Effect of a community-based intervention for cardiovascular risk factor control on stroke mortality in rural Gadchiroli, India: study protocol for a cluster randomised controlled trial

Yogeshwar Kalkonde
SEARCH https://orcid.org/0000-0003-3543-3618
Mahesh Deshmukh
SEARCH
Sindhu Nila
SEARCH
Sunil Jadhao
SEARCH
Abhay Bang (search.gad@gmail.com)

Study protocol

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Abstract

Background Stroke has emerged as a leading cause of death in rural India. However, well tested healthcare interventions to reduce stroke mortality in rural under-resourced settings are lacking. The aim of this study is to evaluate the effect of a community-based preventive intervention on stroke mortality in rural Gadchiroli, India. Methods The study is a two-arm, parallel group, cluster randomised controlled trial where 32 villages each will be randomised to the intervention and the enhanced usual care (EUC) arm. In the intervention arm, individuals ≥ 50 years of age will be screened for hypertension, diabetes and stroke by trained Community Health Workers (CHWs). Screen positive individuals will be referred to a mobile outreach clinic which will visit intervention villages. A physician in the clinic will confirm the diagnosis, provide guideline-based treatment and follow up patients at periodic intervals. The CHWs will make home visits once a month to ensure medication compliance and counsel patients to reduce salt consumption and quit tobacco and alcohol. In the EUC arm, households will be provided information on the ill effects of tobacco and steps to quit it. Individuals from both the arms will have access to government's national programme for prevention and control of non-communicable diseases where treatment for hypertension, diabetes and preventive treatment after stroke is available, nearest at the primary health centres (PHCs). The intervention will be implemented for 3.5 years. The primary outcome will be reduction in stroke mortality in the last 2.5 years of the intervention. Discussion This trial will provide important information regarding the feasibility and effect of a community-based preventive intervention package on stroke mortality in a rural under-resourced setting and can inform India's non-communicable diseases prevention and control programme. If successful, such an intervention can be scaled up in rural regions of India and other countries.

Background

Epidemiological transition from communicable to non-communicable diseases has occurred in India [1–3]. Close to two third of India's population lives in rural areas[4]. Studies conducted by us and others have shown that stroke has emerged as a major public health problem in rural areas of India [1,5,6]. In rural areas of Gadchiroli district in India, stroke was the leading cause of death and accounted for 14% of all deaths[5]. Prevalence of stroke was also high (535/100,000 population)[6]. Stroke is also a global health problem. It is a leading cause of death in the world [7,8]. The burden of disease due to stroke has now shifted from higher income countries to low- and middle-income countries (LMICs) with 71% of stroke deaths occurring in these countries[9]. A large population of LMICs lives in rural areas and does not have easy access to preventive or curative care for stroke. Consequences of stroke could be severe in such communities where resources are scarce. Therefore, well tested interventions to reduce stroke deaths in rural areas of India and other LMICs are urgently needed. However, such interventions are currently lacking.

Stroke is preventable. The INTERSTROKE study has identified ten modifiable risk factors, which account for 90% of the risk of stroke [10]. Among these, hypertension is the leading risk factor and accounts for about 50% risk of stroke [10]. Hypertension control, therefore, emerges as an important target for stroke prevention. Hypertension is also the leading risk factor for death globally killing 9 million people every year [11] and the World Health Organization considers hypertension control a 'best buy' to reduce cardiovascular deaths[12]. Despite this, screening, diagnosis and control of hypertension remains poor in rural India. In a nationally representative study, hypertension was undetected in 60% women and 70% men in rural India and it was

controlled in only 50% of those who were diagnosed with hypertension [13]. Thus only 15-20% of hypertensive patients had their blood pressure adequately controlled. Another large study based on the fourth round of the National Family Health Survey (NFHS-4) showed similar findings[14]. Among rural individuals aged 15-49 years diagnosed with hypertension, only 72% had received a previous blood pressure measurement, 42% were aware of their diagnosis, 12% were treated, and only 8% had achieved control[14].

Diabetes is another risk factor for stroke and control of diabetes also remains poor in rural India. A large multi-state study conducted by the Indian Council of Medical Research involving 14,277 participants showed that good glycaemic control (HbA1c<7%) was present in only 30% of diabetes patients [15]. Secondary prevention of stroke also remains poor in India[16]. The Prospective Urban Rural Epidemiological (PURE) study which included patients from rural India found that only 27% patients in the rural regions of LMICs were receiving anti-platelet agents[17]. Collectively, these studies highlight a significant care gap in stroke prevention in rural India where 12% of world's population lives.

There are several challenges to prevention and control of stroke and its risk factors in rural India. Awareness about these conditions remains low [18–23]. Hypertension and diabetes often do not have symptoms and their diagnosis gets delayed. Screening facilities are not widely available and even after screening only a fraction of patients get their diagnosis confirmed. Continuity of care remains a challenge due to lack of affordability, accessibility and prioritization of care leading to suboptimal control of these conditions. In order to address the rising burden of NCDs, the Government of India has launched an ambitious National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS). This programme has started screening individuals at village level and for diagnosis and treatment patients have to travel to the PHCs, the closest point of contact with a physician in public health care system in rural areas where treatment is provided free of cost [24]. However, its implementation has been slow and travel to the PHCs is challenging for patients due to lack of transportation facilities in rural areas.

In order to reduce stroke mortality, we have designed a community-based healthcare delivery intervention package which tries to address major barriers to effective control of hypertension, diabetes and secondary prevention of stroke in a rural under resourced setting in India.

Methods

Study hypothesis

The study will test a hypothesis that a community-based healthcare delivery intervention for primary and secondary prevention of stroke is feasible and will reduce stroke mortality in a rural community in Gadchiroli.

Objectives

1. To study the effect of the trial intervention on-
    1. stroke mortality
    2. all-cause and cardiovascular mortality
    3. percentage of hypertensive patients taking blood pressure medications in the community

4. blood pressure control
5. blood glucose control
6. awareness about stroke and its risk factors

2. Identify facilitators and barriers for the delivery of the intervention
3. Document intervention delivery and costs of the intervention to provide insights for scale up if the intervention is found to be successful

Trial design

The study is a community-based, two-arm, parallel-group, cluster-randomised controlled trial. As the intervention package is community-based, a cluster randomised design was preferred over individual randomisation.

Study site and population

The study will be conducted in Gadchiroli, one of the most underdeveloped districts of India [25]. Gadchiroli is located in the state of Maharashtra in central India (Figure 1). According to the Indian National Census 2011, the total population of the district was 10,72,942[26]. Ninety percent of the population of this district lives in rural areas, literacy rate is 66% and farming and manual labor are the predominant occupations in the district[26].

The government healthcare services remain an important source of healthcare in the district and provide care through one district hospital (DH), 12 rural or sub-district hospitals (SDH), 45 primary health centres (PHCs) and 365 sub-centres[27]. Each SDH typically covers a population of 100,000 while one PHC covers a population of 20,000-30,000. Care for hypertension, diabetes and preventive care for stroke is available free of cost at the PHCs, SDHs and the DH through the NPCDCS. Screening of individuals with hypertension, diabetes and cancer at the village level through a community level worker called ASHA has recently started through this programme. In addition to the government-run health services, care is also provided by formal and informal private healthcare providers and some non-governmental organisations. After acute stroke, patients are either admitted to the district hospital, private hospitals or seek care from herbal medicine providers. Brain imaging is not easily available as there is only one computerized tomography (CT) scanner available in the entire district. In a population-based study conducted by us in villages of Gadchiroli, only 12% of stroke patients had brain imaging[6]. Facilities to give intravenous tissue-plasminogen activator (t-PA) are also not available in the district.

SEARCH (Society for Education, Action and Research in Community Health) is a non-governmental organization working in Gadchiroli district since 1986. It has a service area of 86 villages distributed in 3 administrative blocks (Gadchiroli, Armori and Chamorshi, Figure 1) of the district. In these villages SEARCH has an active demographic surveillance system where all births and deaths are regularly recorded. Information on cause of death is obtained on all deaths through verbal autopsies[28]. A population census is conducted every 10 years and the last census was conducted in 2015. A population register is maintained which is updated annually. SEARCH also runs a rural hospital where primary and secondary level outpatient and inpatient care is provided at a nominal cost and includes care for hypertension, diabetes and stroke. SEARCH,

in collaboration with the state government of Maharashtra also runs a district wide campaign to reduce consumption of tobacco and alcohol by way to awareness generation, enforcement of legal restrictions on sale and community mobilisation.

Randomisation and blinding:

From the sampling frame of 86 villages in the service area of SEARCH, 32 villages will be randomly assigned to the intervention arm and 32 to the EUC arm (Figure 2) so that equal number of villages from each of the three blocks are assigned per arm. Allocation of villages will be done by the statistician at SEARCH using the random number generator in the statistical software Stata (College Station, TX, USA). Randomisation will be done before the participants are recruited.

Due to the nature of the intervention it is not possible to blind patients or the intervention implementers to the allocation group. However, the primary outcome assessors will be blinded to the allocation group.

Inclusion and exclusion criteria

Villages will be included in the study if a) they belonged to the service area of SEARCH and b) have population >400 so that the average village size of the selected villages is close to the average village population in India which is about 1250 [29]. The highest population of a village in the service area is 2,372. Villages within five kilometers of Gadchiroli town will be excluded as the purpose of the study is to assess the impact of the intervention in a larger rural community which has difficulty in accessing healthcare.

Individuals from the selected villages will be recruited if they are resident of the village for >6 months and are ≥50 years of age at the time of screening. We selected this age group for the intervention as >90% of stroke deaths and prevalent strokes in rural Gadchiroli occurred in this age group[5,6]. In order to receive the treatment intervention the individual should have one of the following- a) hypertension, defined as- systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg or should be on antihypertensive medications at the time of screening by the CHWs which is further confirmed in the outreach clinic by a physician, b) diabetes, defined as- glucosuria during screening by the CHWs and random capillary blood glucose of ≥200 mg/dL in the outreach clinic or outside records showing fasting plasma glucose ≥ 126 mg/dL or a single random venous blood glucose value of ≥ 200 mg/dL or previous diagnosis of diabetes and taking treatment for it, c) has had stroke, defined using the World Health Organization's (WHO) definition of stroke as a focal (or at times global) neurological impairment of sudden onset, and lasting > 24 hours (or leading to death), and of presumed vascular origin [30]. Patients diagnosed with hypertension, diabetes or stroke will be invited to receive the trial intervention if they agree to provide a written or audio consent (for individuals who can not read or write). Those who are terminally ill will be excluded and those have symptoms of acute cardiovascular compromise (suspected acute cardiac chest pain, heart failure or cardiac arrhythmia with pulmonary oedema, hypotension or hypoxia) or kidney diseases (oliguria, clinically suspected acidosis, pulmonary oedema) that can not be managed in primary care setting at the time of evaluation by the outreach physician will be referred for higher care and will be excluded until their clinical condition is unstable.

Recruitment

Individuals will be recruited in the trial from the villages selected in the intervention arm. A list of individuals ≥50 years of age at the time of commencement of the trial will be drawn from the census conducted by SEARCH in 2015. These individuals will be contacted by the trained CHWs after making a home visit and offered screening followed by treatment for hypertension, diabetes and secondary prevention of stroke.

Intervention

The intervention package was designed considering the risk factors for stroke [10], local relevance of these risk factors, current barriers to treatment (Table 1), feasibility of delivering the intervention and preferences of the community regarding providers and their roles. The intervention will be community-based and all the services will be delivered at the level of the community[31–33]. Hypertension, diabetes, alcohol and tobacco use will be targeted. Obesity and lack of physical activity will not be targeted as they are not locally important risk factors given that the population is lean and is engaged in physical labour. Modification of diet and addressing psychosocial factors were not considered feasible given limited food choices and lack of availability of an effective intervention which could target psychosocial factors in this area. In a formative study conducted before starting the trial, people felt that it would be convenient for them if a physician could visit the village and then a village-level worker could follow up patients and provide counseling.

The intervention will include following four components

1. *House to house screening for hypertension, diabetes and stroke by community-level workers*

Women community members aged 25-40 years with 7-12 years of school education will be selected. We plan to select women community health workers for the following three reasons. First, in this region men often travel outside villages for small jobs in non-farming seasons and hence are not available in the village. Second, one of the responsibilities of the CHW is to counsel patients to quit tobacco and alcohol. In Gadchiroli, tobacco consumption is very common among men and less so in women [34] while alcohol use is almost completely restricted to men[5,6]. Therefore, finding a male worker who will not be using alcohol and tobacco would be very challenging. Third, the acceptance of a male worker examining women is low in this traditional community. We will select one CHW each for villages with population ≤ 1500 and two for villages with population > 1500. After a rigorous selection process they will be recruited and trained. The CHWs will visit every household with individuals ≥ 50 years of age and after obtaining informed consent will-

1. measure their blood pressure using an electronic blood pressure monitor (Omron HEM-7121) after the patient is seated for 5 minutes. If the initial systolic blood pressure (SBP) is ≥ 140mm Hg and/or diastolic blood pressure (DBP) is ≥ 90mm Hg, another reading will be taken at 5 minutes after the first reading. The average of the two readings will be considered as the blood pressure of the patient.
2. check urine glucose on all individuals≥ 50 years of age using urine dipsticks
3. measure weight, height, waist and hip circumference
4. refer patients with hypertension (defined above), glucosuria (urine glucose more than trace on urine dipstick) to the outreach clinic for evaluation and initiation of treatment.

Stroke patients will be screened using a validated questionnaire as described by us earlier [6]. It had sensitivity of 85.7% and specificity of 99% in diagnosing stroke in the community where the trial is being conducted

[6].Given the logistics of the trial, the initial house to house screening for stroke will be conducted during baseline assessment of stroke prevalence in the intervention arm (Figures 2 and 3) by the community-level stroke surveyors who will be a part of the evaluation team under the trial and will be separate from the intervention CHWs (Supplementary figure 1) . This will be done to avoid the inconvenience caused to the target population due to double screening by the community-level surveyors and the CHWs. The community-level surveyors will screen all individuals ≥50 years of age in the intervention villages for symptoms of stroke using the questionnaire which will inquire if any of the family members ever had a)weakness on one side of the body, b) numbness on one side of the body, c) drooping of face on one side or d) slurring of speech. If any of these are present then the respondent will be asked d) if these were acute in onset and e) whether they lasted more than 24 hours. Individuals with one or more of the first four symptoms which were acute in onset and lasted >24 hours will be suspected of having stroke and will be referred to a stroke survey physician for confirmation of diagnosis.

2. *Evaluation, guideline-based treatment and follow up of patients with hypertension, diabetes and stroke by a mobile outreach clinic and referral where necessary*

A mobile outreach clinic comprising of an outreach physician (OP), a pharmacist and a driver will visit each intervention village once in two to three months. The OP will evaluate patients referred by the CHWs, confirm diagnosis of hypertension by rechecking blood pressure, diagnosis of diabetes by checking random capillary blood glucose (RCBG) using a glucometer (Accu-Check Active) and clinically confirm the diagnosis of stroke using WHO's definition of stroke as described before [6]. Hypertension will be treated using hydrochlorothiazide, amlodipine and atenolol and diabetes with metformin and glipizide (Tables 2 and 3). At the beginning of the trial, a stroke survey physician will confirm the diagnosis stroke and a list of stroke patients will be provided to the OP to evaluate these patients and start treatment. Stroke patients will receive secondary prophylaxis using low dose atorvastatin (10mg) and enteric coated aspirin (75mg) as per the treatment algorithm of the study (Tables 2 and 3). Stroke patients who had loss of consciousness or seizures at the onset of symptoms will be presumed to have a hemorrhagic stroke. These patients and those with intra-cerebral hemorrhage on brain imaging will not be prescribed aspirin. The goal of the anti-hypertensive treatment will be to keep blood pressure <140/90 mm Hg among those with hypertension and <130/80 mm Hg among those with diabetes and chronic renal failure but to keep it > 100/60mm Hg. Among diabetes patients, the target will be to keep RCBG between 100-200mg/dL. Patients with stroke, if they have hypertension or diabetes, will be treated according to the guidelines for treatment of these conditions. All the trial medicines, urine and blood glucose testing will be provided free of cost to the patients during the study period. The OP will refer patients to the rural hospital of SEARCH if hypertension or diabetes can not be controlled with trial medications, if patients are unable to tolerate any of the trial medications or when cardiac diseases (angina, atrial fibrillation or heart failure) or renal failure are clinically suspected. If screened individuals or patients who are being followed up develop acute stroke during the intervention period, they will be started on treatment for secondary prevention of stroke once they are back to their homes after receiving acute care for stroke. Also, individuals who did not have hypertension or diabetes at the time of screening but are incidentally diagnosed with hypertension or diabetes at a later date by the OP or another physician during the study period and wish to take treatment from the outreach clinic will be enrolled in the intervention and will receive treatment as per the study treatment algorithm. Patients will be allowed to continue medications for other ailments from their regular physicians. If patients wish to take medications for hypertension, diabetes or stroke from other physician but wish to get their

blood pressure or blood glucose checked by the OP, they will be allowed to do so if they provide a consent. Patients who wish to discontinue treatment provided in the trial will be free to do so at any point during the trial.

3. *Follow up by the CHW to ensure medication compliance, risk factor control and health education*

The CHW will follow each patient with hypertension, diabetes and stroke once a month to assess if the patient is taking medications as prescribed, tolerating them and whether the blood pressure is adequately controlled (<140/90 mm Hg). The CHW will also counsel patients not to have added salt during meals and quit tobacco and alcohol. CHWs will have stock of trial medications available with them. If blood pressure control is inadequate or the patient is not tolerating a medication then the CHWs will inform the OP over phone and make modifications to the treatment as instructed. This will be done to ensure that side effects are addressed in timely manner and hypertension control is ensured before the next village visit of the OP. If a patient fails to attend the mobile clinic then the OP will instruct the CHW to provide medications prescribed during previous visit to ensure uninterrupted supply of medications. CHWs will also provide individual health education to patients regarding hypertension, diabetes and stroke using videos and animations in local language Marathi specifically designed for this purpose. These videos and animations will be shown using hand held computers. In every home visit, the CHW will inquire about current alcohol and tobacco use among the patients. She will provide information regarding adverse health effects of tobacco and alcohol, counsel the patient to stop these and give tips to quit. Patients with hypertension, diabetes or stroke who do not wish to take their medications from the mobile outreach clinic but consent to follow up by the CHWs will also be visited every month and provided health education and counseling. If screened individuals or patients being followed develop stroke they will be screened by the CHWs and referred to the OP if they meet screening criteria for stroke described earlier[6]. Work of the CHWs will be supervised by two field supervisors by making visit to every CHW once every 15 days.

4. *A community awareness programme to provide health education about stroke and its risk factors*

The awareness programme will be designed based on the insights gained in the formative study on the knowledge, attitudes and practices for stroke[23]. The information on hypertension, diabetes and stroke will be provided through short movies and animations developed in the local language Marathi for this purpose. The awareness programmes will be conducted by field supervisors once every year in each intervention village. The supervisors will conduct these sessions in the evening after announcing the programme and it will be open for all villagers to attend.

Enhanced usual care: The usual care in the villages in this arm includes availability of free screening and treatment facilities for hypertension and diabetes and secondary prevention of stroke at the PHCs, rural hospitals and district hospital under the government's NPCDCS programme. Villagers also seek care at private providers in nearby towns which are block headquarters or the district place. In addition to this care, , all households in this arm will be provided information regarding harmful effects of and information to quit tobacco at the beginning of the intervention using information pamphlets. This will be done as close to 60% of individuals ≥ 50 years of age use tobacco in this district [34]. The villages in this arm are also a part of the campaign of SEARCH to reduce tobacco and alcohol use in the entire district as discussed earlier.

Details of services available for treatment of hypertension and diabetes, for prevention of stroke and for alcohol and tobacco control in both the arms are as shown in the supplementary table 1..

Adverse events

As this is a pragmatic trial and we are using standard medications, we anticipate adverse events commonly reported with these medications. We will use case definitions, standardised operating procedures and a reporting protocol to record all adverse events and treatment of these will be covered under the trial.

Primary and secondary outcomes and evaluation of outcomes

The primary outcome of the trial will be reduction in stroke mortality. We will compare stroke mortality in the two arms in the last 2.5 years of the intervention period. We selected stroke mortality as the primary outcome for two reasons – first, the trial was planned in an attempt to address a local public health problem i.e. high stroke mortality in rural Gadchiroli [5] and second, non-randomised studies of community-based interventions from Taiwan and Japan have shown the feasibility of reducing stroke mortality over a reasonably short period of time[35,36]. All deaths will be recorded by the demographic surveillance system. Stroke deaths will be determined using verbal autopsies as described before[5,28]. Verbal autopsies will be conducted on all deaths in the intervention and EUC arms during the intervention period using a verbal autopsy tool which has been validated in the Million Death Study[37]. Verbal autopsies have relatively high sensitivity (≥75%) and specificity (>90%) in diagnosing stroke in validation studies conducted in India and other countries and remain an important tool to assess stroke mortality in resource poor settings[38,39]. Verbal autopsies will be coded by two trained physicians independently. If the two coders do not agree a third physician will adjudicate the cause of death. Verbal autopsy coders and adjudicators will be blinded to the identity and location of the deceased. For diagnosing death due to stroke verbal autopsy coders will use definition of stroke provided by the WHO[30]. Deaths with diagnostic codes of I64 through I69 as per the tenth revision of the International Classification of Diseases, (ICD-10) will be counted as stroke deaths[5]. For estimating stroke mortality rate per 100,000 population in individuals ≥50 years of age, stroke deaths in each arm between July 1st 2017 and December 31st 2019 will be considered.

The secondary outcomes include

2. reduction in all-cause and cardiovascular (ICD 10 codes I00-I99) mortality in the intervention area, in the last 2.5 years of the intervention compared to that in the EUC arm over the same period. These will be estimated using the method of verbal autopsy as described above.
3. percentage of hypertensive patients taking antihypertensive medicines
4. blood pressure reduction in the intervention arm
5. percentage of diabetic patients who have random capillary blood glucose of 200mg/dL or less in the intervention arm, and
6. awareness about stroke and its risk factors- the respondents will be asked two questions. Which body organ is affected in stroke? and which diseases or factors increase the risk of stroke? The appropriate answer to the first question would be brain and for the second question would be any of the following correct responses namely hypertension, diabetes, obesity, cardiac ailments, lack of physical activity,

tobacco use, alcohol use, consumption of excessive salt, lack of fruits and vegetables in the diet and mental stress.

The outcomes b,d and e will be assessed in the intervention and the EUC area at baseline and at the end of 3.5 years of intervention (Figure 3) through a survey conducted on a randomly selected subsample of individuals ≥ 50 years of age from both the arms (Figure 2). The outcome c will be assessed at the baseline and at the end of 3.5 years among those on treatment in the intervention arm (Figure 3). The prevalence of risk factors for stroke including tobacco and alcohol use, blood pressure and glucose control as well as medication adherence and awareness about stroke will be evaluated in these sample surveys (Figure 2). In addition, in the sample survey conducted at the end of the intervention, information on change in medications or side effects due to medications used for hypertension, diabetes and stroke and any hospitalizations in the past one year will also be collected.

We will estimate prevalence of stroke in two arms at baseline and at the end of the intervention using a three-stage survey as described before [6]. Briefly, a house-to-house screening for symptoms of stroke will be conducted using a well-validated questionnaire. Diagnosis of stroke will be made by a trained stroke survey physician using WHO's clinical definition of stroke[30]. Clinical diagnosis alone will be used when no supporting documents are available irrespective of whether the patient had any residual neurodeficit at the time of evaluation by the physician. Assessment of disability among stroke survivors will also be done using the modified Rankin Scale. Doubtful cases will be evaluated by an external neurologist. Evaluation of all study outcomes will be conducted by an evaluation team which will be separate from the study implementation team (Supplementary figure 1).

Strategies to reduce contamination

The likelihood of contamination will be low as villages are the units of randomization and are physically separated. Also,the intervention will be limited to the residents of the intervention villages. The list of the eligible village residents will be provided to the CHWs as well as the OP based on the population register maintained by SEARCH. CHWs and the OP will be actively instructed to provide medications only to those who belong to the intervention villages.

Impact evaluation

Sample size

We calculated sample size based on the primary outcome of the trial which is reduction in stroke mortality. We hypothesized that the community-level intervention will produce at least 40% reduction in stroke mortality over the last 2.5 years of intervention. This assumption was based on a study in Taiwan where a community-based hypertension control programme resulted in 40% decrease in stroke mortality rate in the entire population over 3 years[36]. As we plan to measure stroke mortality in only the high risk population (≥ 50 years of age) with relatively less access to care and the intervention uses strategies for both primary and secondary prevention, we assumed that the intervention will result in at least 40% reduction in stroke mortality in the given period. We used the formula by Hayes and Bennett to estimate the sample size[40]. We assumed between-cluster correlation coefficient of variation (k) for stroke mortality to be 0.2 as such data were not available from

population-based studies. The baseline crude stroke mortality rate was taken as 688/100,000 population based on our previous study in these villages [5]. To detect 40 % reduction in baseline stroke mortality in a population ≥ 50 years of age with 80% power and at 5% level of significance and *k* of 0.2 , we needed 27 villages per intervention group. After adjusting the sample size for 75% coverage, the required sample size was 32 villages per group.

Prevalence of risk factors for stroke, awareness about stroke and hypertension and blood glucose control in both the arms will be evaluated in sample surveys on a randomly selected subsample of individuals ≥ 50 years of age. The sample will be drawn from the list of individuals in this age group available in the census conducted by SEARCH in 2015. We calculated sample size for this survey assuming that 40% of individuals aged ≥ 50 years will have hypertension, and among these, at the end of the intervention, 65% and 35% of the hypertensive individuals in the intervention and EUC arm will have their blood pressure controlled (<140/90 mm Hg) respectively. Using 80% power, 5% level of significance, design effect of 1.6 and non-response of 20% the required sample size was 330 individuals per arm.

Data collection and management

Information on the individuals ≥ 50 years of age will be obtained from the census conducted by SEARCH. Information of stroke deaths will be collected using verbal autopsies and stroke prevalence will be estimated using a house to house survey as described above. Quantitative data will be collected in the field by the CHWs, field supervisors, OP and surveyors of the sample surveys using standardized pre-tested questionnaires. This will be done to assess indicators specified in Figure 3. We will monitor the progress of the study and response of the community to each component of the intervention using process indicators which will be captured through standardised management information system (MIS) reports. This will provide key information regarding operational aspects of the study which can be used for mid-course corrections and for scaling up of the intervention if the intervention is effective. Qualitative data will be collected to explore reasons for success or failure of various components of the intervention package. Four to six focus group discussions (FGDs) will be conducted with patients and their relatives and individual interviews will be conducted with the CHWs, field supervisors and OP to understand the implementation process and facilitators and barriers to the implementation of the intervention. After checking and entry of paper forms, they will be kept in locked cupboards. Data will be stored in databases on a central server in the research department of SEARCH and will be backed up at regular intervals. Qualitative data will be audio recorded and the audio files will be kept on a computer which is password protected. Access to intervention information will be limited to the study team. Databases will only be accessible to the data management team of the study. We will make the research data from this study available for use by other researchers after publication of trial results in academic journals and this information will be publicised through research manuscripts.

Data analysis

The analysis and presentation of results will be according to the Consolidated Standards of Reporting Trials (CONSORT) Statement for cluster randomised controlled trials[41]. We will first compare baseline demographic features in the intervention and EUC villages such as total population, population ≥ 50 years of age, sex distribution in this population, socioeconomic and education status and the average distance from the district town in order to assess if there are any baseline imbalances after randomisation. We will also compare stroke

mortality, point prevalence of stroke and the prevalence of selected risk factors for stroke such as hypertension, diabetes, use of tobacco and alcohol, body mass index, waist hip ratio and awareness about stroke in both the arms.

The impact of the intervention in the intervention villages will be analysed by comparing the primary and secondary outcomes in these two arms under the intention-to -treat principle with use of two-sided tests and significance level of 5%. Cluster level as well as individual level data will be used to compare primary and secondary outcomes. Results will be presented as effect sizes (difference in means between arms, odds ratios). Unadjusted and adjusted results will be presented. We will use regression methods applying generalized estimation equation or logistic regression with random effects models to account for the clustered design of the intervention. Age, sex, occupation, socioeconomic status, education, baseline stroke mortality will be used as covariates in the multivariate analyses based on their bivariate association with the outcomes of interest. We will also use Cox proportional hazards regression to compare time to first occurrence of death due to stroke, cardiovascular diseases as well as any-cause death between the two groups. Pre-planned subgroup analyses will include assessing the effect of the intervention by age, sex, socioeconomic status, education, individual risk factors (hypertension, diabetes, tobacco use, alcohol use, waist hip ratio, BMI), antihypertensive medication use, number of visits to the outreach clinic and number of visits by the CHW. These will be interpreted with caution. In addition, we will also evaluate the effect of the intervention on disability due to stroke among stroke survivors in both the arms. Pre-planned exploratory analysis will include a Bayesian analysis of the primary trial outcome[42]. Given that we will be working closely with the community, we expect that the amount of missing data will not be large and hence we will not have to account for it in analyses. Data will be analysed using statistical software Stata Version 14(College Station, TX, USA).

Qualitative data will be transcribed and analysed using a thematic approach as described earlier [23].

Economic evaluation

All intervention related costs will be audited through the project accounting system. We will estimate the cost per stroke, cardiovascular and all-cause death averted and the cost of delivering these interventions per 100,000 population per year.

Process evaluation

Process evaluation will be conducted to understand-a) how the intervention was delivered, b) what were the barriers and facilitators for the implementation of the intervention and c) mechanisms through which the intervention may or may not have worked. Quantitative data from process indicators, review of various process documents and qualitative data obtain through FGDs and individual interviews with patients, their relatives, implementation team members will be used for this purpose.

Quality control measures

Quality control measures will be taken at all levels of intervention delivery, data collection and entry. These include- a) rigorous training and evaluation of the CHWs, field supervisors and the OP, b) use of pre-tested standardized questionnaires to collect data by the surveyors, the CHWs and the OP, c) refresher training of implementation team members at periodic intervals, d) cross- checking as well as re-survey of 5% of the

screened population during screening as well as follow up visits by the CHWs to check for the accuracy of data collection, e) evaluation of adherence to treatment protocol by the OP, f) range check on data values and g) cross-checking of entered data. Blood pressure monitors, glucometers and weighing scales will be calibrated every one to three months and equipment showing errors as per pre-defined criteria will be replaced.

Interim analyses or stopping rules

As we will be using standard medications in the intervention, we have not planned for any interim analyses. However, we will conduct an urgent safety review of the study if in the intervention arm serious adverse events are reported by >5% or minor side effect are reported by > 25% study participants or the crude death rate in the intervention arm exceed one standard deviation above the baseline crude death rate (average of crude death rates over three years before the intervention) in the intervention villages.

Trial management

The implementation of the trial will be overseen by the trial execution committee and a trial steering committee. Data and safety will be monitored by an independent external data safety and monitoring board (DSMB). It will review trial and adverse events data every six months.

Dissemination of findings

We will communicate the results of the trial to study participants, district health officials, state and national health ministries, the national chronic diseases programmes and the Indian Council of Medical Research. The study findings will be presented in the national, regional and international conferences. We plan to publish the results of the trial in a PubMed-listed peer-reviewed journal in an open access format.

Discussion

Stroke is the second leading cause of deaths globally and has emerged as an important public health priority in rural parts of India where healthcare services are inadequate[5,7,43]. In these resource-poor areas, community-based interventions involving community members could be an important strategy to reduce stroke mortality. Such interventions have been shown to be effective in reducing infant mortality and controlling infections[44–47]. However, there is paucity of evidence regarding effectiveness of community-based interventions for chronic non-communicable diseases in rural areas of LMICs [48]. Hypertension is one of the key risk factors for stroke and recent trials show that community-based approaches for hypertension control could be useful [49–51]. The primary outcomes of these trials have been reduction in blood pressure and not reduction of cardiovascular events. To our knowledge this is the first cluster randomised controlled trial from a rural area of a LMIC to evaluate the effect of such an intervention to reduce stroke mortality. Our study thus provides an important value addition over previous studies by combining primary and secondary prevention of stroke at the community level and going a step further to evaluate if such an intervention would reduce stroke mortality in a resource poor setting. The insights gained from this study will provide important inputs for the Government of India's ambitious programme for prevention and control of chronic diseases (NPCDCS), which is one of the largest programmes in the world of its kind to reduce the risk of non-communicable diseases. This programme currently focuses on community-level screening and facility-level treatment of chronic diseases but currently

does not have a component of community-level follow up. Our study will help to evaluate the importance of community-level treatment and follow up. If successful, the study intervention can be scaled up in other rural and under-resourced settings in the world.

Trial Status

The trial will be recruiting patients till December 2019. The final outcome assessment of all outcomes will be completed by the end of June 2020. Protocol version 1.2; 15 January 2016.

Declarations

Ethics approval and consent to participate

The study is approved by the Institutional Ethical Committee of SEARCH (Protocol number-2014/0628-01) formed in accordance with the guidelines of the Indian Council of Medical Research. Participation in trial will be completely voluntary. Written or audio (for those who can not read or write) informed consent will be taken from participants by CHWs, outreach clinic team and surveyors after explaining the study to them in local language including a need for collecting a blood or urine sample for biochemical analyses where needed. All information regarding study participants will be kept confidential.

Consent for publication

Not applicable.

Availability of data and material

All data underlying the results are available as part of the article and no additional source data are required.

Competing interests

The authors declare that they have no competing interests.

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Trial Sponsor: Society for Education, Action and Research in Community Health (SEARCH)

Contact Name: Dr Abhay Bang, Director, SEARCH

Address: SEARCH. Shodhgram, Post-Chatgaon, Taluka-Dhanora, District-Gadchiroli, Maharashtra, India 442606

Telephone: +(91) 7138 255 407

Email: search.gad@gmail.com

Author Contribution

YK designed the study with inputs from AB. YK and SN developed detailed intervention implementation plan. YK, SN, MD developed analysis plan. YK, SN, SJ developed training material. YK and MD developed data collection and entry tools. AB provided advice in all these processes. YK drafted the initial manuscript. AB, MD, SN, SJ supported the first author by reading the manuscript critically and providing comments. All authors critically reviewed and approved the final manuscript.

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Author details

All authors are from the Society for Education, Action and Research in Community Health (SEARCH), Gadchiroli, Maharashtra, India.

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Tables

Table 1. Common barriers to effective control of hypertension, diabetes and secondary prevention of stroke and interventions to address these barriers

Barriers to effective control	Intervention
Lack of awareness about diseases and their risk factors	· Mass awareness programme for hypertension, diabetes and stroke · Individual patient education using culturally appropriate awareness material · Counseling about risk factors (e.g. tobacco, alcohol and high salt use)
Lack of screening facilities at the village level	· Home-based screening of individuals ≥50 years of age for hypertension, diabetes and stroke
Lack of confirmation of diagnosis	· Referral of screen positive individuals to the village outreach clinic · Evaluation and confirmation of diagnosis of hypertension, diabetes and stroke by the OP
Difficulty accessing healthcare facilities on regular basis	· Periodic Village clinic by the OP · Monthly home visits by the CHWs to reduce need to travel outside the village for seeking care
Lack of treatment adherence	· Monthly follow up by the CHW by making a home visit · Follow up by the OP every 2-3 months
Loosing or running out of medications	· Availability of medication stock with the CHWs · After consulting the OP the CHW will replenish patients medications
Stopping medications due to side effects	· Change of medications by the CHW after consulting the OP when there are side effects due to medications
Affordability of medicines	· Free medications

CHW-Community Health Worker, OP-Outreach Physician

Table 2. Formulary of trial medications

Drug	Staring dose	Increments	Maximum dose	Tablet strengths	Dosing frequency per day
Hypertension					
HCT	12.5 mg	12.5mg	25mg	12.5, 25mg	1
Amlodipine	5 mg	2.5, 5mg	10 mg	2.5, 5mg	1-2
Atenolol	25mg	25 mg	50mg	25, 50mg	1
Diabetes					
Glipizide	5mg	2.5mg	20mg	5mg	1-2
Metformin	500mg	250 to 500mg	2000mg	500mg	1-2
Stroke					
Aspirin	75 mg	-	-	75mg	1
Atorvastatin	10mg	-	-	10mg	1

HCT-Hydrochlorothiazide

Table 3. The preferred sequence of medications by selected criteria

Criterion	First line	Second line	Third line
Hypertension			
Age <65 years	HCT	Amlodipine	Atenolol
Age ≥65 years	Amlodipine	Atenolol	HCT
Diabetes			
BMI<19	Glipizide	Metformin	-
BMI≥19	Metformin	Glipizide	-
Stroke			
Loss of consciousness or seizures at the onset of stroke or ICH among those who had brain imaging	Atorvastatin	-	-
All other stroke patients	Aspirin Atorvastatin	-	-

HCT-Hydrochlorothiazide, ICH- Intra-Cerebral Haemorrhage

Trial Registration

Clinical Trials Registry of India: CTRI/2015/12/006424. Registered on 8 December 2015.

Supplementary File Legend

Supplementary figure 1. Trial manpower and management

Figures

Figure 1

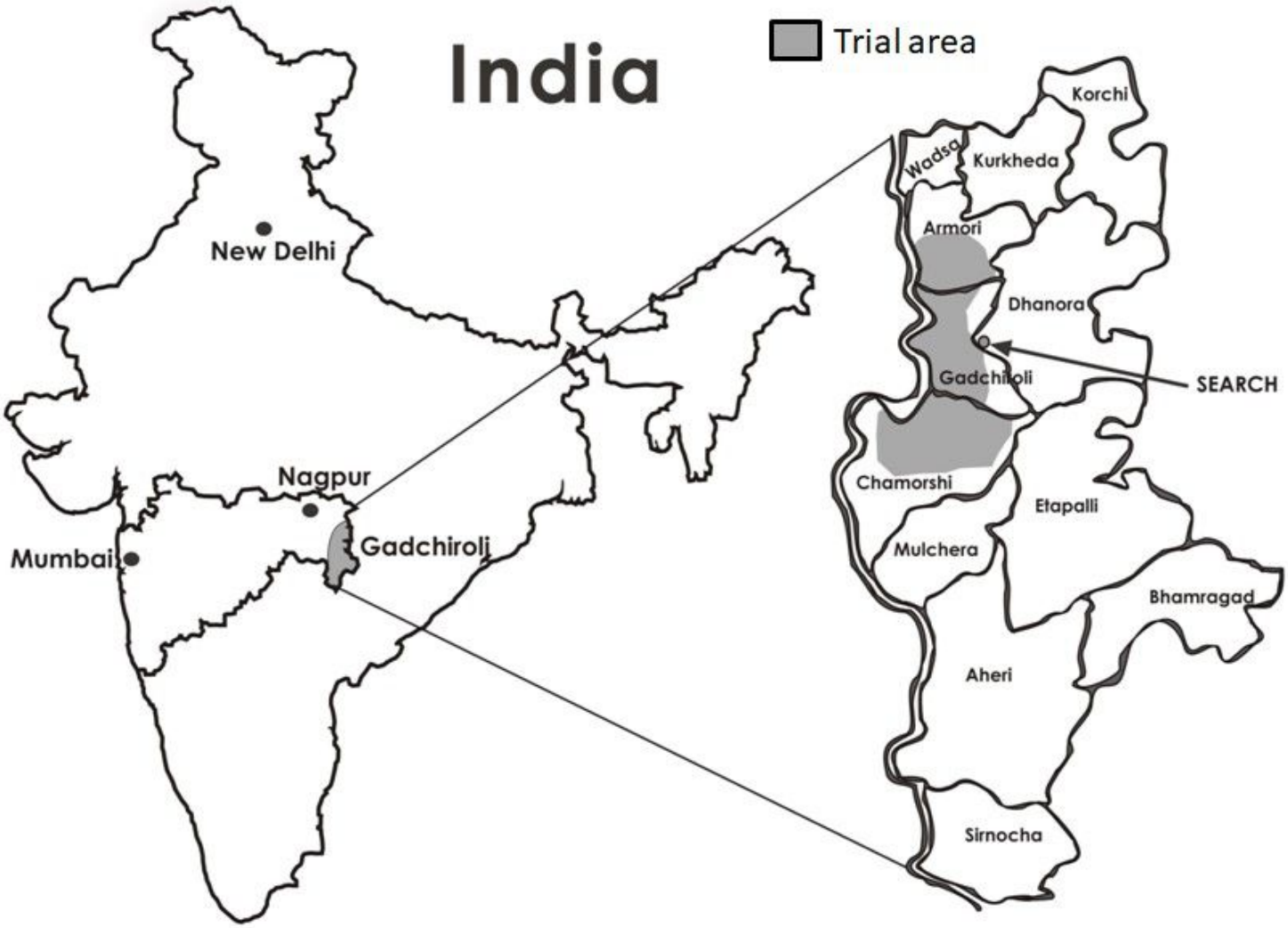
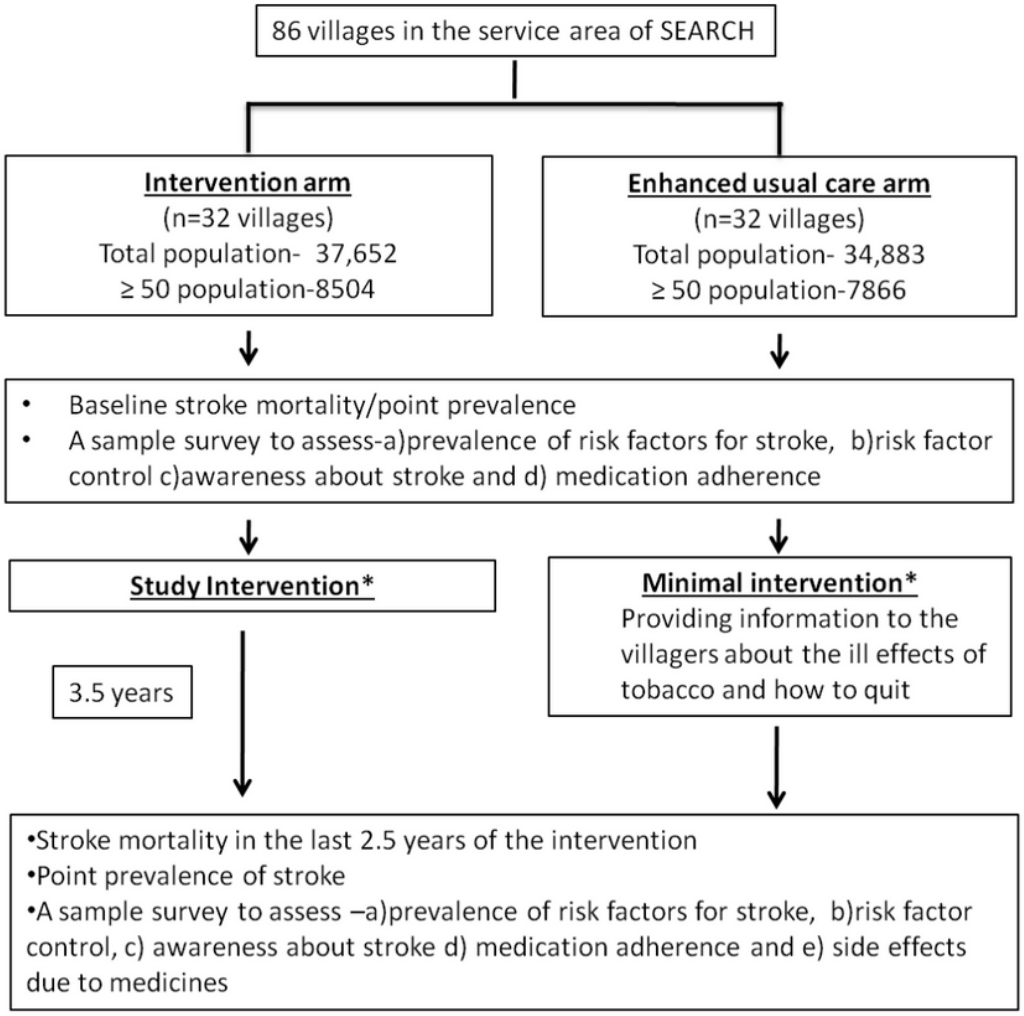


Figure 1

Map of the trial site in Gadchiroli, India

Figure 2



* Patients from both the arms have access to Government of India's chronic non-communicable diseases prevention and control programme
# Adverse effects due to medicines will also be actively monitored throughout the intervention in the intervention arm

Figure 2

Trial scheme

Demographic characteristics of intervention and enhanced usual care villages		X						
Baseline stroke mortality in the intervention and EUC arms		X	X					
Baseline stroke prevalence survey in the intervention and EUC arms		X	X					
Sample survey to assess the prevalence of hypertension, diabetes and other selected risk factors in the intervention and EUC arms		X	X				X	
Stroke mortality in the last 2.5 years of the intervention					←	←	←	X#
All-cause and cardiovascular mortality in the last 2.5 years of the intervention					←	←	←	X#
Number of individuals with hypertension taking antihypertensive medications		X	X				X	
Blood pressure reduction in the intervention arm							X	
Diabetic patients with random capillary blood glucose ≤200mg/dl in the intervention arm		X	X				X	
Awareness about stroke and its risk factors		X	X				X	

CHWs- Community Health Workers

Analyses of causes of death using verbal autopsies will be completed during the close out period.

Figure 3

Schedule of enrolment, interventions and assessments (as per Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigure1.pdf
- StrokestudyIECapprovalletteryogeshwarkalkonde.pdf
- supplementarytable1.pdf
- SPIRITchecklist.doc