Original Article

Medication-Adherence and Management of Risk Factors for Secondary Prevention of Stroke Using Smartphone-Based Application: Protocol for MAMORs-Randomized Controlled Trial

Veena Babu, P N Sylaja[1], Biju Soman[2], Ravi Prasad Varma[2], Manju M S[1], Geethu G L[1], Suresh Kumar B[3]

Comprehensive Stroke Care Program, Department of Neurology, Sree Chitra Tirunal Institute of Medical Science and Technology, [1]Department of Neurology, Sree Chitra Tirunal Institute of Medical Science and Technology, [2]Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, [3]Computer Division, Sree Chitra Tirunal Institute of Medical Science and Technology, Thiruvananthapuram, Kerala, India

Abstract

Background: In LMICs, the medication adherence and risk factor control are suboptimal in the post-stroke follow-up period. With shortage of physicians, smartphone-based interventions can help stroke survivors in secondary stroke prevention. **Objectives:** We aim to validate a digital innovative technology-based intervention to improve the awareness, medication adherence, control of risk factors through timely intervention of physician among the stroke survivors. **Methods:** MAMOR is a smartphone-based application to improve the stroke awareness by heath education materials, reminders to timely adherence of medication, alerts on control of risk factors, video files, and timely physician intervention. The study will involve development of the app using contextual research (Delphi qualitative method) followed by a randomized, single center, double arm-controlled trial with 1:1 assignment. The app will be evaluated over a period of 6 months with a target to enroll 192 participants. Process evaluation will be conducted. The sample size was calculated as 192, considering medication adherence of 43.8%, 20% increase in medication adherence by app, power of 80%, and 10% loss to follow-up. **Results:** The primary outcome will be medication adherence, changes in the lifestyle and behavioral and control of vascular risk factors. The secondary outcome will include vascular events and functional outcome. **Conclusion:** This study will be one among the few studies for secondary prevention of stroke through digital technology innovation in LMICs with resource constraints. The evidences generated from this study will provide translational evidence for other similar settings for stroke survivors.

Keywords: Medication adherence, risk factors, secondary prevention, stroke

Introduction

Stroke is a major global health concern. Of the 15 million people suffering from stroke, 5 million die and another 5 million are left permanently disabled, placing a burden on family as well as to the community. The crude incidence of stroke ranged from 108 to 172/100000 people per year. The burden of stroke is increasing in India; stroke is now the fourth leading cause of death and the fifth leading cause of disability.[1] There is an increased recurrence of stroke, and one out of four strokes is recurrent. The leading risk factors for stroke are high systolic blood pressure, diabetes mellitus, high body mass index, smoking, and air pollution.[2]

Secondary stroke prevention strategies are important in preventing stroke recurrence. Adherence to medication is a key issue in treatment success and control of risk factors. The adherence to secondary prevention medications after a stroke is known to be suboptimal especially in low- and middle-income countries (LMICs) where there is shortage of primary care providers and neurologists and poor adherence to treatment leading to worse outcomes. It is evident that the stroke recurrence could be minimized by educating the survivors and their caretakers on stroke, its risk factors, targets of risk factors, and lifestyle and behavioral modifications.[3] There are several barriers that result in the suboptimal implementation of these secondary prevention strategies in the country.

Evidence shows that medication adherence by means of daily reminders and providing the survivors with financial assistance can help them to prevent another stroke in their life.[4] Limited geographic access and financial barriers pose additional challenges in accessing appropriate health services among stroke survivors living in rural areas as compared to urban patients. Feasibility of task-shifting for secondary stroke prevention is well evident from community health worker (CHW)-based intervention in resource-constrained

Address for correspondence: Dr. P N Sylaja, Department of Neurology, Sree Chitra Tirunal Institute of Medical Science and Technology, Trivandrum, Kerala, India.
E-mail: sylajapn@hotmail.com

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setting which is as per WHO report 2006.[5] This paves way for non-human interventions for secondary stroke prevention.

The role of mobile telephones in promoting adherence to medication and secondary prevention in stroke has not been extensively explored adequately in our setting. India is particularly suited for a mobile telephone-based intervention given the widespread geographical connectivity, cheaper costs, and the growing popularity of the mobile phones. Integration of mobile phone technology into secondary prevention of stroke care holds immense potential, particularly in resource-constrained settings. Relatively higher proportion (66%) reported using phones to call their healthcare provider.[6] There is sufficient data suggesting routine usage (87%), ownership of mobile phone (88%), and willingness to receive m-health advice (92%) among Kerala population.[7] Of the total mobile phone users in India, Kerala shares 3.81 percent users with more than 4.5 crores mobile connections in the state[8] and total internet connections stands at 3.1 crore.[9]

So, there is a scope for non-human interventions for secondary stroke prevention which was proven in other parts of the globe.[10] Owing to the rapid popularization of ubiquitous network connectivity and as most people have a mobile phone, mobile apps offer a platform for a personalized support tool.[11] We intend to use a smartphone-based personal monitoring app among survivors of stroke visiting our tertiary care setting to improve adherence to the medication, risk factor control and provide health education to the patients for lifestyle and behavioral modifications. The app also allows the physicians to timely intervene with the medication alterations to keep the risk factors under control. Hence, it paves a way for direct feedback to the user and can be owned by the patient or the care giver.

This is going to be a free app which is to be personalized. This will in fact be used for medication adherence and risk factor control and allow the physician to timely intervene with the medication alterations to keep the risk factors under control. It will also provide health education to the patients for lifestyle and behavioral modifications. Hence, this app is different from other apps.

Study Hypothesis

The primary aim of the study is to test the hypothesis that use of a smartphone-based personal monitoring app among survivors of stroke will have a better adherence to the medication and control of their vascular risk factors when compared to survivors of stroke without using the app (control group).

Further hypotheses assume that stroke survivors using the app will show significantly improved knowledge on the lifestyle and behavioral modifications.

Methods

Ethics clearance

The study received Institutional Ethics committee approval: -SCT/IEC/1791/DECEMBER/2021.

CTRI registration

The study is registered in clinical trial registry, and the registration number for this trial is CTRI/2022/06/042980.

Informed consent

A written consent will be obtained from all the participants.

Study setting

This study will be conducted in Comprehensive Stroke Care Unit, Department of Neurology, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala, India, with an intention to generate solutions that can be adapted in other resource-limited settings. Yearly, around 450–500 patients are admitted in the stroke care unit, and these patients are followed up in outpatient clinic. The institute caters to the tertiary stroke care needs of whole of population of Kerala state especially southern part. Kerala state has a population of 3.46 crores.

Design

This study is an unblinded, randomized, single-center, double arm-controlled trial with 1:1 assignment. The duration of the study will be 1 year and includes development of app, patient recruitment, data collection, and analysis.

Contextual research, development of m-health system

Contextual research

Considering the possibilities of mobile app designing and programming, qualitative iterative Delphi method will be done to integrate the experiences of healthcare providers, app developers, stroke team members, and app users along with various literature reviews in Trivandrum, Kerala, India. Five stakeholders each from group of healthcare providers, stroke team members, developers of health-related apps, and users of the health apps will be identified for the Delphi method. A modified Delphi method that provided a common starting point of discussion with the modules developed using literature searches and initial discussion with the neurologists and stroke team members will be created for other stakeholders to reach consensus by answering questions in an iterative process. The identified stakeholders will be informed about the study and the need to participate. Each item will be scored from 1-Strongly agree to 5-Strongly disagree. The participants will be given a stipulated time to respond, during which reminders will be sent to maximize the involvement of as many participants as possible.

The consensus on the statement will be reached on a particular statement as accepted when 65% of the participants scored one or two and rejected when 65% participants scored 5. All those statements with scores 3 or 4 will be considered for the second round of Delphi.

Member checking will be done among a subsample of population after the first round of Delphi among the population who scored 3 and 4 to know whether the participants had rightly understood the statements in the Delphi method. This iterative process is repeated till all the statements are either accepted or rejected.

Finally, the statements will be finalized to develop the content for the mobile app.

Development of the mobile app

Based on the results from the contextual research (qualitative Delphi method), an app development team developed a m-health system for this study and future scale-up, which consists of an android-based app and text messaging system with the help of a third-party owner customized for the stroke patients enrolled in the study. The app contains modules on baseline information, health education materials on secondary stroke prevention, set reminders of follow-up visits, follow-up visit data collection, and interaction with the team.

Participants and recruitment

The recruitment of the participating patients will be done after informed consent by the principal investigator and study coordinator from May 2022 to August 2022.

Eligible patients must meet the following inclusion criteria:

- Adult (≥18 years) patients with onset of stroke within 1 month.
- Severity:- (modified Rankin scale) mRS <5
- Presence of one or more vascular risk factors such as hypertension, diabetes mellitus, smoking, and dyslipidemia.
- Patients who could fully understand the use of an android-based smartphone.

Exclusion criteria include:

- Patients with severe disability-modified Rankin scale score >4
- Patients who do not consent.
- Severe cognitive impairment.
- Stroke survivor without a primary caregiver in patients with mRS 3 and 4.

Participants assigned to the intervention group who failed to download or are experiencing any technical issue in accessing the app in their mobile phones will be excluded.

Sample size

Considering a medication adherence of 43.8%,[2] 20% increase in medication adherence by app (10% rise by SMS alerts),[12] power of 80%, sample size was calculated to be 172 using OpenEpi. Expecting 10% loss to follow up the final sample size was calculated to be 192. Considering the ratio of sample size (exposed/unexposed) to be 1, 96 participants in each arm were planned to be enrolled for the study.

Randomization

Randomization will occur in a 1:1 ratio to either smartphone group (intervention) or usual care (control) group. Once the patient meets all study eligibility criteria and sign the consent form, randomization takes place centrally via REDCap software. The patient will not be blinded to procedures as the patient will be verbally informed by the investigator to what treatment group he/she has been assigned. The first patient was recruited on May 13, 2022.

Study procedure

The study team will screen the stroke patients from the stroke clinic and comprehensive stroke care unit. The participants enrolled into the study will be randomized to control and intervention arm [Figure 1]. The data collection will be conducted following a standard protocol by trained staff. The baseline data including the clinical and demographic will be collected using the developed mobile-based app. The etiology of stroke will be documented as per the TOAST classification. Baseline BP, height and weight of patients, fasting blood sugar, post-prandial blood sugar, HB1AC, lipid profile, lifestyle factors, and dietary patterns at the baseline will be collected.

Control Group

The control group will receive usual care and health education on stroke, its type, symptoms, risk factors, lifestyle modification, and diets for secondary stroke prevention. They will be given a pamphlet along with their dates of monthly follow-up and visit dates.

Intervention group

Patients assigned to the intervention group will receive smartphone app in addition to the usual care received by the control group along with the help from the study coordinators to install the app.

Intervention

To facilitate medication adherence, lifestyle and behavioral modification of the stroke survivors, the intervention will have the following components.

Introductory session

An introduction about the intervention, its benefit in secondary prevention will be briefed to the study particpants.

Baseline data collection

The baseline data which include vascular risk factors, functional outcomes, lifestyle and behavioral modifications, and dietary pattern will be collected through the mobile app.

Installation of mobile app

After randomization, the participants in the intervention group install the mobile app with the help of study coordinator. An instruction manual will be given to the users in the basic language for easy understanding.

The participants in the intervention arm will receive text messages from third day onwards regarding the education on stroke, lifestyle and behavioral modification, nearby Government facilities and reminder for medication periodically till 6th month of follow-up which will be confirmed by the study team. Participants will be instructed to upload their vascular risk factor values in the mobile app, and in return, they receive the text messages on the control status of their vascular and behavioral risk factors.

All the participants will be followed up in the stroke clinic at third and sixth months.

Quality assurance and control

To ensure the quality of intervention, several key measures will be taken.

- The PI will monitor the knowledge gained by all the participants in the direct follow-up visit by randomly asking the participants and the caregiver few questions from the stroke education given.
- The research coordinators telephone and ensure whether the intervention group is receiving the messages and reading them.

To ensure the unbiased results, the final evaluation will be done by a researcher who is blinded to the group the patient will be assigned, and special efforts will be taken to avoid the contamination of the results.

Outcome evaluation

Primary outcome: -

- Medication adherence will be evaluated based on Morisky Medication taking Adherence Scale-MMAS (4 item) scores ranging from 0 to 4.
- Changes in the lifestyle and behavioral factors using WHO STEPS instrument, physical activity questionnaire, and FADS questionnaire
- Control of vascular risk factors at third and sixth months.

Secondary outcome: -

- Vascular events-TIA/Stroke/Cardiac events/Vascular deaths
- Functional outcome assessed by modified Rankin scale (mRS).

Statistical analysis

We are planning to analyze the participant-level outcome data following intention to treat principle whereby all participants will be analyzed in the intervention arm to which they are assigned. All the continuous variables will be reported as mean and standard deviation if symmetric or as median with IQR if not. Categorical variables will be reported as categorical variables. Changes in the variables from baseline to 6-month study period will be reported. Additional analyses will be performed that additionally adjust for baseline covariates. All analyses will be conducted blinded so that the treatment arm is not revealed until all results have been generated. The trial also focuses to minimize the missing data in the follow-up period by monthly contacting the participants. As the smartphone app is a multicomponent intervention, there is possibility of different level of fidelity to the intervention and so we intend to use a strategy that is commonly adopted in the trials of complex, multicomponent interventions as to describe and summarize levels of adherence to the intervention activities among participants according to different components of intervention rather than formally defining the degrees of fidelity in advance. Fidelity indicators on the patient side include proportion of follow-up visits, proportion of text messages received and read, proportion of regular data upload, videos viewed, etc.

Study Funding

The study is funded by the World Stroke Organization Pilot Research Project 2021.

Process evaluation

Six waves of process evaluation will be conducted in the intervention arm, while two waves of process evaluation at third and sixth months will be done for control group. Face-to-face in-depth interviews will be conducted by the research team in selected participants of intervention and control arm at the sixth month to explore the acceptance of this app . A standard interview guide will be developed, and all interviews will be recorded transcribed and analyzed to interpret the results. If in case of loss to follow-up, we will try to reach the participants in their contact details.

Current trial status

The app development was completed by May 2022. The participant recruitment was started on May 16, 2022. By September 2022, the recruitment ended with recruiting 209 participants.

Discussion

The raising burden of stroke reinforces the need to implement effective primary and secondary prevention strategies in resource-limited settings. This study aims to develop a smartphone-based app for medication adherence and secondary prevention of stroke among first-ever stroke survivors, to test the feasibility of using a smartphone-based app to assess the medication adherence, risk factor control, and lifestyle modification for secondary stroke prevention and to compare the event rate between conventional and smartphone app-based follow-up through a randomized control trial. As per the existing knowledge, this trial is one among the few studies that aim to evaluate digital technology-based intervention for secondary prevention of stroke in limited resource setting like India. We expect that findings of our study could also provide translational evidence for other resource-constrained settings. Equipping the non-human resources with skills and knowledge on the secondary prevention of stroke will shift the laborious secondary care to a more comprehensive and integrated care in settings like India. Considering the extensive usage of the mobile phones in Indian settings, this is an attempt to reduce the burden of neurologists who are limited in our country.

The content of the intervention will be developed meticulously by extensive contextual research using qualitative technique-Delphi addressing the needs of the stroke community including the stroke team and the survivors. We expect this will help to make this upcoming intervention to be innovative but feasible at the individual level in controlling their risk factors by making it a personalized and interactive app.

Though there are other mobile apps for secondary prevention of stroke, this app is an endeavor to bring multiple components of secondary prevention of stroke into one platform. This includes timely monitoring of risk factors, measures to take based on

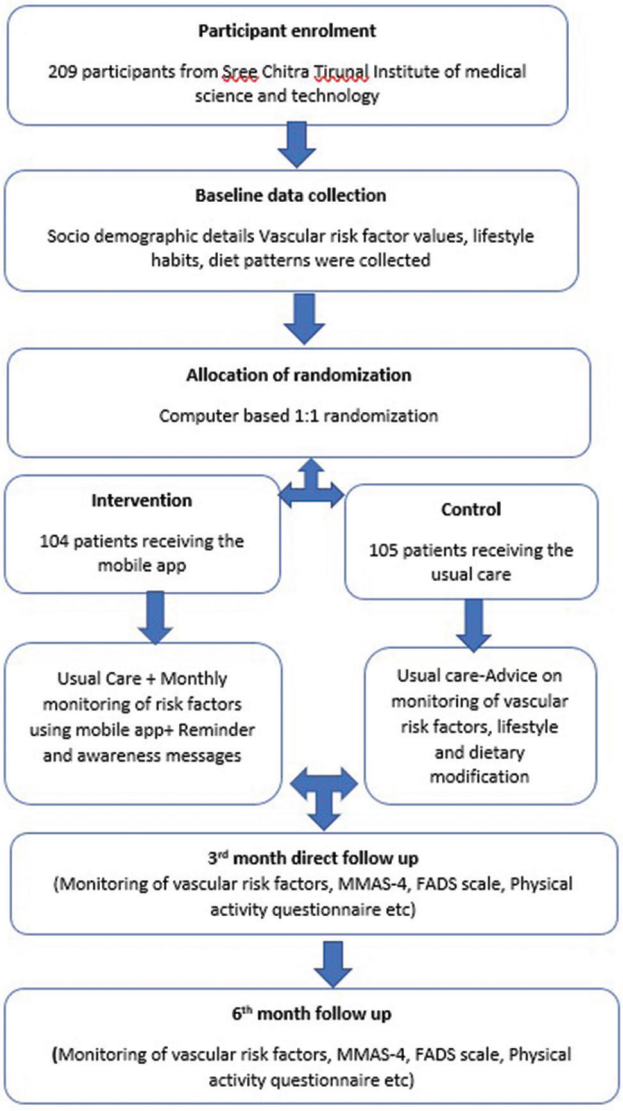

Figure 1: Recruitment of patients in the study

the control of the risk factors, timely physician intervention based on the control status, stroke awareness, and reminders for medication adherence.

This study also intends to develop smartphone-based app in a least expensive platform. Ultimately, we expect an improvement in medication adherence of stroke survivors, modification in their lifestyle and behavioral patterns to prevent the recurrence of stroke in the future in the community.

Summary and Conclusion

The mobile phone app is expected to monitor the medication adherence and increase stroke awareness. It is presumed that this smartphone-based app will be a personalized app which will in fact allow the physician to timely intervene with the medication alterations to keep the risk factors under control and also allow for lifestyle and behavioral modifications of the stroke survivors. We look forward to implement this less expensive, easy-to-use mobile app in the LMIC with comparably less resources to help all the stroke survivors lifelong.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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