STATISTICAL ANALYSIS PLAN

FOR CLINICAL TRIAL

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Official Study Title: The Comparison of Virtual and Real Boxing Training in Hemiparetic Stroke Patients: a Randomized Controlled Study

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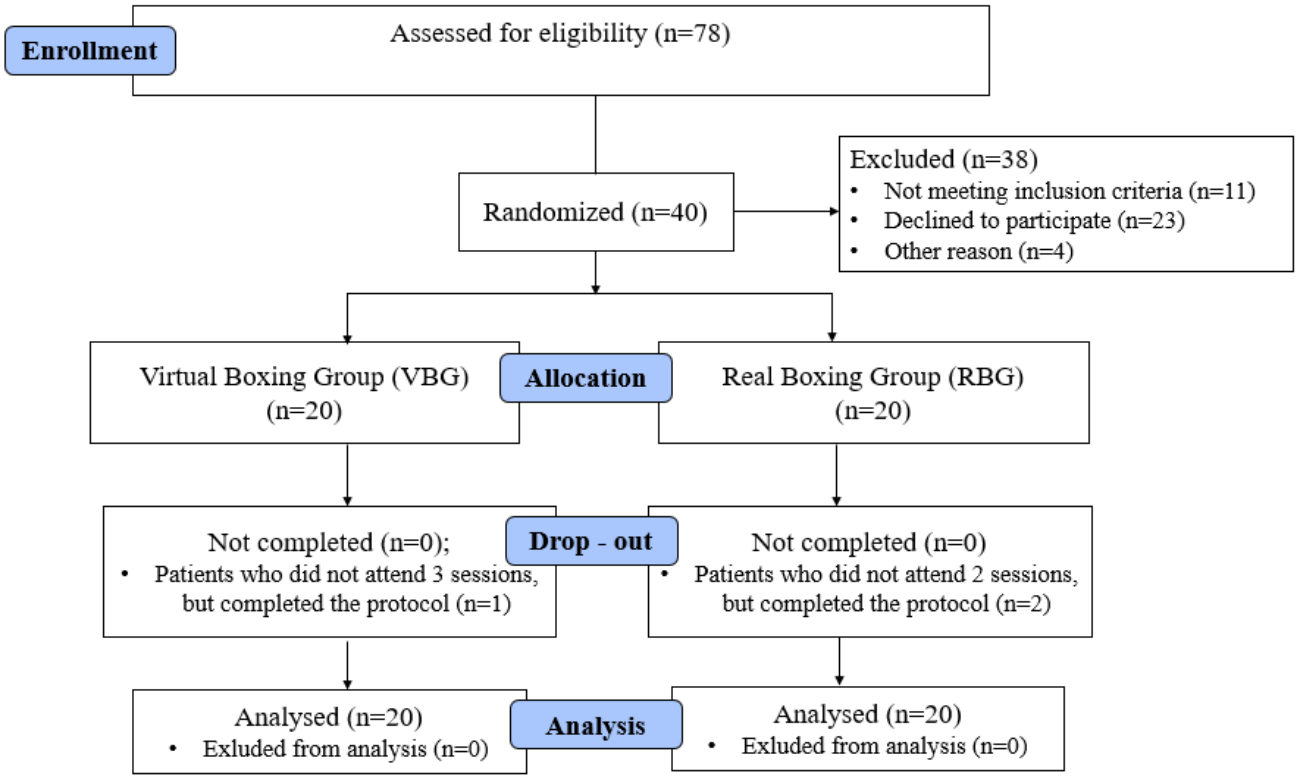
1. **Introduction**: The most common presentation of a stroke patient requiring rehabilitation is contralateral hemiparesis or hemiplegia. Upper extremity hemiparesis is one of the most common conditions requiring rehabilitation and upper extremity dysfunction occurs in rates ranging from 30% to 66%.[1] Upper extremity functional recovery is often slower than the recovery of lower extremity functions. [1,2] Only a small portion of stroke patients with upper limb motor impairment (12%) is able to regain full function, while the majority of the patients require constant care from family or social services.[3] The aim of this study is to compare the effects of virtual and real boxing training on upper extremity functions (primary outcome measure), cognitive functions, balance functions and activities of daily living (secondary outcome measures) in hemiparetic individuals with stroke. This statistical analysis plan (SAP) will give more detailed descriptions of the endpoints in the study and the corresponding analyses.

2. **Study design:** In this study participants who had a documented diagnosis of stroke from their neurologist from the local community will be screened for eligibility. The participants who are being diagnosed as first time ever stroke, who has hemiparesis, who are between the ages of 18-70, who has Mini Mental Test score ≥23, whose functional level is less than 4 according to the Modified Rankin Scale and who has upper extremity spasticity <3 on Modified Ashworth Scale will be included in this study. Individuals will be excluded from the study if they have any of the following criteria: hypertension, heart disease, subluxation and fracture at the shoulder, visual impairment, limitation in passive normal joint movement in hemiplegic side and botulinum toxin administration or surgical operation in the last 6 months. If the participants are eligible to participate they will be randomized to either the virtual boxing group (VBG) or the real boxing group (RBG). Each participant will be randomly assigned to either treatment group with simple randomization (odd - even numbers: odd numbers will represent VBG and even number will represent RBG). The study protocol is presented in *Study protocol - CONSORT diagram* below.

3. **Sample size calculation:** Sample size will be calculated by using G* Power 3.1.9.2 program. The mean and standard deviation values are taken as a reference from the study of Jo et al.[4] Statistical power analysis calculations suggested 15 subjects for each group ($\alpha = 0.05$, 95% confidence interval), considering the dropouts the number was increased by 33% and finally 20 subjects planned to be included for each group. Based on the power calculation (n=20+20) we will enroll 40 individuals in each treatment group; n=20 in virtual boxing group (VBG) and n=20 in real boxing group (RBG).

Study protocol (CONSORT diagram)



4. **Aims and objectives:** To compare the effects of virtual and real boxing training on upper extremity functions (primary outcome measure), cognitive functions, balance functions and activities of daily living (secondary outcome measures) in hemiparetic individuals with stroke.

5. **Outcomes:** This section will present the outcomes investigated to answer the study aims and objectives.

5.1. Primary outcome: The primary outcome is Wolf Motor Function Test (WMFT) which quantifies upper extremity motor ability through the use of timed and functional tasks. The original version of the WMFT was developed by Wolf et al in 1989 to examine the patients with moderate to severe upper extremity motor deficits. [5] Than, the modified version of the test was developed by Taub et al to assess the motor abilities of chronic patients who had suffered mild to moderate stroke. [6] The widely used version of the WMFT consists of 17 items, items 7 and 14 are related to subject strength and the other 15 to subject functional ability during various tasks. Performances are scored using a 6-point functional ability scale and the less affected upper extremity followed by the most affected side. The total score, also referred to as Functional Ability score (WMFT-FAS), is the sum of the 15 items score (with a 6-point ordinal score from 0 to 5). The maximum

total score is 75, with lower scores indicating lower functional levels.[7] It will be measured at baseline (0 weeks) and at the completion of the treatment (8 weeks). The change in scores from Baseline to 8 weeks will be calculated.

5.2. Secondary outcomes: Minnesota Manual Dexterity Test (MMDT), Video Boxing Analysis (VBA), Fullerton Advanced Balance (FAB), Addenbrook Cognitive Assessment (ACE-R) and Frenchay Activity Index (FAI). The secondary outcome will be measured at the baseline (0 weeks) and at the completion of the treatment (8 weeks). The change in scores from Baseline to 8 weeks will be calculated. The estimated difference in mean change from baseline to 8 weeks and the corresponding 95 % confidence interval (CI) will be presented.

5.2.1. Minnesota Manual Dexterity Test (MMDT): MMDT measures the speed of gross arm and hand movements (arm-hand dexterity) during rapid eye-hand coordination tasks. The MMDT material consists of a plastic collapsible board with 60 holes and 60 cylindrical blocks (3.7 cm in diameter and 1.9 cm high). The MMDT involve five subtests: Placing Test, Turning Test, Displacing Test, One-hand Turning and Placing Test, and the Two-hand Turning and Placing Test. The Placing Test (1st item: taking the blocks with one hand and putting them in the holes on the board in a standardized order) and Two-hand Turning and Placing Test (5th item: taking the blocks with two hands and putting them in the holes on the board in a standardized order) were the two items selected for this study. Participants were given a 15 second trial for both items. The test was timed with a stopwatch and each item was measured three times. The number of seconds it took to complete the task on each of the trials was recorded. An average score from the three trials was calculated. The high performer should score higher on the MMDT than the low performers.[8,9]

5.2.2. Video Boxing Analysis (VBA): For boxing analysis patients were videotaped while punching with their right side, punching with side left and punching bilaterally. Than the videotape were watched to analyze and the number of right unilateral punches in 1 minute, number of left unilateral punches in 1 minute and number of bilateral punches in 1 minute were recorded. This analysis were done for the quantitative assessment of punch number per minute (number of punch/minute). This measurement method is created and constructed by the authors of this study. The lower the score, the better the outcome.

5.2.3. Fullerton Advanced Balance (FAB): The FAB scale is a performance-based scale which was developed to evaluate changes in many aspects of balance.[10] The FAB scale consists of 10 test items for the evaluation of static and dynamic balance status. These test items are: 1. Feet together, eyes closed, 2. Reach forward to retrieve an object, 3. Turn in a full circle, 4. Step up and over a bench, 5. Tandem walk, 6. Stand on one leg, 7. Stand on foam, eyes closed, 8. Two-footed jump, 9. Walk with head turns, 10. Reactive postural control. Each test

item is scored using a 0-4 scale. The highest score indicating better balance abilities is "40" points, and the lowest is "0". The FAB-T (Fullerton Advanced Balance – Turkish) scale was found to be a reliable and valid measurement of balance in Turkish population. [11]

5.2.4. Addenbrook's Cognitive Assessment – Revised (ACE-R) is sensitive in the differential diagnosis of early stage dementia.[12] However, the design and psychometric properties is also suitable to provide information about cognitive functions and cognitive deficits in patients without dementia after a stroke.[13] The ACE-R consists of five domains including attention/orientation, memory, verbal fluency, language and visuospatial ability.[14] The total score in ACE-R is '100' points, higher scores indicates better cognitive functioning. ACE- R scale was found as reliable and valid in Turkish population. [15]

5.2.5. Frenchay Activities Index (FAI) is a measure of instrumental activities of daily living (IADL) for use with patients recovering from stroke.[16] The FAI assesses a broad range of activities associated with everyday life. The benefit of the FAI is that while activities of daily living scales tend to focus on issues related to self-care and mobility and it is an appropriate measure for functional outcome in stroke patients.[17] The FAI comprises 15 activities, each of which is scored on a 4-point scale (0 to 3), to yield a total score ranging from 0 (inactive) to 45 (active). Scoring is based on the frequency with which the activities are carried out. It can be broken down into three subscales: domestic chores, leisure/work, and outdoor activities. Each subscale's score ranges from 0 to 15.[18]

6. Statistical Methodology

The statistical analysis will be carried out using the statistical package SPSS version 24.0. The variables will be reported by percentage (%) and mean ± standard deviation (x ± sd). Shapiro-Wilk test will be used to determine whether the data had a normal distribution. Pearson's Chi-Squared Test and Fisher's Exact Test will be used for comparison of the categorical data between the groups. Mann-Whitney U test will be used to analyze the intergroup differences, and Wilcoxon Signed-Rank Test will be used to analyze the intragroup differences. $P<0.05$ will be accepted as the statistically significant level. The arithmetic means will be presented with a 95% confidence interval (95% CI) with lower and upper limit values. Both "p" values and 95% CI values will be considered while interpreting the differences between the groups. To analyze the intergroup changes, effect sizes will be calculated with "Cohen's d". The effect sizes will be interpreted as small effect ($d \geq 0.2$), medium effect ($d \geq 0.5$) and large effect ($d \geq 0.8$).[30]

The mean difference (MD) will also calculated to evaluate the change from the baseline to post-treatment as mean change ± standard deviation.

7. References

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