateral aspect of the brachium, distal dorsal aspect of the antebrachium, dorsum of the hand at the base of the third metacarpal, thumb nail, index finger nail. These sensors will record body segment and finger movements in 3D space with a sampling rate of 120 Hz. The procedure for identifying landmarks and generating segment local coordinate frames is integrated into the Motion Monitor software. The output metrics will be grasp aperture and range of motion at the trunk, glenohumeral, elbow and wrist joints. After training, we expect less trunk movement, larger range of movement at the glenohumeral and elbow joints, and larger grasp aperture. Biomechanical data is not required to test the hypotheses of the study, but will be used in secondary analysis to further explore the changes in clinical scales observed in subjects.

Data analysis

Prior to conducting the main analyses, summary statistics, histograms, and scatter plots will be inspected to verify that distribution assumptions are met. Adjustments (e.g., transformations) to the main dependent measures will be made as necessary to address any problems (e.g., skewness, outliers) that these preliminary analyses uncover. To test Hypotheses, a series of mixed model ANOVAs will be tested, one for each dependent variable, with the within-subject variable being timepoint (pre, after 12 hours of treatment, after 24 hours of treatment, 6 month followup) and the between-subject variable of group (experimental vs. control). A significant effect of timepoint or a significant timepoint x group interaction would be followed with a series of paired t-tests, with Bonferoni corrections. Hypothesis I will be tested with a paired t-test between the pre and post-robotic timepoint (after 12 hours of robotic treatment). Hypothesis II will be tested with a paired t-test between the pre and post-treatment timepoint in the experimental group (after 12 hours of robot and 12 hours of conventional therapy). Additionally a z-test will be performed for the hypothesis that the proportion of subjects with 10% or greater gain at the post-treatment timepoint is significantly greater than zero. A final paired t-test and z-test between pre and 6-month followup timepoints will be performed. If a change is statistically significant, mean changes will be compared to predetermined MCID values of 10% of full scale. To test Hypothesis III, the timepoint x group interaction effect will be examined in the mixed model ANOVA. If significant, gains in the dependent variables will be calculated at the post-treatment and 6-month timepoints (relative to the pre timepoint), and between-group differences will be tested with unpaired t-tests, with Bonferoni corrections.

In secondary analysis, we will look to identify the characteristics of patients who are most responsive to the treatment. Potential predictors include initial impairment level, and time-varying predictors such as amount of home use (MAL) at the previous assessment. The subjects will be divided into severe (Fugl-Meyer<30), moderate (30<Fugl-Meyer<50) and mild impairment groups (Fugl-Meyer>50). This division is based on a previous study that reported subjects with initially moderate impairment (Fugl-Meyer = 40) benefited the most from robotic therapy, with reduced effectiveness in severe and mildly impaired subjects (Hsieh 2012). The dependent variables will be gain in the FM, ARAT and MAL at each timepoint. A fixed effects (mixed) model will be used to determine if the gains over time were the same across the 3 impairment groups, and whether use at home in the preceding time interval predicts later improvement.

Power Analysis

The power analysis was based on data from our previous pilot study (Brokaw 2014). To address Hypothesis I, we calculated power to detect significant gains after only the robotic training. Using the pre-post changes after the initial period of robotic therapy from our pilot study, the effect size for the ARAT was dz=1.2, with pre-post correlation r=0.94. In order to detect an effect this large, when using a 1-tailed paired t-test with alpha=.05, a sample size of **N=8** is required for power > 0.90 (Faul 2009). For the Fugl-Meyer, the effect size was dz=0.74, with pre-post correlation r=0.85, which would require a sample size of **N=18** for power > 0.90.

To power Hypothesis II, the pre-post effect size for gains on the ARAT after the experimental treatment (12 hours of robot + 12 hours of conventional therapy) was dz=0.77, with pre-post correlation r=0.95 (only using data from subjects who received robotic therapy followed by conventional therapy). In order to detect an effect this large, when using a 1-tailed paired t-test with alpha=.05, a sample size of **N=16** is required for power > 0.90. For the Fugl-Meyer, the pre-post effect size was dz=1.41, with pre-post correlation r=0.91. In order to detect this difference, only **N=6** subjects are required for power > 0.90.

To address Hypothesis III, we calculated the power to detect the expected differences in gains between the experimental and control groups. The experimental treatment in our pilot study produced gains of 7 (sd=4.9) in the Fugl-Meyer. A recent study reported gains of 2.47 (sd=1.67) on the Fugl-Meyer after 24 hours of conventional therapy in 35 stroke subjects with similar intake Fugl-Meyer scores as in our pilot study (FM = 22.4 vs. 21) (Klamroth-Marganska 2014). Using these data, the mean difference in treatments will have an effect size of 1.9. For a 1-tailed unpaired t-test, **N=5** subjects in each treatment group are needed to detect this difference with power > 0.80. Similarly for the ARAT, we had gains of 5.6 (sd=4.7) after the experimental treatment in our pilot study. A different study (Fleming 2015) reported gains of 1.0 (sd=5.7) after 24 hours of conventional therapy in 17 chronic stroke subjects with similar intake ARAT scores as in our pilot study (ARAT = 26.6 vs. 20.9). Using these data, the mean difference in treatments will have an effect size of 0.84. For a 1-tailed unpaired t-test, **N=19** subjects in each treatment group will detect this difference with power > 0.80.

Therefore with **N=19** subjects in each treatment group, we will detect the anticipated pre-post changes and group differences in the ARAT and Fugl-Meyer. We had a dropout rate of 0.167 in the pilot study. Therefore, we will plan for this and recruit 23 subjects into each treatment group. We have no pilot data on the MAL to perform a power analysis for the outcome.

6. Data Monitoring, Information Security and Safety

The PI and co-investigator (Dromerick) will oversee safety for the study; and an independent study monitor will be identified if the DCVAMC requires one. Frequent rest breaks

will be offered during the laboratory-based testing. Should complications occur, Dr. Dromerick will oversee management until care can be transferred to the participant's caregivers. All data collected will remain confidential. Data will be coded by subject number according to an established laboratory convention and reference made to individual subjects only in this manner. All raw data in the form of hard copy materials and computer files remain property of the laboratory under the direction of the Principal Investigator. The study records will remain the property of the Prinicipal Investigator's laboratory and be destroyed according to the VA Records Control Schedule (RCS). All identifying personal information will be removed from the data. The master list of subject codes and the corresponding subject names will be kept in a locked filing cabinet and not leave the DC VA Medical Center. All data will be stored in the Clinical Research Center, Human Performance Research Unit, room #1043. All electronic data will be stored on VA networked drives. If data is stored on PC hard drives, the PC will be encrypted. No mobile devices will be used to store data and data will not be removed from the VA-protected environment. Study personnel who leave the study will not longer have access to the data. Standard procedures are in place for reporting incidents, i.e. theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls.

7. Facilities

Washington DC VAMC will be used to conduct various aspects of the research study. All data will be stored at:

Washington DC VA Medical Center
Clinical Research Center
Human Performance Research Unit
50 Irving St. NW, #1043
Washington, DC 20422

8. Project Organization

All testing will be conducted by the Primary Investigator (Lum), Sub-Investigator (Dromerick), or project coordinator (Holley). Analysis will be performed by the statistician (Amdur).

9. Project Schedule

Testing will begin approximately on 6/16 and continue for four years.

10. Problems / Weaknesses

Identifying and recruiting the participation of appropriate subjects will be a challenge for this study. Substantial plans have been established to address subject accrual and have been budgeted accordingly. Recruitment efforts will begin at the DCVAMC and expand to local facilities as needed.

11. Monitoring and Reporting Adverse Events

The anticipated adverse events are all mild. These adverse events will be retained in a study binder for review by the study team. Unanticipated adverse events of a serious nature will reported to the IRB within 2 days.

12. Risk / Benefit Assessment

Potential risks posed to those who decide to participate in this study include the rare possibility of muscle and/or joint soreness related to over-exertion; similar to the soreness felt after using exercise equipment. Additionally, the possibility exists that participants may experience skin irritation from the use of tape on the skin during the motion capture, or from pressure points from contact with the robot. Subjects will be encouraged to discuss such risks with the investigator, the subjects' primary care physicians, and/or family and friends before agreeing to participate in study.

According to FDA guidelines, the robot and hand exoskeleton are classified as a non-significant risk investigational device because:

1) The device is not an implant.
2) The device is not used in supporting or sustaining life.
3) The device is not of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health.
4) The device does not present a potential for serious risk to the health, safety, or welfare of the subject.

There may be direct benefits related to subject participation in this research study; however, this is not guaranteed to be the case for all subjects who participate.

13. Study Population

No gender and/or ethnicity will be excluded from participating in the study. The study will attempt to maintain a balanced cohort based on both gender and ethnicity.

14. Recruitment Plan

Subjects will be recruited from the outpatient clinics at the Washington DC VAMC. The DC VAMC annually has over 100 admissions for stroke. Co-investigator Dromerick, MD, has WOC status at the DC VAMC and will confirm that patients meet study criteria. Additionally, veterans will be recruited from nearby MedStar National Rehabilitation Hospital (NRH), Washington Hospital Center (WHC), and Medstar Health outpatient clinics.

15. Vertebrate Animals

N/A

16. Consultants

N/A

17. Curriculum Vitae

Attached

18. Compliance

The trial will be conducted in compliance with the protocol, HHS, FDA, ICH, VA and all applicable institutional state and local requirements.

19. References

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