Stroke

CLINICAL TRIAL

Higher Doses Improve Walking Recovery During Stroke Inpatient Rehabilitation

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BACKGROUND AND PURPOSE: We investigated the effect of higher therapeutic exercise doses on walking during inpatient rehabilitation, typically commencing 1 to 4 weeks poststroke.

METHODS: This phase II, blinded-assessor, randomized controlled trial recruited from 6 Canadian inpatient rehabilitation units, between 2014 and 2018. Subjects (n=75; 25/group) were randomized into: control (usual care) physical therapy: typically, 1 hour, 5 days/week; Determining Optimal Post-Stroke Exercise (DOSE1): 1 hour, 5 days/week, more than double the intensity of Control (based on aerobic minutes and walking steps); and DOSE2: 2 hours, 5 days/week, more than quadruple the intensity of Control, each for 4 weeks duration. The primary outcome, walking endurance at completion of the 4-week intervention (post-evaluation), was compared across these groups using linear regression. Secondary outcomes at post-evaluation, and longitudinal outcomes at 6 and 12-month evaluations, were also analyzed.

RESULTS: Both DOSE1 (mean change 61 m [95% CI, 9–113], *P*=0.02) and DOSE2 (mean change 58 m, 6–110, *P*=0.03) demonstrated greater walking endurance compared with Control at the post-evaluation. Significant improvements were also observed with DOSE2 in gait speed (5-m walk), and both DOSE groups in quality of life (EQ-5D-5 L) compared with Control. Longitudinal analyses revealed that improvements in walking endurance from the DOSE intervention were retained during the 1-year follow-up period over usual care.

CONCLUSIONS: This study provides the first preliminary evidence that patients with stroke can improve their walking recovery and quality of life with higher doses of aerobic and stepping activity within a critical time period for neurological recovery. Furthermore, walking endurance benefits achieved from a 4-week intervention are retained over the first-year poststroke.

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Key Words: exercise ■ follow-up ■ walking ■ rehabilitation ■ stroke

Walking is one of the most commonly stated rehabilitation goals for individuals poststroke. Although best-practice stroke rehabilitation guidelines globally recommend both aerobic exercise and task-specific therapy (ie, walking practice) to improve walking recovery,[1,2] there are no studies to date that have systematically investigated the optimal dose of exercise to maximize walking recovery. A meta-analysis demonstrated that an increased dose of physical therapy may be beneficial to optimizing functional outcome; however, these studies focused on the hours of any types of therapy, and not specific aspects of exercise prescription, such as number of repetitions, which are known to influence motor learning.[3]

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The Determining Optimal Post-Stroke Exercise (DOSE) randomized controlled trial (RCT) was designed

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Nonstandard Abbreviations and Acronyms

6MWT	6-minute walk test
DOSE	Determining Optimal Post-Stroke Exercise
HRR	heart rate reserve
PT	physical therapy
VAS	visual analogue scale

to specifically address this knowledge gap. We investigated whether 2 higher doses of task-specific, progressive, walking-related exercise manipulated from the subject's heart rate and step counter data within 1 to 10 weeks poststroke was more effective than usual care at improving walking recovery. We hypothesized that our experimental higher dose programs would result in greater walking distance, as well as in improved secondary outcomes of overall function and quality of life, over usual care. The population targeted individuals during their inpatient rehabilitation (typically occurring 2–10 weeks poststroke), when neurological recovery is believed to be peaking. The seminal Copenhagen Stroke Study found that the vast majority of those with initially moderate stroke reached their best neurological recovery within 10.5 weeks for moderate stroke and 15 weeks for severe stroke.[4]

METHODS

Study Design

The study protocol and design for this phase II multi-site RCT has been described elsewhere.[5] In brief, this study used an open-label, parallel, single-blind (evaluators), 3-group design. Ethics approval was obtained from the university and hospital institutional review boards for each site, and subjects provided written informed consent. A Data Safety and Monitoring Board reviewed reports on adverse events and subject recruitment 3×/year.

Patients

Before commencing the research study, each site confirmed that the inpatient stroke rehabilitation physical therapy treatment approach included progressive, task-specific, exercise to promote upper and lower extremity functional recovery but did not focus on high repetition aerobic exercise. Consecutive patient admissions into each of the 6 study inpatient rehabilitation units over 3 provinces (G.F. Strong Rehabilitation Centre, Holy Family Hospital, Laurel Place, Carewest Dr Vernon Fanning Centre, Foothills Medical Centre, Riverview Health Centre) with a confirmed primary diagnosis of stroke (infarct or intracerebral hemorrhage) by a neurologist using either magnetic resonance imaging or computed axial tomography (CT scan) between March 1, 2014 to July 1, 2018, were screened, and as appropriate, followed for study eligibility. In Canada, patients are typically admitted to inpatient rehabilitation units once they are medically stable but have serious residual effects from the stroke and can tolerate at least 3 hours of activity per day (typically 1-week poststroke or later). Inclusion criteria were within 10 weeks poststroke with lower extremity hemiparesis (<4/5 manual muscle grade in at least one of the major lower extremity muscles); prestroke disability <2 on the modified Rankin Scale; ability to ambulate ≥5 meters with up to one person maximum assist and assistive/orthotic device as required; over-ground walking speed <1.0 m/s; able to understand and follow directions; >18 years of age; and successful completion of a graded exercise stress test using criteria established by the American College of Sports Medicine.[6] Exclusion criteria were a prestroke health condition that included a gait disorder, another neurological condition (eg, Parkinson's), serious medical or painful condition (eg, active cancer), or enrolled in a drug or exercise rehabilitation study.

Randomization and Masking

At the completion of the baseline evaluation, subjects were randomized to an intervention group (Usual Care, DOSE1, or DOSE2) on a 1:1:1 ratio and stratified by age (<60 or ≥60), using a fully concealed internet-based dynamic allocation randomization that was generated in real time. All outcome evaluations were conducted by blinded study evaluators.

Procedures

Only 1 to 2 front-line physical therapists per site were trained to deliver the DOSE intervention (DOSE1 and DOSE2) and participated in a 4-hour protocol workshop. Weekly audits of the intervention data (ie, walking steps, time in heart rate zone, total time in physical therapy) were conducted by the site research coordinator for the DOSE1 and DOSE2 subjects to ensure that the protocol was being administered as designed. The other physical therapists were therefore responsible for treating the subjects randomized to Usual Care.

Usual Care

The control intervention consisted of usual care, inpatient physical therapy which progressed upper and lower limb functional exercises as tolerated and typically provided 5, 1-hour sessions per week, until the subject was discharged (normally after 4–6 weeks of inpatient rehabilitation). To quantify the actual exercise intensity, wearable sensors (Alpha Mio heart rate monitor wrist watch, MioGlobal, Vancouver and Fitbit One step counter, Fitbit, Inc, San Francisco) were worn during 10 of the sessions (sessions 6–15). These middle 10 sessions were selected as therapy sessions at the beginning and end of rehabilitation primarily include assessments and discharge planning. We have previously demonstrated the validity of the Fitbit One in capturing slow-walking steps poststroke in the study population when worn on the nonparetic ankle.[7] The heart rate monitor watch collected total time in the therapy session spent at ≥40% heart rate reserve (HRR). Data obtained from the monitoring equipment was not disclosed to the subject or treating therapist.

DOSE1

The DOSE1 intervention replaced standard inpatient physical therapy session for a total of 20 sessions (1 hour/day, 5 days/week, for 4 weeks). The therapist progressed the subject to (1) complete a minimum of 30 minutes at an intensity ≥40%

HRR, gradually progressing to >60% HRR by the end of the 4 weeks; (2) achieve >2000 walking steps using the same monitoring equipment as the control group, but all 20 intervention sessions were monitored. Details of the DOSE intervention protocol, along with progression guidelines and algorithms can be found at https://neurorehab.med.ubc.ca/. The remaining time of the session was dedicated to other physical therapy activities specific to the subject's recovery (eg, upper extremity exercises, instruction of home exercise program).

DOSE2

In addition to the DOSE1 activity (typically morning), the DOSE2 group also received an extra, 1-hour exercise session, 5 days/week, for 4 weeks, which occurred later in the day (ie, typically from 4 to 5 PM daily). The content of the second daily exercise session was similar to the DOSE1 protocol; it contained a minimum of 30 minutes of weight-bearing walking related activities; however, the remaining time within the hour session was dedicated to weight-bearing lower extremity exercises (eg, strengthening, balance exercises). The monitoring equipment was worn for all 40 intervention sessions.

Intervention Protocol Fidelity

Subjects were considered adherent to the intervention if they attended at least 75% of the sessions over the 4 weeks. To assess whether the 3 groups actually exercised at different intensities, data were averaged across the 10 middle intervention sessions (sessions 6–15 across each group) for 2 indicators: Time spent (minutes) at ≥40% HRR, and number of steps (measured by the Fitbit step counter) in the exercise session(s) per day.

Outcomes

Subject characteristics, including age, sex, date and type of stroke, and stroke severity were collected at the baseline evaluation. All outcome measures were conducted at 4 time points: baseline, post-evaluation (end of the 4-week intervention and approximately 5 weeks after the baseline evaluation), 6- and 12-month poststroke.

The primary end point was the 6-minute walk test (6MWT) at the post-evaluation, which is a valid and reliable measure to assess walking endurance and recovery early after stroke.[8] During the 6MWT, the subject was instructed to cover as much distance as possible walking, using their customary walking/orthotic devices, and the total distance (in meters) was recorded.[9] If necessary for the walking outcome measures, the minimum amount of external physical assistance was provided to the subject to maintain personal safety (up to 1 person maximum assist). Secondary outcomes at the post-evaluation were paretic maximal isometric quadriceps strength (paretic knee strength) measured from a handheld dynamometer[10]; 5-meter walk test[11]; Berg Balance Scale[12]; Patient Health Questionnaire-9[13]; and EQ-5D-5 L.[14] An EQ-5D-5 L index score was calculated by applying the Canadian value set[15] across the 5 dimensions (mobility, self-care, usual activities, pain, anxiety/depression). In addition, each subject's health value score (/100) was used, which is based on a visual analogue scale (VAS) with "0" being "the worst health you can imagine" and "100" being the "best health you can imagine".

Adverse Events

Study staff reported any adverse events that occurred during the 4-week intervention or any outcome evaluation. Study subjects also self-reported any adverse events during follow-up phone calls (6- and 12-month evaluations). A serious adverse event was defined as an incident that was life-threatening, required hospitalization, and/or resulted in death.

Statistical Analyses

A priori, we identified a minimal clinical important difference of 50 m between Usual Care and DOSE1 and Usual Care and DOSE2 at post-evaluation for the primary outcome (6MWT).[16] From this, we calculated that a sample size of 75 subjects (25/group) was required to detect this change with 85% power, at 0.05 alpha, and adjusted for an attrition rate of 15%.

The distribution of all variables was visually and statistically assessed for normality.

Therapeutic intensity (heart rate intensity and step count during the middle 10 intervention sessions) was compared across groups using an ANOVA, followed by post hoc Tukey test.

Between-group differences for the primary and secondary measures at the post-evaluation were compared by multiple linear regression, while controlling for the baseline score on each outcome centered on the mean.[17] The intercept in each model can be interpreted as the estimated mean of the control group (Usual Care) at follow-up for the outcome in question, when the outcome value at baseline is equal to the mean (thus the centered value of the baseline score would be zero). R software was used for the analyses.

Longitudinal modeling was undertaken for outcomes that had a significant relationship with the intervention (DOSE1 and/or DOSE2) at the post-evaluation using linear mixed effects modeling, with a random effect for each subject. To test the null hypothesis that the initial improvement from the intervention was maintained at 6- and 12-month poststroke compared with Usual Care, an interaction term between time and intervention group was included in each model. Because of the challenges of longitudinal models with small sample sizes,[18] DOSE1 and DOSE2 were collapsed into one group (DOSE) and compared with Usual Care. Time was included as a categorical variable (post-evaluation, 6, 12 months) to allow for a nonlinear slope of recovery with the initial follow-up as the referent category. Baseline scores for the outcome of interest were included in all models. The package lme4: Linear Mixed-Effects Models used "Eigen" and S4 (R software), which utilizes all available data and has been demonstrated to be valid in the presence of data missing at random.[19]

To explore the mechanism of missing data, the relationships between demographic (age, sex) and stroke-related function (6MWT, 5-meter walk, EQ-5D-5 L VAS) with loss to follow-up were assessed using bivariable logistic regression to compare the population lost to follow-up (those missing at 6 and 12 months) to those who completed follow-up.

For all analyses, the significance level was set at 0.05, and all statistical tests were 2-tailed.

Anonymized data and materials will be made publicly available at the University of British Columbia Scholars Portal Dataverse (https://dataverse.scholarsportal.info/dataverse/ubc) beginning 18 months and ending 60 months following article publication.

RESULTS

Between March 2014 and July 2018, 2387 patients with stroke were admitted to participating study sites, of which 2141 of them were assessed for study eligibility. The 3 most frequent reasons for exclusion upon patient interview/chart screening were that the patient did not have leg hemiparesis (n=606); had a stroke >10 weeks on rehabilitation admission (n=315); or was unable to ambulate 5 meters (n=208). Seventy-five subjects were randomized to Usual Care (n=25), DOSE1 (n=25), or DOSE2 (n=25). One subject (randomized to DOSE2) completed the baseline, but not the post-evaluation, because of ongoing investigational work for a suspected cardiac arrhythmia, which resulted in discontinuation of the protocol and further evaluations. After the 12-month post-evaluation, one subject was found to not meet the inclusion criteria of having a primary diagnosis of stroke and their data were removed from the study. Please see Figure 1 for subject recruitment and flow.

Descriptive characteristics for the 74 subjects are displayed in Table 1. At the baseline evaluation, there were similarities across all groups with respect to mean age, time from stroke to study randomization, and 5-meter walking velocity. The mean baseline 5-meter walking velocity (SD) was 0.42 m/s (0.24), 41% were female, 61 had an ischemic stroke, and subject randomization to an intervention group was within 4-weeks poststroke. These baseline characteristics are similar to other stroke rehabilitation trials conducted.[20] Based on logistic regression results, none of the tested variables were statistically significantly associated with attrition at 12 months (Table I in the Data Supplement).

Intervention Protocol Fidelity

The DOSE1 intervention session was designed to be ≈1 hour in duration, matching the customary inpatient rehabilitation physical therapy duration. On average, the duration of the sessions was (mean [SD]): (1) Usual Care=44 (12) minutes; (2) DOSE1=52 (5) minutes; and (3) DOSE2=104 (15) minutes (51 [6] minutes for session 1 and 53 [8] minutes for session 2).

A total of 226/240 sessions (94%) from Usual Care, 494/500 sessions (99%) from DOSE1, and 904/960 (94%) sessions from DOSE2 were completed. One subject in the study (from DOSE2) was discharged from inpatient rehabilitation within the first 2 weeks of the intervention (after completing 18/40 sessions) and was not able to continue the intervention secondary to the remote discharge destination. All other subjects were adherent to the protocol, completing at least 3 weeks (75%) of the intervention.

There was a significant group effect on the 2 intensity variables measured: total time spent in an aerobic training zone (≥40% HRR) within the therapy session and total steps taken within the therapy session, with all 3 groups being significantly different from one another ($P<0.005$; Table 2). On average (mean [SD]), the Usual Care subjects spent 11 (9) minutes, DOSE1 subjects spent 27 (11) minutes, and DOSE2 subjects 52 (24) minutes within an aerobic training zone (≥40% HRR). The mean step count (SD) for Usual Care was 580 (440) steps, while DOSE1 subjects walked more than double (2169 [1106] steps), and DOSE2 subjects walked more than quadruple (4747 [2083] steps) compared with Usual Care. The Usual Care activity was similar to audits of other Canadian inpatient stroke rehabilitation settings.[21]

POST-EVALUATION

Primary Outcome

The primary outcome, the 6MWT, was completed by 74 subjects at baseline and 73 subjects at post-evaluation (97% completion rate; Table II in the Data Supplement). When controlling for the baseline 6MWT, the linear regression model (Table 3) demonstrated that both DOSE1 (mean difference [meters] from Usual Care [95% CI], *P*-value; 61 m, 9–113, $P=0.02$) and DOSE2 (58 m; 6–110; $P=0.03$) walked a statistically and clinically significantly greater distance than Usual Care subjects.

Secondary outcomes

A summary of the secondary outcomes is displayed in Table II in the Data Supplement. Significant differences between the Usual Care and DOSE groups were observed with the 5-meter walk and both the EQ-5D-5 L Index and VAS scores at the post-evaluation, but not for paretic knee strength, Berg Balance Scale or Patient Health Questionnaire-9 (Table 3). For the 5-meter walk, a significant difference was only observed between Usual Care and DOSE2.

For the EQ-5D-5 L VAS score, a significant increase was seen with both DOSE1 (mean difference from Usual Care [95% CI], *P*-value; 9.00 points, 1.11–16.88, $P=0.029$) and DOSE2 (11.51 points, 3.79–19.23, $P=0.005$) over Usual Care. Similar findings were also observed with the EQ-5D-5 L index score, with both DOSE1 and DOSE2 having significant increases compared with Usual Care (DOSE1=0.11, 0.05–0.17, $P=0.001$; DOSE2=0.11, 0.05–0.17, $P=0.001$).

LONGITUDINAL ANALYSES

DOSE1 and DOSE2 were collapsed into one group (DOSE) and compared with Usual Care for the following reasons: (1) our apriori hypothesis was focused on comparing higher doses to standard of care[5]; (2) we anticipated that longitudinal models with small sample sizes could cause convergence problems[18]; and (3) our primary analyses showed that the mean changes for the DOSE1 and DOSE2 groups were similar in direction and

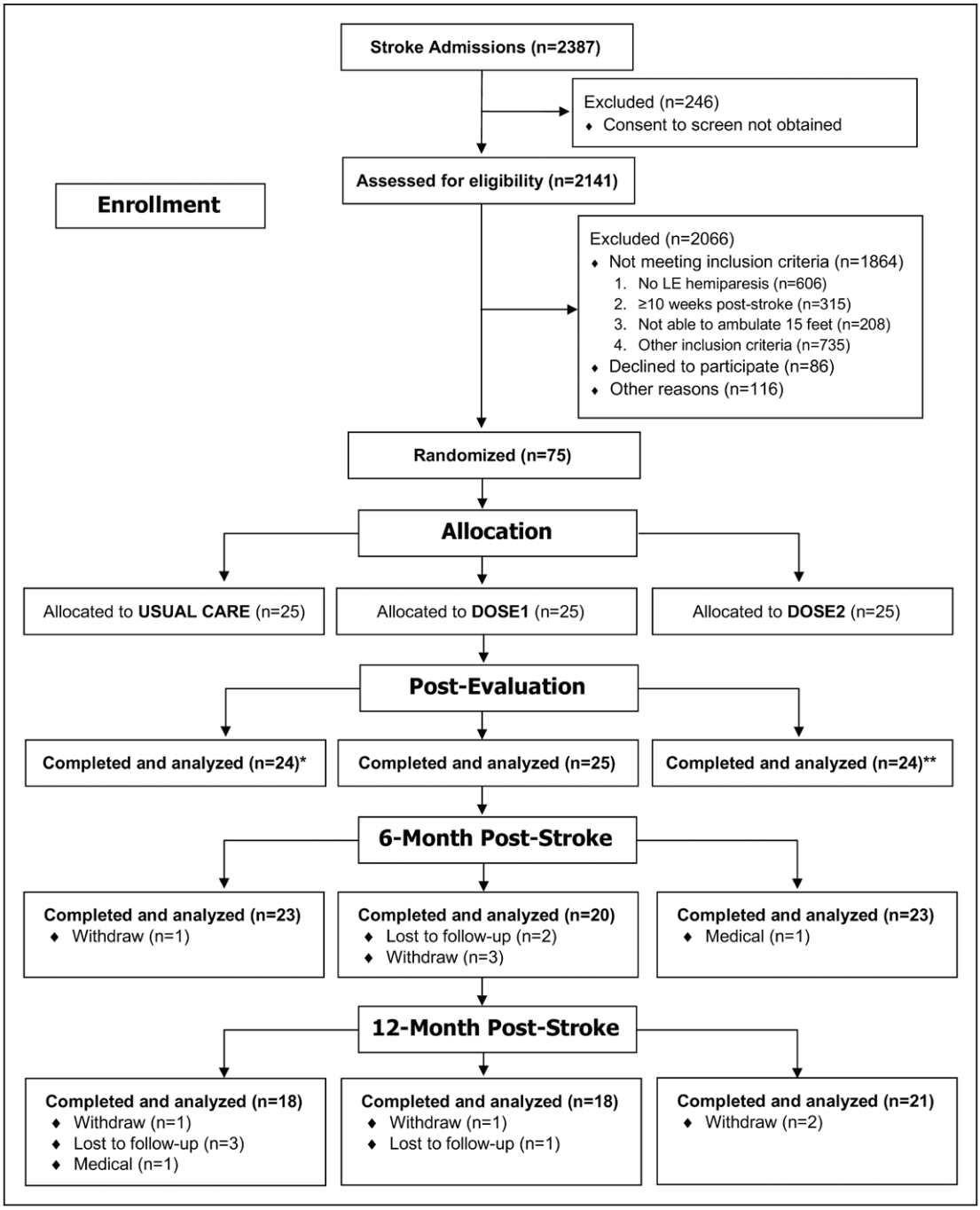

Figure 1. CONSORT flow diagram for the primary outcome (6-minute walk test).
*After completion of the study, one subject in Usual Care was found to not meet the inclusion criteria of having a primary diagnosis of stroke. Therefore, this subject's data were not included in the demographic or statistical analyses. **One subject in Determining Optimal Post-Stroke Exercise2 (DOSE2) did not complete the intervention. During this subject's fifth intervention session, he was clinically asymptomatic, but the heart rate monitor could not accurately capture his heart rate. Suspecting an undiagnosed irregular cardiac arrhythmia, the subject was removed from the trial by the study investigators and referred for follow-up cardiology. Although his follow-up results were negative for any cardiac condition, it was too late at this point to resume his intervention.

magnitude. At the 6-month follow-up, 66 subjects (89%) completed the 6MWT, 5-meter walk, EQ-5D-5 L Index, and EQ-5D-5 L VAS (Table II in the Data Supplement). At the 12-month follow-up, 57 subjects (77%) completed the 6MWT and 5-meter walk and 58 subjects (78%) completed the EQ-5D-5 L Index and EQ-5D-5 L VAS.

Primary Outcome (6MWT) at 6- and 12-Month Follow-Up Evaluations

Although subjects who received the 4-week DOSE intervention and Usual Care continued to improve from the end of the DOSE intervention (4 weeks) to 12 months

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Table 1. Subject Demographics and Clinical Characteristics

	All Groups (n=74)	Usual Care (n=24)	DOSE1 (n=25)	DOSE2 (n=25)
Age, y; mean±SD (range)	57±11 (27–76)	58±13 (35–76)	56±11 (27–73)	58±10 (31–76)
Male sex, n (%)	44 (59)	14 (58)	16 (64)	14 (56)
Time from stroke to randomization (d); mean±SD (range)	27±10 (6–58)	26±11 (6–43)	27±10 (16–58)	29±10 (11–50)
Side of hemiparesis	L=42; R=32	L=16; R=8	L=10; R=15	L=16; R=9
Type of stroke	Ischemic=61	Ischemic=20	Ischemic=22	Ischemic=19
	Hemorrhagic=13	Hemorrhagic=4	Hemorrhagic=3	Hemorrhagic=6
Stroke location	Cortical=14	Cortical=5	Cortical=3	Cortical=6
	Subcortical=56	Subcortical=16	Subcortical=21	Subcortical=19
	Unknown=4	Unknown=3	Unknown=1	Unknown=0
Baseline 5 m walk (m/s); mean±SD (range)	0.42±0.24 (0.06–1.08)	0.39±0.22 (0.07–0.86)	0.44±0.25 (0.15–1.08)	0.42±0.25 (0.06–1.0)
Baseline MOCA (/30); mean±SD (range)	23±6 (7–30)	24±5 (10–30)	23±7 (7–30)	24±5 (12–30)
NIH Stroke Scale (/42) (at rehabilitation baseline); mean±SD (range)	5±3 (0–14)	5±3 (1–11)	5±3 (0–11)	5±3 (0–14)

DOSE1 indicates Determining Optimal Poststroke Exercise; and NIH, National Institutes of Health.

poststroke, the DOSE groups were able to maintain their improvements in the 6MWT over Usual Care (mean difference [meters] from DOSE [95% CI], *P*-value) at the 6- and 12-month evaluations as the time and group interaction term was not significant (6 months=−29.72, −71.33 to 11.89, *P*=0.162; 12 months=−33.55, −78.26 to 11.16, *P*=0.141; Figure 2; Table 4).

Secondary Outcomes at 6- and 12-Month Follow-Up Evaluations

DOSE subjects maintained their improvements in the EQ-5D-5 L VAS at 6 months from the post-evaluation (mean difference from DOSE at post-evaluation [meters; 95% CI], *P*-value; −5.12, −13.73 to 3.49, *P*=0.244), but by 12 months, the time and group interaction was statistically significant (−10.08, −19.16 to −1.00, *P*=0.029; Figure 2; Table 4) indicating that the gains were not maintained. The initial improvements by the DOSE group in the 5-meter walk and EQ-5D-5 L index observed at the post-evaluation do not seem to be maintained over the year following stroke based on the crude data and longitudinal modeling (Figure 2; Table 4).

Adverse Events

Two Usual Care subjects experienced an serious adverse event: (1) hospitalization for a transient ischemic attack during the 4-week intervention; (2) myocardial infarction reported at 12-months poststroke, and 2 DOSE subjects reported an serious adverse event at 6-month poststroke: (1) recurrent stroke and (2) leg fracture from a fall on ice. The subject with a transient ischemic attack returned to the rehabilitation hospital and completed the remaining evaluations, but the others did not complete their remaining evaluations.

DISCUSSION

We systematically investigated the dose effect of exercise on walking and functional recovery in the early phase after stroke (1–10 weeks) with a 97% completion rate of our proposed sample size of the primary outcome (6MWT) at the primary end point (post-evaluation). We demonstrated that a 4-week exercise program with high movement repetitions (step counts) and greater exertion (heart rate) can immediately result in greater walking recovery and improved quality of life, compared with usual care, for stroke survivors. The improvements were meaningful for both DOSE groups, which exceeded the minimal clinically important difference for the 6MWT (50 m),[16] and EQ-5D index score (0.102).[22]

The 60-minute DOSE1 session was consciously designed to optimize the future translation of the protocol into clinical practice. The DOSE1 protocol encompassed all activities of a typical 60 minute Usual Care

Table 2. Intervention Fidelity: Summary of the Therapeutic Intensity Data

	Usual Care (n=24); Mean±SD (95% CI)	DOSE1* (n=25); Mean±SD (95% CI)	DOSE2* (n=24); Mean±SD (95% CI)
Total time spent ≥40% HRR during PT session, min	11±9 (7–14)	27±11 (22–32)	52±24 (42–63)
Total Fitbit step count during PT session	580±440 (394–766)	2169±1106 (1712–2626)	4747±2083 (3868–5627)

DOSE indicates Determining Optimal Post-Stroke Exercise; HRR, heart rate reserve; and PT, physical therapy.

**P*-value <0.005 when comparing Usual Care to DOSE1; Usual Care to DOSE2; DOSE1 to DOSE2 with respect to total time spent above 40% HRR and total step count.

Table 3. Primary and Secondary Outcomes From the Linear Regression Model

Outcome Measure	Predictors	Estimates	95% CI	*P*-Value
6MWT, m	(Intercept)	249.42	213.07 to 285.76	<0.001
	DOSE1	61.17	10.29 to 112.04	0.021
	DOSE2	58.06	6.61 to 109.50	0.030
	Baseline 6MWT	1.07	0.84 to 1.30	<0.001
	Observations=73; R^2/adjusted R^2=0.563/0.544			
5-m walk, m/s	(Intercept)	0.77	0.66 to 0.88	<0.001
	DOSE1	0.11	−0.04 to 0.26	0.167
	DOSE2	0.19	0.04 to 0.34	0.017
	Baseline 5 m walk	0.98	0.72 to 1.24	<0.001
	Observations=73; R^2/adjusted R^2=0.475/0.452			
EQ-5D-5 L: Index Score	(Intercept)	0.7	0.66 to 0.74	<0.001
	DOSE1	0.11	0.05 to 0.17	0.001
	DOSE2	0.11	0.05 to 0.17	0.001
	Baseline index	0.16	0.03 to 0.29	0.019
	Observations=72; R^2/adjusted R^2=0.301/0.270			
EQ-5D-5 L: VAS	(Intercept)	64.71	59.14 to 70.28	<0.001
	DOSE1	9.00	1.11 to 16.88	0.029
	DOSE2	11.51	3.79 to 19.23	0.005
	Baseline VAS	0.16	0.01 to 0.32	0.045
	Observations=72; R^2/adjusted R^2=0.193/0.158			
Berg Balance Scale (BBS)	(Intercept)	46.83	44.35 to 49.31	<0.001
	DOSE1	0.46	−3.02 to 3.94	0.795
	DOSE2	2.20	−1.30 to 5.70	0.223
	Baseline BBS	0.44	0.33 to 0.55	<0.001
	Observations=73; R^2/adjusted R^2=0.494/0.472			
PHQ-9	(Intercept)	5.07	3.30 to 6.84	<0.001
	DOSE1	−0.7	−3.19 to 1.80	0.585
	DOSE2	−1.93	−4.41 to 0.55	0.132
	Baseline PHQ-9	0.52	0.30 to 0.73	<0.001
	Observations=72; R^2/adjusted R^2=0.265/0.233			
Paretic knee strength, N/kg	(Intercept)	19.89	17.67 to 22.10	<0.001
	DOSE1	0.91	−2.26 to 4.09	0.575
	DOSE2	0.25	−2.87 to 3.38	0.874
	Baseline paretic knee strength	0.92	0.79 to 1.05	<0.001
	Observations=69; R^2/adjusted R^2=0.759/0.748			

Model results use the Usual Care group as the reference group. 6MWT indicates 6-minute walk test; DOSE1, Determining Optimal Post-Stroke Exercise1; and VAS, visual analogue scale.

physical therapy session (including upper extremity activities), without having to add on time. To respect the therapist's professional competencies in developing an effective program, therapists were encouraged to use their clinical judgment to select appropriate exercises for their patient, as long as they integrated the targets for step counts and heart rate into their activities. Therapists used a wide range of stepping activities, including, but not limited to: walking intervals, stair climbing, walking obstacle courses, and body-weight supported treadmill.

Our higher intensity protocol was well tolerated by subjects, of which some were only 1- or 2-weeks poststroke, and approximately three-quarters of subjects were dependent on physical assistance to walk at the baseline evaluation. Qualitative investigations of the DOSE protocol showed that although subjects and therapists expressed positive experiences toward the high intensity intervention, therapists were often surprised at how hard subjects could work and tolerate the intensive regimen.[23] Therapists felt that the use of heart rate monitors and step counters as objective measures increased their confidence to push people harder.[23]

Inexpensive commercial wearable sensors were used in our study to set intensity targets, confirm the fidelity

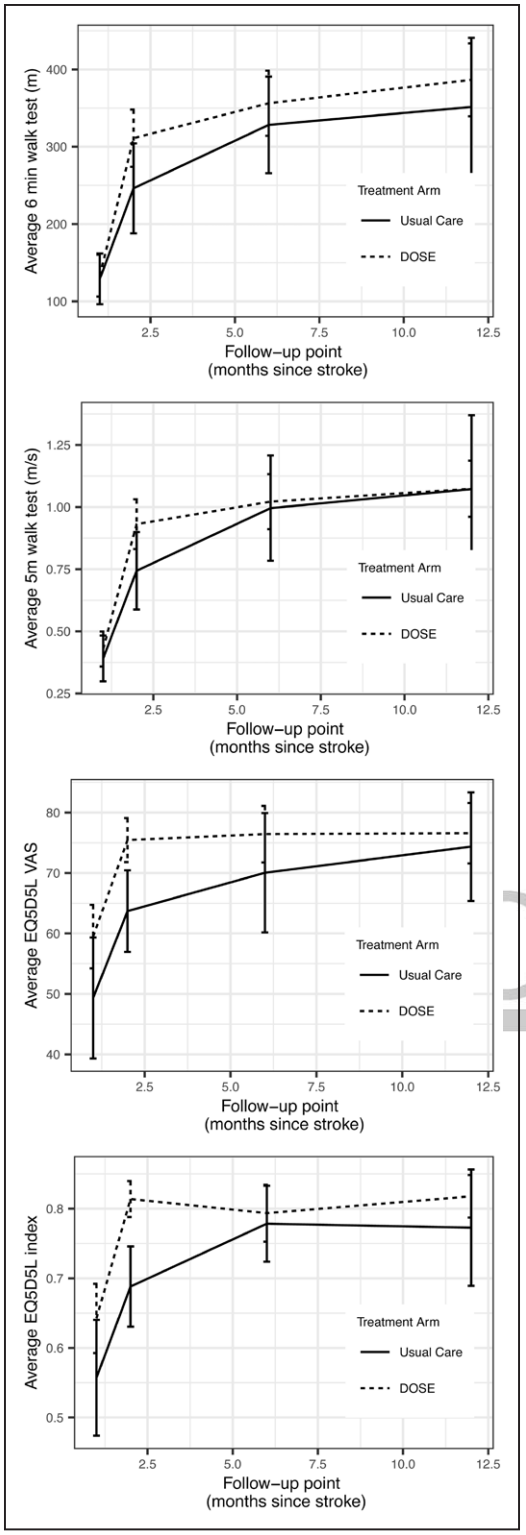

Figure 2. Walking and quality of life outcomes over the first year poststroke.
DOSE indicates Determining Optimal Post-Stroke Exercise; and VAS, visual analogue scale.

of the protocol, and will help to replicate the protocol for future implementation.

The doses were distinctly increased with DOSE1, at least doubling the heart rate and step count intensity from Usual Care, and then as well with DOSE2, at least quadrupling the intensity from Usual Care. The high number of walking steps used in this study to improve walking recovery (DOSE1:2169; DOSE2:4747 steps) is consistent with the thousands of functional, challenging, repetitions observed in the animal model studies to promote neurological changes.[24] However, the effects were not necessarily additive, and some physical outcomes did not demonstrate any benefits. There were no differences between groups with respect to recovery of balance, as measured by the Berg Balance Scale. This may be secondary to subjects within all groups receiving a similar challenge in their physical therapy sessions with respect to balance exercises or due to a ceiling effect of the balance measurement scale (Berg Balance Scale). There was also no effect on paretic quadricep muscle strength, which is likely because of the focus of the protocol on stepping, rather than high force generation.

Both DOSE1 and DOSE2 exceeded 50 m on the 6MWT over the control group immediately following the 4-week intervention, which is considered a meaningful clinical change in this measure early after stroke.[16] DOSE2 intensity was double that of DOSE1 and resulted in greater gait speed measured by the 5-meter walk, but a similar response was not seen with walking endurance, as measured by the 6MWT. Perhaps the extra walking practice completed by subjects in the DOSE2 intervention contributed to improved performance over shorter walking distances (ie, 5-meter walk), but further training duration beyond the 4-week intervention protocol may be necessary to see the increased gait speed translate to improvements in gait endurance (6MWT).

Despite no additional physical therapy or physical activity counseling occurring beyond usual care after completing the 4-week intervention, both DOSE subjects and Usual Care continued to improve in the 6MWT at the same rate (ie, slope) until 12 months. Since the DOSE subjects start at a higher 6MWT value at 4 weeks, they end at a higher value at 12 months compared with Usual Care. This suggests that walking endurance improvements obtained during a time of critical neurological recovery may be retained long term.

Prior research has been inconclusive on the efficacy of aerobic activity in improving quality of life poststroke.[25] Thus, our results demonstrate that aerobic walking activity can improve quality of life, with both DOSE groups having benefits over Usual Care. Although these benefits were not retained to the 1-year follow-up evaluation, this may be attributed to the many other factors (ie, social supports, coping strategies, depression, cognitive function) that are known to contribute to quality of life as patients poststroke reintegrate into the community.[26]

Although DOSE2 demonstrated significant improvements over Usual Care in walking velocity (5-meter walk) at the post-evaluation, there was no significant difference between the groups (Usual Care, DOSE1, DOSE2)

Table 4. Longitudinal Analyses: Primary and Secondary Outcomes From the Linear Mixed Effects Model

Predictors	6-Minute Walk			5-Meter Walk			EQ-5D-5 L:VAS			EQ-5D-5 L:Index		
	Estimates	CI	*P* Value	Estimates	CI	*P* Value	Estimates	CI	*P* Value	Estimates	CI	*P* Value
(Intercept)	249.32	207.14 to 291.50	<0.001	0.77	0.64 to 0.90	<0.001	65.18	58.83 to 71.54	<0.001	0.7	0.65 to 0.75	<0.001
Time												
Post-evaluation	Ref			Ref			ref			ref		
6 mo	80.02	46.37 to 113.68	<0.001	0.25	0.15 to 0.34	<0.001	6.35	−0.65 to 13.34	0.075	0.09	0.04 to 0.14	<0.001
12 mo	115	78.17 to 151.83	<0.001	0.34	0.23 to 0.44	<0.001	11.17	3.72 to 18.63	0.003	0.08	0.03 to 0.13	0.002
Group												
Usual Care	Ref			Ref			Ref			Ref		
DOSE*	59.8	8.31 to 111.29	0.023	0.15	−0.01 to 0.31	0.062	9.51	1.77 to 17.26	0.016	0.11	0.05 to 0.17	<0.001
Baseline	1.04	0.79 to 1.28	<0.001	0.95	0.67 to 1.24	<0.001	0.24	0.10 to 0.38	0.001	0.2	0.07 to 0.32	0.002
Time×group interaction												
Post-Evaluation×DOSE	Ref			Ref			Ref			Ref		
6 mo×DOSE†	−29.72	−71.33 to 11.89	0.162‡	−0.14	−0.26 to −0.02	0.021	−5.12	−13.73 to 3.49	0.244	−0.11	−0.17 to −0.05	<0.001
12 mo×DOSE†	−33.55	−78.26 to 11.16	0.141	−0.18	−0.31 to −0.05	0.007	−10.08	−19.16 to −1.00	0.029	−0.08	−0.14 to −0.02	0.014
Random effects												
σ2	3413.34			0.03			146.53			0.01		
τ00	7697.49 ID			0.07 ID			90.97 ID			0.01 ID		
ICC	0.69			0.72			0.38			0.49		
N	73 ID			73 ID			72 ID			72 ID		
Observations	196			196			196			196		
Marginal R2/ conditional R2	0.472/0.838			0.367/0.822			0.149/0.475			0.176/0.576		

*DOSE1 and DOSE2 groups were combined.
†6 mo×DOSE and 12 mo×DOSE interaction interaction used Post-Evaluation×DOSE as the reference.
‡Tests the null hypothesis that the effect of the intervention is maintained compared with Usual Care. A significant *P*-value (<0.05) for the Time×Group Interactions indicate that the effects were not maintained.

in this measure by the 12-month evaluation. All 3 groups continued to have improvements in their walking velocity over the first year poststroke and have similar walking speeds at 12 months (1.07, 1.04, 1.11 m/s, respectively). As these walking speeds are nearing normal walking velocities for healthy individuals of a similar age (≈1.3 m/s),[27] there may be a ceiling to the walking speed that can be obtained within the first year poststroke.

A number of study limitations do exist for this study. Although our study was a multisite, multiprovince trial, the study needs to be replicated with a larger sample size. With respect to our subject recruitment, we included individuals that could ambulate at least 5 meters with up to 1-person maximum assist, so subjects commenced at times ranging from 1 to 9 weeks poststroke. However, despite subjects starting the intervention at slightly different times, we did see significant improvements with the intervention groups. The therapy sessions for both DOSE1 and DOSE2 were ≈10 minutes longer than Usual Care because the protocol dictated the duration of the DOSE sessions while the Usual Care duration varied depending on the site's usual practice. It would be extremely unlikely, based on the subjects' baseline walking velocity (0.42 m/s) that the additional 1500 steps undertaken by the DOSE groups in their physical therapy sessions could be accounted for if an extra 10 minutes was provided in the therapy session. Also, our subjects mean age was younger than typical stroke. Although 3/6 sites recruited subjects with a higher mean age (65, 69, and 73), the majority of our subjects were recruited from the remaining 3 sites that had a lower mean age (49, 54, and 57) secondary to a mandate for admitting younger adults with stroke.

CONCLUSIONS

A 4-week exercise program, which has at least double the aerobic and step intensity of usual care delivered during stroke inpatient rehabilitation, is safe and feasible, and results in improved walking recovery and quality of life. The use of low-cost commercially available wearable sensors to monitor and set intensity targets will enable the replication and implementation of this protocol.

ARTICLE INFORMATION

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None.

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