Multi-Center, Cluster-Randomized, Controlled, multifaceted intervention trial to improve stroke care quality in China:

The GOLDEN BRIDGE-Acute Ischemic Stroke

Organization Institute:

Beijing Tiantan Hospital, Capital Medical University
Local Investigators and Clusters Participating in this trial

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Shijiazhuang First Hospital; People's Hospital of Tailai County.
Introduction

Stroke is a major cause of death and long-term disability in China. The annual cost of stroke care is about 5.76 billion US dollars.\textsuperscript{1-3} Improving stroke care quality and clinical outcomes is a national priority.\textsuperscript{4} Large-scale randomized trials and systematic reviews have established the efficacy and safety of interventions for acute ischemic stroke (AIS), such as intravenous recombinant tissue plasminogen activator (IV rtPA), antiplatelet therapy, anticoagulation for patients with atrial fibrillation, deep vein thrombosis (DVT) prophylaxis, swallowing dysfunction management, statin treatment, antihypertensive and hypoglycemic treatment.\textsuperscript{5-16} Nevertheless, the adherence to these evidence-based interventions is suboptimal in China.\textsuperscript{17-19} Research studies in other countries have demonstrated that quality improvement programs can be effective in improving the quality of stroke care. Interventions include clinical pathway or standardized order sets, training and distribution of educational materials to health care providers, and audit with timely feedback.\textsuperscript{20-22} Combination of different methods targeting different barriers have been shown effective in patients with acute coronary syndromes.\textsuperscript{23, 24} However, to date these quality improvement interventions have been limited to high income countries and not evaluated in less well developed health care settings such as China.

Using hospitals participating in the China National Network of Stroke Research, we design a cluster-randomized trial to evaluate the effectiveness of a multifaceted quality improvement initiative to bridge the gap of evidence-based medicine in AIS management in China (GOLDEN BRIDGE-AIS).
Study aim

The aim is to evaluate whether a multifaceted quality improvement intervention will improve the adherence to individual, composite and all-or-none measures for patients with AIS presenting within the first 7 days from stroke symptom onset and reduce the incidence of in-hospital death, a new vascular event, disability, and all-cause death at 3, 6, and 12-months after the initial symptom onset.

Design

Golden Bridge-AIS is a multicenter, 2-arm, open label, parallel, cluster-randomized, controlled trial with blinded adjudication of outcomes and intention-to-treat analysis to assess the feasibility and efficacy of this intervention (Figure 1). Forty hospitals from Mainland China participate in the trial.
Figure 1. Flow diagram of the progress through the phases of the trial

- Hospitals from China National Network of Stroke Research in China
- Randomization
- Allocated to intervention group
  - Intervention protocol: 1 evidence-based clinical pathway; 2 written care protocols for implementations of performance measures; 3 a quality coordinator; 4 monitoring and feedback system of performance measures
- Usual care
- Patient recruitment
  - Excluded
    - 1 ineligible
    - 2 refused to participate
  - In-patient data collected
  - Patient 3,6,12-month data collected
  - Lost to follow-up
  - Medical record Audit
- Analyzed
  - Excluded from analyses
- Patient recruitment
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    - 1 ineligible
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  - Patient 3,6,12-month data collected
  - Lost to follow-up
  - Medical record Audit
- Analyzed
  - Excluded from analyses
Participants: study clusters and their patients

Hospitals (clusters) participating in the China National Network of Stroke Research and that meet the inclusion and exclusion criteria (Table 1) are eligible for inclusion in the GOLDEN BRIDGE-AIS. The China National Network of Stroke Research, developed by the National Center of Quality Management in Stroke Care includes 563 hospitals from 27 provinces and 4 municipalities in Mainland China, with about 20 hospitals in each province or municipality.

Table 1. Eligibility criteria of hospital and patient participants

Hospital eligibility criteria and recruitment

Inclusion criteria

One of nationwide network hospitals of monitoring and improvement of stroke care quality

Secondary or tertiary public hospitals from major urban areas with an emergency department (ED) and neurological wards that receives patients with AIS

Capacity of intravenous rt-PA thrombolytic therapy

Exclusion criteria

Primary hospitals, private hospitals, and hospitals located in rural areas

Hospitals with fewer than 10 patients with suspected AIS per month

Patients eligibility criteria and recruitment

Inclusion criteria

Older than 18

Ischemic stroke (IS) within 7 days of the index event
Direct admission based on physician evaluation or arrival through the emergency department, and ability of patient or legally authorized representative (primarily spouse, parents, adult children, otherwise indicated) to provide informed consent.

Eligible events were confirmed by brain CT or MRI within 7 days after the onset of symptoms

**Exclusion criteria**

Those patients whose final diagnosis was *other cerebrovascular disease* (hemorrhagic stroke, transient ischemic attack, cerebral venous sinus thrombosis, and so on) or noncerebrovascular diseases.

This trial is specifically designed for patients with acute ischemic stroke and excludes those with final diagnosis of other cerebrovascular disease (hemorrhagic stroke or transient ischemic attack, cerebral venous sinus thrombosis, and so on) or non-cerebrovascular disease. Head computed tomography (CT) or magnetic resonance imaging (MRI) scan is required for every suspected stroke patient enrolled in the study no matter they were admitted to an intervention or control site.

**Clusters randomization and blinding**

Forty eligible clusters in Mainland China are stratified by the following characteristics: province, hospital grade (secondary or tertiary), and baseline level of stroke care quality. Stratification details are offered in a de-identified form to an independent statistician not otherwise involved in the study to guarantee blindness of allocation. They are randomized within the strata and assigned (1:1) to a multifaceted quality improvement intervention (experimental group) or to standard of care (control group) using random number generating software (SAS Version 9.3 software, SAS)
Institute, Cary, NC) by the independent statistician who conceal the sequence until the intervention is assigned. In view of the nature of the multifaceted intervention in the GOLDEN BRIDGE-AIS, only the independent outcome evaluators are blinded to the intervention.

The stroke quality improvement interventions

The multifaceted quality improvement intervention includes an evidence-based clinical pathway, written care protocols for implementation of performance measures (Figure 2), a full-time quality coordinator, and monitoring and feedback system for the AIS performance measures. A local quality care initiative (QCI) team at each intervention hospital is established to take responsibility for the implementation of the multifaceted intervention. Two health care providers of the QCI from all intervention clusters (a director of department of neurology who acts as the local investigator and a physician or nurse who acts as a quality coordinator) attend a 2-day workshop on how to perform the GOLDEN BRIDGE-AIS quality improvement intervention. These two trained professionals are charged with sharing these operational methods with cluster personnel who care for the AIS patients, complemented by training video or slides. Each cluster provides to the central coordinating center formal documentation of completed training such as photos and attendance logs to guarantee adequate knowledge translation on the implementation of each quality improvement intervention.
Evidence-based clinical pathway of acute ischemic stroke (A) and written care protocols for implementations of the interventions that are tracked by performance measures (B).

**Evidence-based clinical pathway**

The stroke clinical pathway is added into the care plan on each eligible stroke admission, either in the emergency department or inpatient ward. It contains general guideline-based recommendations about acute stroke management and detailed daily care plan for each of the first 7 days of the acute admission and at discharge. The daily activities are listed under medical, nursing, therapist and discharge planning headings. Daily each item is to be checked, initialed and dated upon completion by the staff on a daily basis. The stroke clinical pathway is developed by a panel of stroke clinical experts according to peer-reviewed empirical literature, consensus statements and guidelines.

**Written care protocols for implementations of performance measures**
1. Intravenous IV rt-PA protocol for AIS patients who arrive within 2 hours after last seen normal and are treated within 3 hours contains mainly indications, contraindications, dosage weight table, the specific user method of operation, management of side effects of rt-PA, assessment of National Institutes of Health Stroke Scale (NIHSS), specific job responsibilities of emergency department physicians and acute stroke care team.

2. Deep venous thrombosis (DVT) prophylaxis protocol contains mainly the evaluation scale of risk factors associated with DVT, Wells scale and the detailed approaches for DVT prophylaxis including non-pharmacological interventions and anticoagulant drugs.

3. Swallowing dysfunction management protocol contains mainly the flow chart for screening and assessment of swallowing function, detailed operation of clinical examination of swallowing function, and methods of training patients with swallowing dysfunction.

4. Evidence-based medications protocol includes the indications, contraindications, and dosage recommendations of antithrombotic therapy by the end of day two, and discharge antithrombotic therapy, anticoagulation for patients with atrial fibrillation, statin, antihypertensive, and hypoglycemic medications as appropriate.

A quality coordinator
A trained physician or nurse from the department of neurology in each cluster acts as a quality coordinator. The role of the quality coordinator includes interacting with physicians once gaps in the applying evidence-based interventions are identified, ensuring that all components of the quality improvement intervention are used for every AIS patient, identifying barriers for the implementation of the quality improvement tools and evidence-based therapies, and training the health care staff involved with the care of AIS patients.

Monitoring and feedback system and cycle model of performance measures

Web-based registry forms developed by the cooperation between the expert advisory panel and Beijing Guide Medical Data Analysis Research Center are used for data collection. The monitoring and feedback system of predefined performance measures is developed to function from the data entered into a web-based registry. An independent quality management account is assigned to all clusters randomized to the experimental group. The intervention cluster’s investigators or quality coordinator have access to view the level of implementation of predefined performance measures at any time (recommended once per week) and compare with previous performance and with performance by other clusters (not identified by name) on addressing, the gap between evidence-based recommendations and clinical practice (Figure 3).
Figure 3. Continuous quality improvement of stroke care model

Abbreviations: CRA: clinical research assistant; CRO: contract research organization.

After 30 consecutive patients (who either died in hospital or were alive at discharge) were recruited per hospital (cluster), the key performance indicators are assessed and summarized for that hospital. The members of the Improvement Committee and the local QCI team hold conference calls to review current adherence to the key performance indicators, discuss potential reasons of low implementation rate, and establish new improvement goals and measures. This monitoring, feedback, and improvement cycle is repeated every 30 consecutive patients enrolled at each cluster (Figure 4).
Primary outcomes

The primary outcomes are the measures of the adherence to the predefined evidence-based performance measures in AIS patients without any contraindication (Table 2). Detailed performance measure specifications are shown in Table 3.

Table 2. Predefined evidence-based performance measures of stroke care

Acute performance measures

Intravenous rtPA in patients who arrive within 2 hours after last seen well and treated within 3 hours

Antithrombotic medication prescribed within 48 hours of admission

Deep Venous Thrombosis (DVT) prophylaxis within 48 hours of admission in patients at risk for DVT

Dysphagia screening before any oral intake
Discharge Performance Measures

Antithrombotic medication prescribed at discharge

Anticoagulation prescribed at discharge in patients with documented atrial fibrillation

Statin medication prescribed at discharge in patients with LDL ≥ 100 mg/dL

Antihypertensive drugs prescribed at discharge in patients with documented hypertension disease

Hypoglycemic drugs prescribed at discharge in patients with documented diabetes mellitus

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Table 3. Specifications of performance measures employed in the trial

<table>
<thead>
<tr>
<th>Performance measure of ischemic stroke care</th>
<th>Performance measure definition for eligible patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute performance measures</td>
<td></td>
</tr>
<tr>
<td>IV rt-PA &lt;2 Hour</td>
<td>Intravenous recombinant tissue plasminogen activator (IV rtPA) in patients who arrive within 2 hours after initial symptom onset and treated within 3 hours</td>
</tr>
<tr>
<td>Early Antithrombotics</td>
<td>Antithrombotic therapy prescribed within 48 hours of hospitalization, including antiplatelet or anticoagulant therapy</td>
</tr>
<tr>
<td>Dysphagia Screening</td>
<td>Dysphagia screening prior to any oral intake</td>
</tr>
<tr>
<td>DVT Prophylaxis</td>
<td>Patients at risk for DVT (non-ambulatory) who</td>
</tr>
</tbody>
</table>
received DVT prophylaxis by end of hospital day
two, including pneumatic compression, warfarin sodium or heparin sodium

Performance measures at discharge

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge Antithrombotics</td>
<td>Antithrombotic therapy prescribed at discharge</td>
</tr>
<tr>
<td>Anticoagulation for Atrial Fibrillation/Flutter</td>
<td>Anticoagulation prescribed at discharge for patients with atrial fibrillation or atrial flutter documented during the hospitalization</td>
</tr>
<tr>
<td>LDL 100 or Not Documented</td>
<td>Lipid lowering agent prescribed at discharge if LDL ≥ 100 mg/dL, if patient treated with lipid lowering agent prior to admission, or LDL not documented</td>
</tr>
<tr>
<td>Antihypertension for hypertension disease:</td>
<td>Antihypertension medication prescribed at discharge for patients with history of hypertension disease or hypertension disease documented during the hospitalization</td>
</tr>
<tr>
<td>Hypoglycemic therapy for diabetes mellitus:</td>
<td>Hypoglycemic medication prescribed at discharge for patients with history of diabetes mellitus or diabetes mellitus documented during the hospitalization</td>
</tr>
</tbody>
</table>

* Eligible patients are those without any medical contraindications (e.g., treatment intolerance, excessive risk of adverse reaction, patient/family refusal, or terminal illness/comfort care only) documented as reasons for nontreatment for each of the applicable measures. Also excludes patients who are discharged to hospice, or another
short-term general hospital, leave against medical advice before the end of hospital day two. For acute performance measures except for rt-PA measure, excludes patients who died before the end of hospital day two. The acute rt-PA measure excludes patients with missing or erroneous onset, arrival or treatment times, those who began IV t-PA at an outside hospital, or who initiated IV t-PA after 180 minutes from onset.

For performance measures at discharge, excludes patients who died during hospitalization.

Adherence is expressed as a composite measure or all-or-none measure. The composite measure is defined as the total number of interventions performed among eligible patients divided by the total number of possible interventions among eligible patients. The all-or-none measure is defined as the proportion of eligible patients who receive all of the performance measure interventions.

Secondary outcomes

The secondary outcomes include in-hospital death, a new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), disability measured by Modified Rankin Score (mRS = 3-5), and all-cause mortality at 3, 6, and 12-months after initial symptom onset.

Trained research personnel at Beijing Tiantan Hospital, blinded to the intervention and using standarded scripts, will contact patients by telephone to collect follow-up information at 3, 6, and 12 months after initial symptom onset. When it is difficult to
communicate with the patient or when the information provided by the patient is regarded as unreliable by the interviewer, the specific care-giver will be contacted and interviewed. During the follow-up periods, just stroke recurrences and rehospitalization will be tracked back to the attended hospitals where the care are provided in order to guarantee accuracy in diagnosis. Each case fatality will either be identified by a death certificate from the local citizen registry or from the attended hospital where the patient is treated. In the event of lack of local citizen registry information or death without hospitalization, case fatality is deemed to be reliable if death is reported on two consecutive follow-up periods from different agencies.

Sample size

A pre-randomization survey at participating clusters was performed. The mean composite score of stroke care quality is 80%. To detect a 5% improvement in the composite measure of evidence-based performance measures in patients with AIS, with 80% power, 5% significance level, and an intracluster correlation coefficient of 0.02 (value determined according to pre-randomization pilot data), we need to randomize 40 clusters and approximately 4800 patients (considering a median of 120 AIS patients per cluster). It is estimated that three monitoring, feedback, and improvement cycles, would be implemented to achieve the predefined improvement of the composite measure; therefore, 30 patients will be enrolled per cycle at every cluster (Figure 4).
Statistical analysis plan

An “intention-to-treat” analysis will be performed. Baseline characteristics of hospitals and patients will be analyzed to assess cluster differences between treatment and control groups. Possible control variables will be identified and included in the final models. Categorical variables will be summarized as proportion; continuous variables with normal distribution will be summarized with mean and standard deviation (SD), and those with skewed distribution will be expressed with median and interquartile range.

In univariate analysis for comparisons between groups, $\chi^2$ test will be used to compare categorical variables, and Student t test or Mann-Whitney U test will be used to compare continuous variables.

In multivariate analysis, a generalized estimation equation accounting for within-hospital correlation will be used to compare between the intervention and control groups at the patient and hospital level for modeling proportions and quantitative variables. The effects of intervention will be demonstrated according the features of variables. Qualitative and quantitative variables and will be expressed as a population average odds ratio and the mean difference separately, both with 95% confidence intervals (CIs). The composite measure was expressed as the odds of fulfilling care opportunities that each measure for which a patient was eligible for.

Thus in the analysis of composite measure, each care opportunity contributed an
observation in the analysis, and the outcome was a dichotomized (1: measure met versus 0: measure not met). For example, if a particular patient was eligible for 5 of the 7 performance measures and only received 3 of them, this patient contributed 5 observations to the analysis, and 3 of them has outcome value as 1 and 2 had outcome value as 0.

The intervention effects on clinical vascular events and mortality at discharge and at 3, 6, 12 months after initial symptom onset will be demonstrated by Kaplan-Meier curves and compared by using proportional hazards Cox models. A sensitivity analysis will be performed including patients with contraindications for evidence-based interventions in the denominator of the overall population. All statistical analyses will be performed by using SAS Version 9.3 software (SAS Institute, Cary, NC). The internal statistical analyses will be performed by the Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease and external analyses will be verified by the Department of Statistics & Operations Research, University of North Carolina at Chapel Hill.

Ethical considerations

This study is performed in accordance with the Declaration of Helsinki and evidence based clinical practice guidelines. The trial has been approved by the central institutional review board at Beijing Tiantan Hospital, all participating clusters submit the study protocol for approval by their research ethics board, and written consent is obtained at the cluster. This is a common and well-accepted approach; the objective of
such an approach is to avoid selection bias that may arise from different consent refusals rates between clusters. However, written consent is signed by patients or their family representative to give the permission so that researchers can contact them after 3, 6, and 12 months after initial symptom onset for a telephone interview.

Organizational structure

This study is administered by an academic steering committee composed of the principle investigator and members. This committee is responsible for the research directions and supports, addressed policy issues about the protocol, and met periodically to evaluate the progress of study. The quality improvement committee is composed of clinical and management experts from the steering committee. This committee is responsible for overseeing the current adherence of the key performance indicators, analyzing the potential causes of low implementation rate, and setting new goals for improvement and measures by conducting conference calls with the QCI team at every cluster. The executive committee is composed of senior experts from the academic steering committee. The mission of this committee is to assess the progress and safety of the study and make any decisions regarding early termination, modification, or continuation of the trial (see Appendix II for committee member list).

Data collection, quality control, and clinical data management system
In all participating clusters, data are captured prospectively and entered in the Web-based data capture system by a trained independent research coordinator who is not involved in the care of patients with AIS. Range checks will be used for inconsistent or out-of-range data and prompt the user to correct or review data entries that outside the predefined range. The system also provides pre-defined logic checks to identify erroneous, illogical data entries. A sample of 20% of all recruitments will be selected at random and checked by research specialists from an independent contract research organization (CRO) throughout the study period. Finally, a data quality meeting will be held monthly to review all the hospital enrollment records and registry data.

References


27. Min Liu SZ, Mingli Rao, Chuanzhen lv, Jizuo Wang, Ruxun Huang. Guidelines for the early management of patients with acute ischemic stroke: A guideline for
