

Original Research Article

Comparison of the outcomes of home based and supervised individually designed exercise programme amongst the patients in chronic phase after guillain barre syndrome: study protocol for a randomized control trial

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ABSTRACT

Background: Guillain barre syndrome (GBS) is an immune mediated polyneuropathy characterized by progressive weakness and variety of symptoms including muscle paralysis, autonomic dysfunction and respiratory involvement that affect one or two persons in 100,000 population. Although immunotherapies including therapeutic plasma exchange (TPE), immunoglobulins (IVIg) and corticosteroids are the available beneficial modes of treatment, the residual symptoms are disabling and long lasting and require long term rehabilitation. Observational studies and RCT on multi-disciplinary care has proven exercises to be an answer to residual long lasting disability. Supervised individually designed exercise prescription after physiotherapy assessment may play a major role in minimizing disability.

Methods: The present study is an open-level, parallel, superiority randomized control trial with blinding of outcome assessors to evaluate the results of the individually designed exercise programme over home based exercise programme. 74 adult referred GBS patients will be recruited and randomize in two groups either to receive 12 weeks individually designed exercise programme or home based exercise programme. The primary outcome shall be assessed as functional independence in activities of daily living and secondary outcomes shall be evaluated in terms of muscle strength, fatigue, pain, and quality of life at baseline, six months and twelve months duration.

Conclusions: This is the first randomized control trial to compare the effect of supervised individually designed exercise over home based exercise programme on pwGBS.

Trial registration: Currently the trial is ethically approved, prospectively registered CTRI/2016/08/007150 and in the process of recruiting its first subjects.

Keywords: Guillain barre syndrome, Superiority randomized control trial, Physiotherapy

INTRODUCTION

Guillain barre syndrome (GBS) is an immune mediated polyneuropathy characterized by progressive weakness in

all four limbs, areflexias, autonomic dysfunction and respiratory paralysis.^{1,2} The onset and presentation of symptoms may vary. It is considered to be the most important cause of muscle paralysis in developing

countries after poliomyelitis.¹ The disease incidence in India is similar to that of other developed countries: 1- 2 patient per 100,000 population with male to female ratio of 2:1.^{3,4} This disease has generally favourable outcome (majority of the patient starts ambulation with-in 6 months of the onset of the symptoms) with low mortality rate, however, 25% of the patients may require ventilatory assistance, and 10-20% of the patient may have severe residual permanent disability.^{1,5,6} It can be a major cause of long term disability in the patients as the most common population which gets affected is relatively younger population (30-50 years), although it can attack at any age.^{4,7,8} Immunotherapies are the available modes of treatment and have shown beneficial effects. Therapeutic plasma exchange (TPE) when applied during first few weeks of the onset of the symptoms and intravenous immunoglobulins (IVIg) in its recommended dosage has shown similar beneficial effects on the disease symptoms.^{9,10} With advances in the acute care of patients with GBS, survival and early acute recovery timing has been achieved but still a lot need to be done to increase the scope on improving the disability of patients and their social participation.^{1,11} The health related quality of life suffers a lot in the patients with GBS showing moderate to severe impact in their ability to participate in work also long term psychological sequelae.^{6,12,13} It has been reported in a study on ten years follow-up that residual disability may last for longer years or life in which 14% of the patient population had moderate to severe disability whereas 50% had more minor symptoms.¹⁴ Fatigue is also reported on 60-80% of patient population as one of the common consequence and also associated with the poor quality of life and activity limitation.¹⁵⁻¹⁸ A systematic review on effectiveness of exercises on patients with polyneuropathy has evaluated poor quality studies and only one trial which failed to show favourable effects of strengthening and endurance training on functional ability of the patients with polyneuropathy however, also suggested the moderate effect of exercises on increasing the muscle strength of the patients.¹⁹ Further, some observational and prospective studies also have reported the improvement in function, fatigue and muscle strength of the patient after supervised cycling or prescribed unsupervised exercises and aerobic activities.²⁰⁻²³ There is no standardized exercise care for the GBS patients with disability and activity limitations although supportive care is considered as important as immunotherapy in GBS patients.²⁴ Some guidelines and exercise models are also reported, however not standardized.^{25,26} Lack of randomized control trial (RCT) and clinical control trials (CCT) were reported in systematic review (SR) and meta-analysis on effects of MD care in patients with chronic phase after Guillain Barre syndrome (pwGBS) and evidenced a research gap in the same, however, the only RCT recently reported the beneficial effects of high intensity supervised MD care including physiotherapy for strengthening, endurance and gait training, on patient's disability of the pwGBS.^{27,28} In view of limited research on utility of exercise on various outcomes among survivors of pwGBS, we intend to

conduct a controlled trial to evaluate the results of supervised individually designed exercise programme over home-based exercise programme on patient's functional ability in activities of daily living, muscle strength, fatigue, pain and quality of life. The outcomes shall help the physiotherapy professionals as well as other health professionals to understand the role of physiotherapy as a key to rehabilitation in terms of patient care in GBS patients.

Objectives and hypothesis

We wish to find whether supervised individually designed exercise programme is better than home based exercise programme in improving the functional independence of the pwGBS patients. We intend to measure functional independence of patient primarily in terms of their activities of daily (ADL) living and by measuring muscle strength, fatigue, pain, and quality of life (QoL) before and after the interventions. ADL would be measured by using Barthel Index.

“We hypothesize that the supervised individually designed exercise programme would perform better than home based exercise program in achieving the outcomes of interest.”

Research question

Does supervised individually designed exercise programme improves functional independence measured in terms of change in ADL score by at least 20 percent as compared to home based exercise programme among patients in chronic phase after Guillain Barre Syndrome (pwGBS)?

Does supervised individually designed exercise programme leads to improvement in levels of fatigue, muscle power, pain, and QoL as compared to home based exercise programme among patients in chronic phase after Guillain Barre Syndrom (pwGBS)?

METHODS

Study design

We shall use an open-level, parallel, superiority randomized control trial with blinding of outcome assessors. The nature of the interventions precludes blinding of investigators and participants. Blinding of outcome assessors would be possible.

Participants (inclusion/exclusion criteria)

The sample size is calculated by calculating the difference in means for Barthel index from a prior RCT on rehabilitation versus standard care in multiple sclerosis patients, and anticipating 20% improvement in the scores in treatment group at significance level of 95% to achieve a power of 80% for a one-tailed test, 66

patients (33 patients in each group) will be needed; therefore 74 patients including 10% attrition will be recruited from Bhopal Memorial Hospital and Research Centre, a 350 bedded tertiary healthcare centre which provides healthcare primarily to the victims of the Bhopal gas tragedy.^{29,30} Apart from the patients from the pools of Bhopal gas victims, usually referred from its other outreach centre (Mini Unit I to VIII) and other gas-rahath hospitals, the hospital is also visited by patients from all over Bhopal as well as nearby districts. All variants of GBS patients above 18 years of age diagnosed as previous cases of “definite” GBS by physician/neurologists using international classification of disease (ICD) criteria of World Health Organization (WHO) would be approached for recruitment in the trial. The enrolled patients should have a current stable medical course and a physical disability as assessed by the international classification of impairment, disability and handicap (WHO 1980) which was updated by the WHO to the international classification of functioning, disability and health (WHO 2001).^{31,32}

Patient those who have received the physiotherapy treatment in the period of previous 6 months shall be excluded from the study. Patients who were diagnosed as pwGBS 6 years prior to date of recruitment would also be excluded. Pregnant females and amputees shall also be excluded.

Recruitment/ randomization allocation concealment/ consent

All the potential participants shall be listed out and invited by the post, telephonic conversation or personal contact to participate in the study. The interested participants shall be recruited for the study (disease duration between 1 and 6 years) after signing an informed consent. The participants will be then randomly assigned to treatment and control group with the help of computer generated block randomization codes with stratification by time since diagnosis (early ≤ 3 years, late ≥ 3 years). The randomization of the patients shall be done by the community and family medicine department at different health facility. After enrolling the participant and obtaining the informed consent, the details of the participant would be entered in a web-based computer programme which would be developed for the trial to assign the group for the participant. The investigator or intervention provider would not be able to control which participant receives which therapy. During interim analysis, if it is found that either of the intervention is highly effective or there are any serious adverse events, the trial would be stopped. Flow chart for allocation of participants and follow ups is depicted in Figure 1.

Assessment

Baseline assessment of all the participants shall be accomplished in six weeks period by two independent assessors (physiotherapists) in a structured pre designed

web-based data collection interface. These two assessors shall be trained to assess the cognitive and functional ability of the patients to maintain reliability of assessment. They will not share any information to the treating physiotherapists. They will complete the demographics, functional assessment in activities of daily living, muscle testing, level of fatigue, intensity of pain, and health related QoL using standardized instrument for all participants. The assessment interview shall take approximately 45 minutes to 1 hour time. Both treatment and control group will be assessed at the time of recruitment, at six month and at 12 months follow-up after the completion of rehabilitation programme. The participants in the control group shall be allowed to continue their usual visits to their physicians. The assessors will not have any access to previous assessments treatment schedule or treating rehabilitation therapy team documentation. They will receive a new format for assessment each time. Participants will be instructed not to make comments on whatever treatment they received in the time interval between examinations. It is not possible to blind the participant and the care-providers. The outcome assessor will be blinded. All assessment will be secured and filed and opened only at the time of entry into the database by an independent data entry person.

Interventions

Treatment group

After recruitment of participants in treatment group a baseline assessment shall be done. The participants in the treatment group will receive an individualized supervised outpatient physiotherapy programme designed on the basis of their clinical symptoms (for up to twelve weeks) over the study period. A two week assessment of the improvement in the symptoms will be done by the physical therapist and further modification in the programme will be done to provide the potential benefit. The supervised physiotherapy programme will include up to three one-hour interrupted physiotherapy session per week for strengthening, endurance training, gait training and pain management.^{19,20,33-37} The treatment protocol shall be designed after rehabilitation assessment of the patients and according to their clinical features, individual need of treatment by the treating physiotherapist.^{27,38-40} The patients will be promoted to attend the out-patient treatment session for more than 80% of all session.

Control group

After recruitment of participants in control group a baseline assessment shall be done. The participants in the control group will receive home based exercise programme of maintenance exercises and education for self-management exercise programme for about 30 minutes once at the time of recruitment. The patients who will need more intensive physiotherapy treatment will be

offered treatment. These patients will receive a two monthly telephone call to get the information about activity levels and their medical visits. Physiotherapy is a relatively safe procedure however any adverse effect of

physiotherapy will be ruled out. The assessment will be done by the trained assessors and in a pre-designed assessment proforma.

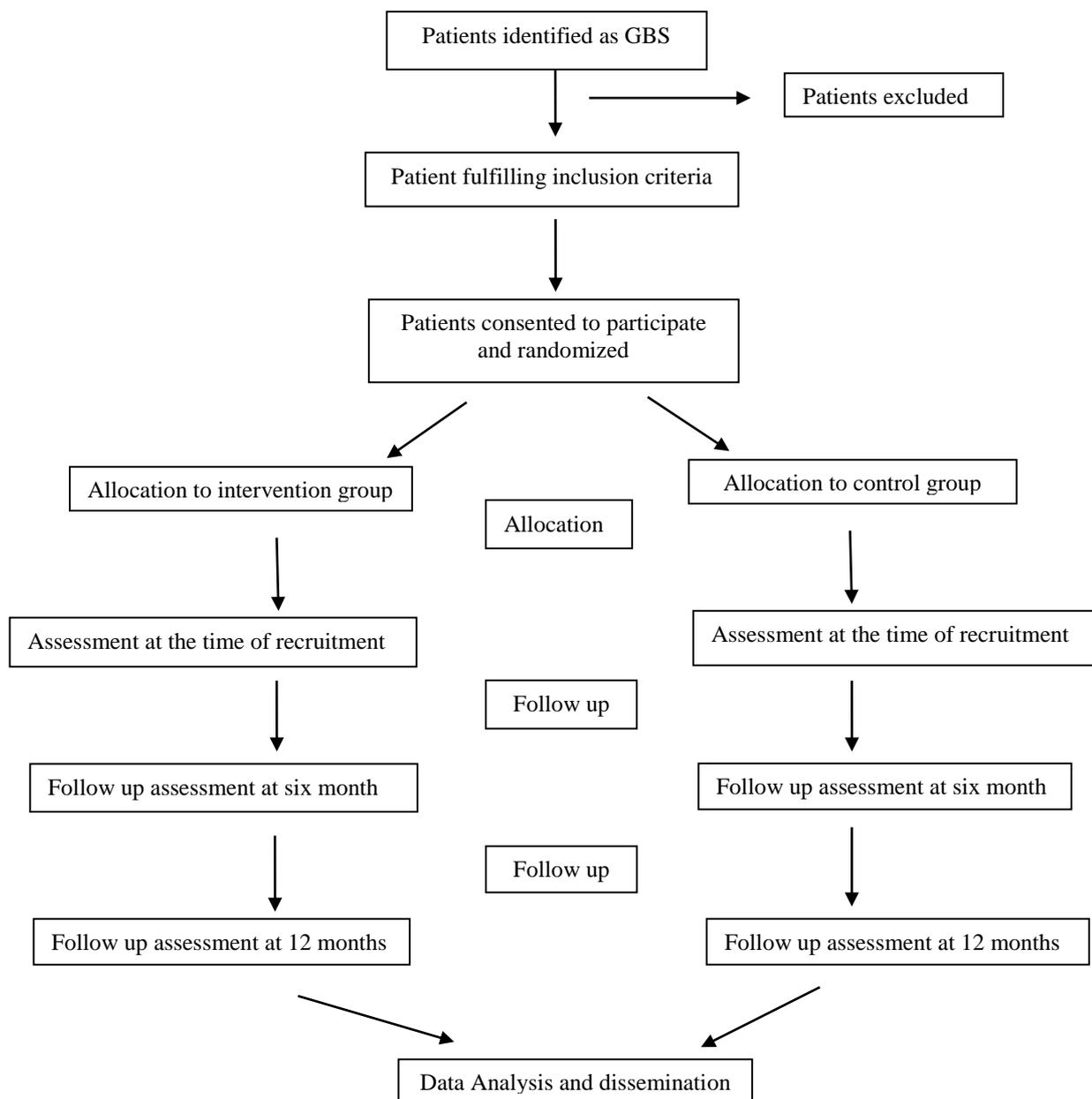


Figure 1: Flow chart for recruitment process.

Adverse event reporting

Although physiotherapy is a relatively safe procedure the participants in both groups will be asked to immediately contact principle investigator or research physiotherapist if they notice any adverse event during the study/ intervention. Any serious event shall be ruled out and referred to the monitoring committee and their decision shall be respected.

Outcome measurements

Information related to demographics, clinical and treatment data, variant of GBS, ventilatory support, duration of hospital stay and associated complications shall be taken out from the past medical records.

The primary outcome measure includes functional independence in activities of daily living which shall be

measured by using Barthel index (BI) for functional independence in personal care and mobility.^{5,41,42} It is a ten item scale and each item is rated in terms of whether the patient can perform the task independently, with some assistance, or is dependent on help. Item scores are added to form an overall score that ranges from 0 to 100, in steps of five, with higher scores indicating greater independence.

The secondary outcomes measures are further a cluster of quantitative measures including level of fatigue, muscle power, pain, and quality of life (QoL) using standardized tools. Level of fatigue shall be measured through a lucid and brief self- assessed questionnaire Fatigue Severity Scale (FSS) containing nine items on seven point likert scale with answers ranging from 1 (“strongly disagree”) to 7 (“strongly agree”) for each inquiry. The mean score of the nine inquiries ranges from 1 (“no signs of fatigue”) to 7 (“most disabling fatigue”).⁴² Medical Research Council manual muscle testing (MRC sum score) measures the muscle strength for the following muscle groups upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsal flexors and is a summation of the Medical Research Council grades (range 0–5). The MRC sum score ranges from 0 (“total paralysis”) to 60 (“normal strength”).^{41–44} Pain would be assessed by using a Visual Analogue scale (VAS): It is a 100 mm scale ranging from 0 to 10, having “no pain” and “unbearable pain” at opposite extremes with higher scores reflecting more pain.⁴¹ To measure health related quality of life the World Health Organization Quality of Life (WHOQoL-BREF) tool shall be administered which is a valid and reliable tool with 26 items for domains assessing physical health, psychological health, social relationships and environment and QoL and health. All items are rated on a 5-point scale with higher scores indicating higher QoL.^{41,46}

Data collection

The data shall be collected in a pre-designed/ structured proforma (Case Record Form/CRF) and shall be sealed immediately after filling it, the assessor shall use a new proforma each time and all sealed envelope shall be opened after completion of trial at the time of data entry. All the measure recorded at baseline, 6 months and 12 months follow up including socio demographic characteristics and quantitative measures will be entered. Data will be stored on secure hospital- based password-protected computer. Each participant will have a unique alpha numeric code assigned which would only be accessible to the principle investigator and one co-investigator. Double data entry and random regular third party checks shall be done to ensure accuracy.

Statistical analysis

Data entry would be performed in Microsoft excel 2010. Before starting, data code-sheet would be generated. Data

analysis would be performed by R software. Intention-to-treat analysis would be performed first on all the data obtained. Per-protocol analysis would also be performed to rule out significant deviation in the outcome measurements. For counts, proportions with confidence intervals would be reported and for continuous data, mean with standard deviation would be reported. The baseline characteristics of the study participants would be compared using t-test for continuous data in dichotomous groups and ANOVA for more than two groups. For baseline categorical data, we shall use chi-square to compare for significant difference between the two groups. Multivariate analysis would be performed for comparing all the primary and secondary outcomes between two groups. We shall obtain adjusted risk ratio, attributable risk reduction and number needed to treat.

Ethical Issues

This study has received Institutional ethical committee approval, scientific committee approval, administrative approval from Bhopal Memorial Hospital and Research Centre. The study has also been approved for funding by Scientific Advisory Committee through Indian Council of Medical Research, India. Appropriate participant safety measures such as privacy and confidentiality shall be observed. Apart from the research team, no one else will be able to have access to the participant data. During analysis, all the personal identifiers shall be excluded. Although we don't expect any adverse events, any untoward events would be managed at the health facilities as per the healthcare guidelines.

DISCUSSION

Physiotherapy in pwGBS patients is a key to rehabilitation but no trial has been published till date. This is the first randomized control trial to compare the effect of supervised exercises over home based exercises on pwGBS. Another protocol has recently been designed as a feasibility trial in tailored home based exercise programme versus usual care and also to rule out the cost effectiveness for the same.⁴⁷ It is anticipated that this study will evaluate the superiority of supervised individually designed exercise program on pwGBS over home based exercise program. We expect participant to be compliant with physiotherapy intervention. The strength of this trial is that integrity and quality of intervention delivery shall be maintained by having one physiotherapist, other than the outcome assessors, for physiotherapy assessment and to conduct all the exercise prescriptions. The success of this trial will establish the role of physiotherapy as an important tool in rehabilitation of pwGBS.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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