Improving the identification of large vessel occlusion stroke during the emergency call: Protocol for the controlled LESTOR study with a stepped-wedge design

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Research Article

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Abstract

Background

Large vessel occlusions (LVO) cause up to 30% of acute ischemic strokes. Mechanical thrombectomy is the first line treatment performed by neurointerventionalists. In Germany, neurointerventionalists are mostly situated in comprehensive stroke centres (CSC). Thus, long transport distances to CSCs may be necessary. The aim of this study is to implement and evaluate an intervention that involves lay first responders in the early identification of LVO, followed by a direct assignment to a CSC.

Methods

This controlled study with a stepped-wedge design and clustering of six emergency control centres in southwest Germany will stepwise implement LVO screening performed during the emergency call. Individuals with suspected LVO in both the control and intervention group (n=250) will undergo the usual treatment. In addition, emergency medical service dispatchers will screen patients in the intervention group for cortical stroke symptoms. For those with suspected LVO, air rescue is initiated immediately by the dispatchers. If the emergency medical service on scene confirms the suspected LVO, the patient benefits from accelerated transportation to the CSC. The primary endpoint is the clinical outcome measured by the modified Rankin Scale 90 days post-stroke. In addition, we will perform a qualitative process evaluation.

Discussion

We will assess the feasibility and cost-effectiveness of a systematic screening for symptoms of acute LVO implemented at the emergency control centre. The process evaluation will provide additional insight into how the participating emergency professionals perceive the intervention and the psychological impact on lay first responders. We hypothesize that early, pre-hospital identification of LVO patients and an optimized rescue chain will enable earlier treatment - especially in rural areas. We expect improved clinical outcomes of LVO patients and a better understanding for future studies with larger sample sizes.

Trial registration

DRKS (German Clinical Trials Register), DRKS-ID: DRKS00022152. Registered 19th October 2020, https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00022152; WHO UTN: U1111-1253-5758.

Introduction

Strokes are the second leading cause of death in adulthood worldwide, with an increasing tendency and are one of the leading causes of long-term disability.[1–5] In 2017, strokes led to 75,861 deaths per year in Germany.[1] Up to 30% of acute ischemic strokes are caused by the occlusion of large intracranial arteries (large vessel occlusion, LVO).[6] Systemic thrombolysis alone results in recanalisation in only 10-20% of these patients.[7] Since 2016, mechanical thrombectomy (MT) combined with thrombolysis has been shown as a highly effective therapy for acute LVO and is therefore widely used since then. [8–14] In Germany, however, MT is not ubiquitously available. Mostly, only comprehensive stroke centres (CSCs) can perform systemic thrombolysis and endovascular stroke therapy 24 hours per day, 7 days per week. As treatment is time-sensitive and the transport of LVO patients between hospitals or from a rural area to the next CSC can be lengthy, the delay from stroke onset to the beginning of MT reduces the chance of functional recovery (“time is brain”).[15–18]

The current practice of pre-hospital stroke care in Germany is mainly based on two concepts: the "drip-and-ship" and the "mothership" approach.[19,20] The majority of healthcare systems use the drip-and-ship concept, initially transporting all patients with suspected stroke to the nearest stroke centre. If indicated, thrombolysis is performed immediately after cerebrovascular imaging. Subsequently, patients with an indication for thrombectomy are transferred to a CSC. In the mothership approach, an emergency team evaluates stroke symptoms on site and transports patients with LVO to the closest hospital capable of MT. In areas distant from a CSC, this may require a transport via helicopter, resulting in a time-consuming sequential disposition.

A novel approach to accelerate endovascular therapy is to send a neurointerventional team to primary stroke centres for mechanical thrombectomy after ensuring eligibility via a telestroke network.[21]

Our new LESTOR (“**L**eitstellen-basierte **E**rkennung von **S**chlaganfall-Patienten für eine **T**hrombektomie und daraufhin abgestimmte **O**ptimierung der **R**ettungskette”) approach aims to involve lay first responders (LFR) to identify LVO already during the emergency call to

shorten the time from symptom onset to treatment and thereby optimise pre-hospital stroke care.

Lay people were successfully involved in phone-assisted cardiopulmonary resuscitation[22] and the application of a tourniquet to stop the bleeding in arterial limb haemorrhage.[23] Previous studies investigated the feasibility of stroke identification by collaboration between emergency medical service (EMS) dispatchers and LFR administering scales over the phone, such as the Cincinnati Pre-Hospital Stroke Scale (CPSS) or the Face-Arm-Speech-Time (FAST) screening tool. [24–26]

To accelerate the initiation of therapy, several studies adapted the transport of patients with suspected acute LVO by applying pre-hospital identification tools such as the Rapid Arterial oCclusion Evaluation (RACE) scale,[27,28] the adopted Prehospital Acute Stroke Severity Scale (PASS),[29] and the modified Prehospital Acute Stroke Severity Scale (mPASS),[30] the FAST-PLUS test,[31] the Emergency Medical Stroke Assessment (EMSA)[32] or the Stockholm Stroke Triage System (SSTS).[33] These pre-hospital stroke identification tools are promising for acute LVO recognition by EMS personnel,[19,27,33,34] but none of these studies included LFR.

The LESTOR study team will implement an intervention that involves LFR by using a newly derived LVO score to identify potential candidates for thrombectomy presenting a left-hemispheric syndrome. The identification is based on the directed assessment of the presence of a right arm paresis in combination with at least one of the following cortical symptoms: gaze deviation to the left, aphasia or erroneous performance of a complex task (earlobe-test: the fingers of the unaffected arm are required to reach to the contralateral earlobe). In the case of a right-hemispheric syndrome, the score assesses the presence of left arm paresis in combination with gaze deviation to the right, neglect or erroneous performance of the earlobe-test (without crossing the midline).[35]

This screening tool aims at the earliest possible identification of cortical symptoms suggestive of acute LVO. Dispatchers at the emergency control centre will apply the screening during telephone calls and examine patients with suspected stroke by the help of the caller. The identification of cortical deficits is also a central element of successfully utilised pre-hospital screening tools such as the RACE score[28] or the Vision, Aphasia, and Neglect (VAN) scale.[36] Currently, there is little experience in using such scores during the emergency call involving LFR.

We will gradually implement the new approach into the emergency system in southwest Baden-Wuerttemberg, where trained emergency professionals (emergency doctors, dispatchers and other EMS staff) administer the LVO score. According to the LESTOR approach, when the screening indicates LVO, EMS dispatchers will alert air rescue in addition to an ambulance, if this happens to be the fastest transport option. Based on usual practice, in addition to the EMS personnel, a ground-based emergency doctor will be sent simultaneously to the patient, where appropriate. The patient's symptoms will be re-evaluated upon arrival on site. Patients with suspected acute LVO will be transported to a CSC as quickly as possible, by either air rescue or ambulance. If a non-acute LVO is suspected, the patient will be transferred to the nearest stroke centre by ambulance.

In addition, all emergency professionals involved in the rescue procedure can perform the LVO score during missions via a mobile application, specifically created for the score assessment at the emergency site and for the consolidation of knowledge by text and video explanations.

Aim of the study

The main study objective is to implement and evaluate an intervention that involves LFR in the early identification of an acute LVO. The recognition of cortical symptoms suggestive of LVO by the EMS dispatcher during the emergency call is then expected to trigger a dispatch strategy optimised for the patient's fastest transport directly to a CSC. For this purpose, we will use a specifically designed LVO score (derived from published scores, specifically adapted to emergency calls via phone).

We hypothesise that the pre-hospital interval will be shortened and thus the intervention group (immediate admission to a CSC in the case LVO is suspected) will show a better clinical outcome compared to the control group (application of the sequential drip-and-ship approach or the mothership approach in LVO patients without LVO screening at the emergency control centre). The primary outcome is measured by the modified Rankin Scale (mRS) 90 days post-stroke.

We further hypothesise that the new approach will be beneficial in terms of cost effectiveness: although the costs of the rescue and primary care procedures might increase in the intervention group, the clinical outcome will generally improve, leading to a reduction in the treatment costs in the long-term.

Moreover, we attempt to gain insight into the professionals' perspective in terms of benefits, barriers and side effects. Finally, the impact of the emergency situation and the examination of stroke patients during the emergency call on LFR will be assessed.

Materials And Methods

Study design

We perform a controlled study with a stepped-wedge design and clusters of six emergency control centres to gradually implement the LVO score. The intervention and control groups include 125 patients, each (N=250). Enrollment began in early summer 2021. During the control phase, emergency control centres carry out the emergency interrogation and disposition in accordance with local standards. Subsequently, the six participating emergency districts move from the control to the intervention phase (stepped-wedge design). Control data is available from the control phase of this design and an existing retrospective dataset of patients who received MT in the Department of Neuroradiology, University Medical Centre Freiburg, between 2016 and present. A retrospective application of the LVO screening tool on historical cohorts is not feasible, as these examination steps of the LVO screening are neither part of the routine clinical examination nor of frequently used stroke-screening tools (such as the National Institutes of Health Stroke Scale (NIHSS)). 90 days post-stroke, a study staff member blinded to group allocation will enquire the mRS by phone from patients or their guardians (unblinded treatment and blinded endpoint evaluation). The LVO score aims to achieve high sensitivity (≥0.75) and specificity (≥0.7) in the range of previously published analyses of pre-hospital stroke scales. [37]

In order to assess the intervention's feasibility clinically, we perform a formative process evaluation. Interviews start at two time-points, during and at the end of the intervention phase, with EMS dispatchers, emergency doctors and EMS staff, air rescue staff, and LFR. The feedback from the first interview round will be used to optimise the intervention, if necessary. A workshop is organised for all the professionals involved in the study to discuss both the data and their experience with applying the procedure. This workshop aims to devise improvements for the implementation of the intervention. We interview LFR about their level of psychological stress during the emergency call and the clarity of the EMS dispatchers' instructions. The survey conducted among EMS professionals focuses on the implementation and feasibility of the LESTOR approach, benefits and undesirable effects of the intervention.

Study setting

The study is planned for a duration of three years in South Baden, Germany, in the districts of Breisgau-Hochschwarzwald, Lörrach, Emmendingen, Waldshut, Schwarzwald-Baar, Tuttlingen and the city of Freiburg in collaboration with six emergency control centres, three air rescue services and eight hospitals.

Inclusion and exclusion criteria of participants

Eligible for inclusion are patients older than 18 years, presenting symptoms indicative of a stroke due to LVO, and meeting evidence-based inclusion criteria for treatment with MT within 24 hours of the onset of symptoms. The treatment group contains patients with suspected LVO from the six participating primary stroke centres transferred to one of the two CSCs and patients primarily treated at the respective CSC. Exclusion criteria is pre-existing severe impairment due to other disease (according to level five of the mRS: "Severe disability. Bedridden, incontinent, requires constant nursing assistance"). In accordance with the ethics committee, stroke patients do not have to sign the informed consent form to be included in the study.

Participants of the formative process evaluation obtain an informational fact sheet about the purpose of the study. Written informed consent will be obtained from all interviewees before their participation.

Data Availability Statement

Our study protocol does not report data yet, therefore the data availability policy is not applicable.

Statistical analysis

We use ordinal logistic regressions to predict the primary outcome mRS based on the following variables:

- Independent variables: group assignment (intervention vs. control)
- Confounders (control variables): e.g. age, severity of stroke (NIHSS) at onset, medical history data, such as atrial fibrillation, diabetes mellitus, and the location of the occlusion of the affected arteries.

We will calculate an adjusted odds ratio for a change in the mRS. Favourable clinical outcome is defined as mRS ≤2 (similar to Goyal et al.).[38] For the sensitivity analysis, we will use different cut-off values and calculate 95% confidence intervals.

We will model a cluster membership corresponding to recommendations in the literature.[39] We will perform imputation of missing values for the predictor variables, but not for the outcome variables. Missing values might occur during three different phases: First, during pre-hospital care, LVO patients might not be recognised as such in the emergency control centre and/or on site. Possible scenarios include, e.g. language barriers or atypical presentations of stroke. In these cases, the pre-hospital LVO scoring might be lacking. Second, missing data might originate during hospital care due to an early patient transfer to external hospitals after MT. As a study nurse follows up patients stringently on time, these cases will be identified quickly and missing data can be tracked. Third, information on the clinical outcome might not be obtained in cases where the systematic follow-up by our study nurse is not successful. Based on our experience during the last >10 years, we expect a high rate of complete follow-up data of >90-95%.

We will perform a complete case analysis if the proportion of missing data is below 5%. Above 5% missing data, multiple imputations with an expectation maximisation algorithm will be conducted.

A power analysis shows that testing for the statistically significant superiority of the intervention over the control group requires far more cases (N=664) than available in our target region during the study period. We therefore conduct a controlled study to explore achievable effects and practicability under routine care conditions. Due to limitations of the sample size, we will explore the clinical significance of the intervention effects and refrain from testing for the statistically significant superiority of the intervention over the control group.

Furthermore, we calculate a propensity score, which represents the probability of a patient with a particular set of initial values receiving the intervention. This enables the monitoring of group differences that may occur in a non-randomised allocation. A cost analysis will be carried out as the first part of the health economic evaluation. For this purpose, the Medical Controlling Department at the University Medical Centre Freiburg will calculate the costs incurred during an in-patient stay for both patients in the intervention and the control group. This data is available, as the University Medical Centre serves as a reference hospital in the maintenance and further development of the German Diagnosis Related Groups (G-DRG) system via the InEK Institute [Institute for Hospital Remuneration Systems].

To determine the costs of the intervention, the training costs and the averaged expenses for the additional helicopter missions are used: if the LVO score, applied by EMS dispatchers, falsely indicates a patient having LVO, the air rescue might have to return to base without a patient, resulting in additional costs. Hence, we will compare the costs of the intervention and control group.

As a final step, we will perform a cost-effectiveness analysis, whereby the primary endpoint (functional capacity, documented according to the mRS) will be expressed in relation to the total costs. Secondary endpoints are, amongst others, length of pre-hospital, in-hospital and, if applicable, inter-hospital treatment.

We also asses the following:

- clinical criteria (e.g., difference between NIHSS at admission and discharge, length of hospital stay, number of hemicraniectomies and mortality)
- imaging criteria at initial imaging:
    - ASPECTS (Alberta stroke programme early CT score)
    - ischemic core volume (ml)
    - perfusion-lesion volume (ml)
    - mismatch (core/penumbra)
    - early signs of ischemia
    - occlusion side
    - extra- and intracranial location of the occluded segment
    - TICI (thrombolysis in cerebral infarction) score
    - bleeding type, side, diameter (mm), and location
    - imaging criteria at follow-up:
    - time and frequency of ischemia or intracerebral haemorrhage, or their combination

- infarct volume
- bleeding volume

As logistics in stroke care is complex, we will systematically record time metrics regarding both the pre-hospital (e.g., emergency call to hospital admission), and intra-hospital processes (e.g., door to recanalisation). This might streamline the management of acute LVO patients.

Trained interviewers conduct guided, semi-structured telephone interviews as part of the formative process evaluation. The interviews allow a broad exploration of diverse aspects of a phenomenon when there are few theoretical and empirical findings within a particular research field, as in the present study.[40] Interview questions deal with the implementation of the intervention, its barriers, any unfavourable side effects, problems, and solutions. The interviews are recorded on tape and transcribed. The qualitative content analysis is performed according to Mayring.[41]

We do not expect any disadvantages for patients when applying the score by the EMS dispatchers, since the ambulance is on its way when the score assessment begins. If the score assessment fails and LVO-positive cases are missed, e.g. due to technical problems or language barriers, patients receive standard care, which might well prove to be disadvantageous compared to the intervention. The detailed assessment of advantages or disadvantages by data and process evaluation is a central purpose of our study.

Ethics approval and consent to participate

Ethical approval for this study was obtained from Ethics Committee at University of Freiburg (Reference number 416/20; 08.10.2020). All procedures were performed in accordance both with the ethical standards of the institutional or national research committee, and the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards. This study protocol adheres to the recommended SPIRIT Checklist.

Discussion

The high mortality and morbidity rates associated with stroke highlight the importance of this study. The LESTOR study aims to promote the ultra-early identification of patients with LVO by addressing the pre-hospital triage phase and optimising the stroke rescue chain. The involvement of LFR along with the administration of a LVO score during the emergency call may be crucial in accelerating the time to treatment for stroke patients with LVO, thereby improving the clinical outcome.

Effect size determination will allow for a preliminary assessment of effectiveness and facilitate power considerations for larger studies with larger sample size. However, due to the limited sample size, we cannot test the hypothesis of a statistically significant difference between the intervention and control groups.

We will report all amendments of the initial study and schedule to the funder and ethics committee.

Conclusions

We assess the innovative approach, applying a pre-hospital score to identify LVO symptoms in collaboration with LFR during an emergency call and evaluate the implementation, feasibility and costs of this intervention.

If the implementation of the LVO score demonstrates positive effects on the pre-hospital identification of LVO, preclinical time metrics, and stroke outcome, its application potential should be assessed in the long-term and in other regions. Results and effect sizes detected in our study will provide an important basis for future studies with larger sample sizes. The process evaluation will provide additional insight into how the participating emergency professionals perceive the intervention and the psychological impact on LFR.

Declarations

AUTHORS' CONTRIBUTIONS

Conceptualization: Jochen Brich, Erik Farin-Glattacker, Florian Schuchardt

Data Curation: Ulrike Bergmann, Florian Schuchardt

Funding Acquisition: Jochen Brich, Erik Farin-Glattacker, Florian Schuchardt

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Writing – Review & Editing: Diana Rau, Nicole Zimmermann, Florian Schuchardt, Anne Nau, Simone Maier, Ulrike Bergmann, Matthias L. Herrmann, Jochen Brich, Erik Farin-Glattacker

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Not applicable.

SUPPORTING INFORMATION

S1 File. SPIRIT checklist.

Fig1. SPIRIT schedule: overview of the study.

Abbreviations

ASPECTS: Alberta stroke programme early CT score; CPSS: Cincinnati Pre-Hospital Stroke Scale; CSC: Comprehensive stroke centre; EMS: Emergency medical service; EMSA: Emergency Medical Stroke Assessment; FAST: Face-Arms-Speech-Time; G-DRG: German Diagnosis Related Groups; LFR: Lay first responder; LVO: Large vessel occlusion; mPASS: modified Prehospital Acute Stroke Severity Scale; mRS: modified Rankin Scale; MT: Mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; PASS: Prehospital Acute Stroke Severity; SSTS: Stockholm Stroke Triage System; RACE: Rapid Arterial oCclusion Evaluation; TICI: thrombolysis in cerebral infarction; VAN: Vision, Aphasia, and Neglect

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Supporting Information

Supporting Information not available with this version