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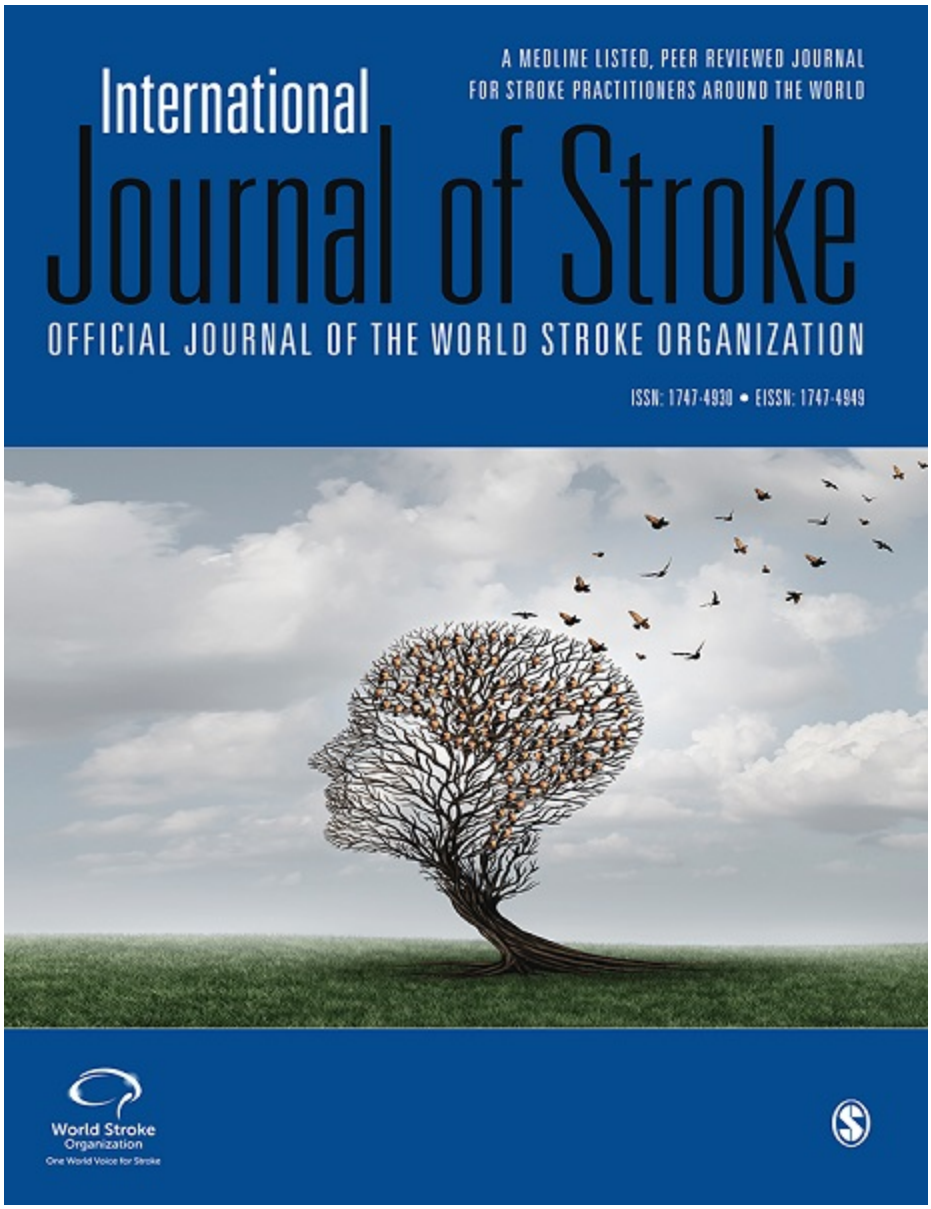

Methodology of the Fatigue After STroke Educational Recovery (FASTER) group randomised controlled trial

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Methodology of the Fatigue After STroke Educational Recovery (FASTER) group randomised controlled trial

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ABSTRACT

Rationale: Post-stroke fatigue (PSF) affects up to 92% of stroke survivors, causing significant burden. Educational Cognitive Behavioural Therapy (CBT) fatigue groups show positive results in other health conditions.

Aims: FASTER will determine if educational CBT Fatigue Management Group (FMG) reduces subjective fatigue in adults post-stroke.

Design: Prospective, multi-centre, two-arm, single-blind, phase III RCT (parallel, superiority design), with blinded assessments at baseline, 6-weeks, and 3-months post-programme commencement. With n=200 (100 per group, 20% drop-out) the trial will have 85% power (2-sided, p= 0.05) to detect minimally clinically important differences of 0.60 (SD=1.27) in Fatigue severity scale and 1.70 points (SD=3.6) in Multidimensional Fatigue Inventory-20 at 3-months.

Outcomes: Primary outcomes are self-reported fatigue severity and dimensionality (i.e., types of fatigue experienced - physical, psychological and/or cognitive) post-intervention (6-weeks). Secondary outcomes include subjective fatigue at 3-months, and health-related quality of life, disability, sleep, pain, mood, service use/costs, and caregiver burden at each follow-up.

Discussion: FASTER will determine whether FMG reduces fatigue post-stroke.

Registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000626167).

Post-stroke fatigue(PSF) affects upto 92% of people post-stroke, can be chronic, impacting daily life. PSF may persist for years[1] with 40% "always" or "often" fatigued two-years post-stroke.[2] PSF decreases mental/physical functioning through reduced energy but not exertion, and isn't ameliorated by rest.[3] PSF management is the greatest unmet need, and a significant barrier to recovery, return to work, and rehabilitation; reducing functional independence, quality of life, recovery, and activities of daily living(ADL), even with other predictors controlled for. [4, 5]

Global stroke guidelines recommend fatigue management.[6] However, with multifaceted etiology[7], "one size fits all" pharmacological strategies are problematic, and evidence for non-pharmacological treatments is inconclusive.[8] Group Cognitive Behaviour Therapy(CBT) interventions have positive results in similar health conditions.[9.3]

CBT advantages include comprehensiveness, individualization, simplicity, and cost-effectiveness. Group benefits include shared goals, reinforced learning, enhanced motivation/engagement, and broader therapeutic alliance.[10] While group CBT programmes are successful in MS, traumatic brain injury, and chronic fatigue syndrome; there is no evidence post-stroke.[11, 12]

This manuscript presents methods of the Fatigue After STroke Education Recovery (FASTER) study; assessing effectiveness of a 6-week Fatigue Management Group(FMG) in reducing fatigue compared to Education Controls(EC). The FMG was previously piloted[13] in comparison to educational controls in 16 adults with PSF, with FMG having greater decrease in PSF assessed by Fatigue Severity Scale (FSS) than controls 3-months post-intervention.

Secondary aims evaluate impact of FMG on fatigue 3-months post-intervention; and ADL, patient and carer-HRQoL, and cost-effectiveness at each follow-up. We hypothesised FMG will result in significantly greater decreases in fatigue post-intervention, and be cost-effective compared to EC.

Methods

Design

The currently underway FASTER is a prospective, multi-centre, two-arm, single-blind, phase-III RCT(parallel, superiority design), with blinded assessments. Ethical approval was obtained from the Health and Disability Ethics Committee(13/NTB/1) and University Ethics Committee(13/59).

Participants

Inclusion criteria: aged ≥18 years, 3- to 24-months post-CT/MRI or clinically diagnosed stroke; clinically significant fatigue; reside in study area; can converse in English (i.e., those with mild anomia are included); and provide informed consent. Exclusion criteria: pre-stroke fatigue, impairments/medical condition precluding participation, other causes of fatigue, and participation in another trial. Clinically significant fatigue is defined as "feeling constantly weary, tired, lacking energy/strength. These are present after rest/sleep"[14], reflected in an MFI-20 score ≥12.

Recruitment

Recruitment is occurring in Waikato and Auckland districts of New Zealand(NZ). On-site research nurses identify potential participants from in-patient and out-patient services through searching medical records at each stroke clinic for the term 'fatigue', and/or attending multidisciplinary team meetings to identify potential participants. Referrals are also invited from primary care health providers and self-referrals. Those potentially eligible are contacted by a study RA by telephone to explain the study. Information and consent forms are sent to interested persons. These are available in Māori to support participation of NZ's indigenous population. One-week later, the same RA makes contact to answer questions, seek verbal consent, and schedule a baseline assessment. Those consenting can nominate an informal caregiver (aged >15 years); an unpaid person who helps with daily activities at least 1.5 hours/week.

Randomization

Block randomisation (conducted by study coordinator (SD)) with 1:1 allocation balances groups for prognostic factors: age (<65; 65+); sex; disability (mRS: non-disabled 0-

1; slight/moderate disability 2-3); and depression (CES-D: no depression <16; depression ⩾16), using an online randomisation programme (QMinim). Participants will know whether they are in the 6 week intervention or single session control, at all assessments, participants are reminded to conceal their allocation. If an RA is unblinded (i.e., learns to which group a participant has been allocated), this is logged as a protocol violation.

Intervention

FMG: six 60-90-minute weekly sessions. All sessions are run by a clinical psychologist following a manualised treatment protocol involving didactic teaching, group activities, and discussions. Table 1 outlines content of each sessions. *EC*: a single group session to account for repeated measurement or spontaneous recovery effects, it offers education on stroke and stroke related topics (i.e. nutrition, exercise), with minimal focus on fatigue.

Outcomes

Assessments are at baseline, 6-weeks/post-intervention, and 3-month follow-up. Stroke details (e.g., stroke type and severity) are obtained from medical records. Mode of data collection (in-person, online, phone), and severe adverse events (SAE; e.g., recurrent stroke) are recorded.

Primary outcomes: Self-reported PSF severity (FSS-9 total score)[15] and dimensionality (MFI-20 general subscale score)[16] at 6-weeks and 3-months post-programme commencement.

*Secondary outcomes:*Includes MFI-20[16]; HRQoL (Short-Form-36)[17]; ADL/disability (Barthel Index)[18, 19]; Pittsburgh sleep quality index and Epworth Sleepiness Scale–8[20, 21]; pain in the past 24-hours (visual analogue); mood (General Health Questionnaire-28)[22]; Bakas Caregiving Outcomes[23]; and service utilisation/costs.

Sample Size

With 85% power, n=200 (100 per group, 20% drop-out; 2-sided, p= 0.05) to detect minimally clinically important differences of 0.60[24] (SD=1.27) in FSS and 1.70 points (SD=3.6)[25]in MFI-20 at 3-months.

Data Monitoring

A data monitoring committee oversees the study (e.g., study statistician, external stroke researcher, external researcher chair). Quality indicators are continuously monitored. Questionnaires are screened by the unblinded Research Coordinator for completeness and accuracy. RAs blind to randomisation undertake assessments and do not interact with those delivering the groups. The study team will be unblinded after analyses. To monitor adherence, group sessions are audio-recorded and a random 10% independently assessed by an external CBT expert. Jones(PI) conducts bi-annual, pre-specified audits for quality control and key trial procedures, with weekly SAE updates.

Statistical Analysis

An intention-to-treat strategy (assuming missing data is missing at random) will be applied according to the Consolidated Standards of Reporting Trials .[26]Descriptive statistics will describe demographics and performance at each assessment. Repeated measures ANCOVA will assess between group treatment effects. Potential confounders and important covariates (including baseline fatigue) will be adjusted for. Two-sided p=0.05 will be used. Economic analysis: Healthcare utilisation and cost self-report questionnaire collected at follow-up will be classified into categories of no need, met need and unmet need. Self-reported service use will be supplemented by electronic administrative data (i.e., the National Minimum Dataset) obtained with consent. Cost analysis will include direct health care costs (i.e. hospitalisation, rehabilitation services, and prescription charges), indirect costs (lost productivity will be assessed by changes in employment.), and out of pocket expenses. *Cost effectiveness evaluation* will be analysed in accordance with the Consolidated Health Economic Evaluation Reporting Guidelines,[27] with modelling repeated by ethnicity and socioeconomic status. Analyses will be conducted in SPSS.[28]

Study organization and funding

This trial is funded by the Health Research Council New Zealand(ref.18/147) and is registered with Australian New Zealand Clinical Trials Registry (ACTRN12619000626167).

Discussion

A multi-site trial of FMG is challenging but feasible. The greatest barrier has been recruitment. Contributing factors are stopping the trial for the 4-weeks lockdown of NZ (6-weeks in Auckland) during the COVID-19 pandemic; it also reflects strict inclusion criteria to ensure that fatigue due to stroke is the target of the intervention . Data on reasons for exclusion will be available at trial conclusion.

Scheduling groups over a large region is challenging. Groups of 4-6 people are scheduled within smaller areas (1-hour travel maximum). If ≥6-weeks occurs between randomization and starting a group, eligibility is re-checked and primary outcomes re-administered 2-weeks before group commencement. Despite these challenges study strengths include a structured/manualised treatment, numerous quality controls, and stringent screening to ensure we treat fatigue due to stroke. As a manualised treatment with verbatim instructions and participant materials available for those providing the intervention, if the intervention is found effective it will be ready for immediate roll-out as a face-to-face intervention. Alternative modes of delivery to support individualised or on-line intervention requires consideration, especially given the COVID-19 pandemic, which has seen an unprecedented move toward online delivery of treatments and health-related services. Further study would need to occur to determine if any loss of benefit from moving to an online format. We are aware of a similar trial (Post Stroke Intervention Trial in Fatigue; POSITIF; ClinicalTrails.gov #NCT03551327) providing a 6-session CBT intervention via telephone, whose findings would be relevant. Unfortunately, despite a 2018 start date, the trial is described as not yet recruiting and has a finish date of December 31, 2021.

Conclusion

There are currently no empirically supported PSF treatments. If effective, FMG is a standardised, easily delivered program.

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Conflict of Interests

There is no conflict of interest.

Table 1. FMG content by session.

Session	Title	Content
1	Introduction	Overview, discuss stroke experiences, define fatigue, introduce fatigue diaries.
2	Fatigue management	Review diaries, PSF education, fatigue management strategies.
3	Sleep/relaxation	Review homework/diaries, sleep hygiene, stress, relaxation exercises.
4	Exercise/nutrition	Review homework/diaries, impact of exercise & nutrition.
5	Mood	Review homework/diaries, cognitive behavioural model of mood/fatigue.
6	Future	Review course, future strategy use.

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