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TAKE A CLOSER LOOK AT TRIALS

Outcomes of Acute Stroke Patients Requiring Mechanical Ventilation: Study Protocol for the SPICE Multicenter Prospective Observational Study

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Abstract

Background: Care pathways and long-term outcomes of acute stroke patients requiring mechanical ventilation have not been thoroughly studied.

Methods and Results: Stroke Prognosis in Intensive Care (SPICE) is a prospective multicenter cohort study which will be conducted in 34 intensive care units (ICUs) in the Paris, France area. Patients will be eligible if they meet all of the following inclusion criteria: (1) age of 18 years or older; (2) acute stroke (i.e., ischemic stroke, intracranial hemorrhage, or subarachnoid hemorrhage) diagnosed on neuroimaging; (3) ICU admission within 7 days before or after stroke onset; and (4) need for mechanical ventilation for a duration of at least 24 h. Patients will be excluded if they meet any of the following: (1) stroke of traumatic origin; (2) refusal to participate; and (3) privation of liberty by administrative or judicial decision. The primary endpoint is poor functional outcome at 1 year, defined by a score of 4 to 6 on the modified Rankin scale (mRS), indicating severe disability or death. Main secondary endpoints will include decisions to withhold or withdraw care, mRS scores at 3 and 6 months, and health-related quality of life at 1 year.

Conclusions: The SPICE multicenter study will investigate 1-year outcomes, ethical issues, as well as care pathways of acute stroke patients requiring invasive ventilation in the ICU. Gathered data will delineate human resources and facilities needs for adequate management. The identification of prognostic factors at the acute phase will help to identify patients who may benefit from prolonged intensive care and rehabilitation.

Trial registration: NCT03335995.

Keywords: Stroke, Mechanical ventilation, Intensive care unit, Outcome

Introduction

Stroke represents the leading cause of morbidity and mortality from neurological disorders [1]. Patients may require intensive care at the acute phase of stroke for various reasons, including altered mental status, seizures, medical complications (i.e., pneumonia, sepsis, hyponatremia), and neuroradiological or surgical procedures [2]. Recent data suggest that mortality of stroke patients admitted to critical care is high, above 50%, and prognostic indicators mainly reflect the severity of disease at stroke onset or intensive care unit (ICU) admission [3, 4]. Furthermore, large multicenter population studies suggest that mechanical ventilation for acute stroke is necessary in 10–15% of cases and varies according to stroke subtypes, being 3 to 4 times more frequent for subarachnoid hemorrhage (SAH) and intracerebral

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hemorrhage (ICH) patients (i.e., 29 and 30% of cases) than for ischemic stroke patients (i.e., 8% of cases) [5]. Factors associated with mechanical ventilation likely reflect potentially rapidly reversible conditions, including status epilepticus, pneumonia, sepsis, and hydrocephalus. Hospital mortality in mechanically ventilated stroke patients is also high, ranging from 47 to 61% depending on stroke subtype. In patients without baseline functional impairment receiving mechanical ventilation in the ICU, the presence of stroke at intubation represents the strongest indicator of functional impairment at 1 year and 3 years [6].

Current management and outcomes of acute stroke patients requiring mechanical ventilation in the ICU have not been thoroughly investigated. Although the global prognosis appears to be poor, most studies conducted to date have important limitations, including a single-center and/or retrospective designs, and the absence of long-term functional outcome measurements [5, 7–13]. Moreover, studies providing information on acute phase parameters that may significantly impact survival and functional outcomes, including stroke subtype and severity, early complications, and decisions to withhold or withdraw life-sustaining therapies are scarce [14–17]. Also, care pathways after ICU discharge are not evaluated, despite potential negative effects, in particular, if patients have no adequate rehabilitation management.

The aim of the Stroke Prognosis in Intensive Care (SPICE) study is to describe care pathways and 1-year outcomes of adult stroke patients requiring invasive mechanical ventilation in the ICU. Moreover, we will assess decisions regarding withholding and withdrawal of care and their impact on outcomes.

Methods and Analysis

Design

The SPICE study is a multicenter observational prospective study conducted in the Paris, France area. The study is promoted by the INSERM (French National Institute of Medical Research) and funded by the *Agence Régionale de Santé* (ARS) *Ile de France*. The study was designed by both the department of intensive care medicine of the Bichat-Claude Bernard University Hospital, the department of Neurology of the Lariboisière university hospital, Assistance Publique-Hôpitaux de Paris, and the INSERM research units U1137 and U1148 (Villejuif and Paris, France). Patients and the public have not been involved in study design, recruitment, or conduct of the study.

Ethics and Registration

This study follows the principles of the Helsinki Declaration 2008. The whole protocol has been reviewed and approved by the *comité de protection des personnes sud méditerranée 1* (ID RCB 2017-A02452-51). The study is registered in Clinical Trials (NCT03335995).

Centers and Participants

Centers in the Parisian area caring for at least 10 mechanically ventilated acute stroke patients per year will be eligible for the study. The study will enroll patients with any type of stroke (i.e., ischemic stroke, intracranial hemorrhage, or subarachnoid hemorrhage, excluding those of traumatic origin) and requiring invasive mechanical ventilation in the ICU.

All the patients fulfilling the following inclusion criteria will be recruited: (1) age $\geq$ 18 years; (2) diagnosis of acute stroke (i.e., ischemic stroke, intracranial hemorrhage, or subarachnoid hemorrhage) diagnosed on neuroimaging; (3) ICU admission within 7 days before or after stroke onset; and (4) need for invasive mechanical ventilation for a duration of at least 24 h. Patients will be excluded if they meet any of the following criteria: (1) stroke of traumatic origin; (2) refusal to participate; and (3) privation of liberty by administrative or judicial decision.

Recruitment, Inclusion, and Consent

Patients will be recruited at ICU admission from 34 ICUs of university and general hospitals, in the Greater Paris, France area. After the first screening about inclusion and exclusion criteria, eligible patients will be included in the study by the local investigator after written information is given and consent is obtained from the patient himself/herself or his/her next-of-kin. If patients regain capacity at one of the follow-up visits, they will be asked to provide the informed consent for the acute data and follow-up, or deny further research participation without any objection against the use for research of data collected during the acute phase, or deny further research participation and require the destruction of collected acute data. For each center, the inclusion period will last for 18 months (recruitment: 6 months, follow-up: 12 months).

Neurological Follow-Up

Each patient included in the study will be monitored by the local investigator during the initial hospitalization. Outcomes at 3 months, 6 months, and 1 year after ICU admission (vital status, score on the modified Rankin scale [mRS]) will be collected via telephone interviews by an independent research assistant trained for neurological evaluation and scoring on the mRS. At 1 year, data on disability and health-related quality of life will also be collected.

Main Outcomes

The primary endpoint is poor functional outcome at 1 year, defined by a score of 4 to 6 on the mRS, indicating severe disability or death. Secondary endpoints include decisions to withhold or withdraw care during hospitalization; functional outcomes measured on the mRS at 3 and 6 months; mortality rates at 3, 6 and 12 months; mRS shift analysis; disability at 1 year, measured on the Glasgow outcome scale-extended; health-related quality of life at 1 year measured on the EQ5D-3L scale, the instrumental activities of daily living scale, the hospital anxiety and depression scale, and the Barthel index; and place of residence at 1 year (home, assisted care or death).

Sample Size

It is necessary to obtain approximately 10 patients meeting the primary endpoint event (i.e., mRS > 3 at 1 year) for each degree of freedom tested in the multivariate model. Considering that approximately 60% of patients admitted to the ICU with stroke have a poor prognosis [3] and that approximately 5% of patients will be lost to follow-up at 1 year, we aim to include a minimum of 300 acute stroke patients in order to test 10–12 variables in the final model.

Data Collection and Monitoring

Data management and statistical analysis will be performed by an independent statistician (Stéphane Ruckly, UMR1137). During the study, data will be collected in an electronic case report form managed by ICUREsearch (ICUREsearch, Paris, France). This data management system allows for direct data entry. Data entry will be monitored by an independent clinical research assistant, according to a predefined monitoring plan. Patient confidentiality will be ensured by using identification numbers.

Statistical Analysis

Continuous variables will be reported as medians (interquartile ranges) and categorical variables as numbers (percentages). For between-group comparisons, we will use the Wilcoxon rank-sum test for continuous variables and either the Pearson chi-square test or Fisher exact test, as appropriate, for categorical variables. Continuous variables will be dichotomized using either predefined cutoff values or median values. Center-related variables, patient-related variables, and stroke-related variables are presented in Table 1. To identify factors associated with endpoints, we will build a hierarchical logistic mixed model. Multilevel modeling will take into account the hierarchical structure of the data, which may manifest as intraclass correlations. To obtain a conservative estimate of the standard error, a separate random-error term should be specified for the center level. Variables potentially associated with the endpoint, with a p value < 0.10 in univariate analysis, will be introduced into the multivariate model and selected using a backward approach. The hierarchical model comprises two levels: center and patient (including stroke characteristics). In case of missing values of independent variables, we plan to input a multiple imputation process, depending on the pattern of missing data and variables types, for the primary analysis. A sensitivity analysis on complete cases will be reported.

Table 1 Main variables of interest

Variables	Type	Description
Center-related variables		
University hospital	Categorical	University-affiliated hospital
Neuro-ICU	Categorical	Neurointensive care unit with onsite neurosurgery 24/7
Stroke unit	Categorical	Presence of a stroke unit in the hospital
Stroke-related variables		
Stroke subtype	Categorical	Ischemic stroke, intracranial hemorrhage, or subarachnoid hemorrhage
Time between stroke diagnosis and initiation of mechanical ventilation	Continuous	Number of days between stroke diagnosis and initiation of mechanical ventilation
Patient-related variables		
Age	Categorical	< 70 or ≥ 70 years
Comorbidities	Categorical	Charlson comorbidity index ≥ 2 points
Pre-admission disability	Categorical	Pre-admission score on the mRS > 3
Direct ICU admission	Categorical	Initial ICU admission (vs. initial admission to the hospital wards)
Coma at ICU admission	Categorical	Score on the GCS < 8 in the absence of sedation
Non-neurological SOFA score at ICU admission	Continuous	SOFA score without the neurological component

GCS Glasgow coma scale, *ICU* intensive care unit, *mRS* modified Rankin scale, and *SOFA* sepsis organ failure assessment

The following clinically relevant potential 2×2 interactions between variables will be tested: neuro-ICU and stroke subtype, stroke unit and stroke subtype, age and stroke subtype, and comorbidities and pre-admission disability.

To understand the impact of acute phase therapy on outcomes, subgroup analyses defined on stroke subtypes will be performed. Briefly, three additional models will be carried out on ischemic stroke patients (adjusted for intravenous thrombolysis, mechanical thrombectomy, and craniectomy), on ICH patients (adjusted for hematoma evacuation), and on SAH patients (adjusted for endovascular and/or surgical aneurysm treatment). All three models will be additionally adjusted for variables with a univariable p value < 0.1. We will not correct for multiplicity of statistical tests of the secondary endpoints. All tests will be two-sided, and a p value < 0.05 will be considered significant. We will use SAS 9.4 for all statistical analyses.

Pre-planned Ancillary Studies

We plan to extend patient follow-up up to 10 years through record linkage between the SPICE database and the two following datasets: (1) The national death registry (RNIPP, *Registre National d'Identité des Personnes Physiques*) to assess the vital status and identify the cause(s) of death and (2) the national health insurance information system (SNIIR-AM) to collect data about patient use of health resources.

We plan to study the following points in ancillary studies:

- The impact of each of the center-related variables (university hospital, neuro-ICU, stroke unit) on outcome;
- The effect of age subgroups (< 60 years, ≥ 60 and < 70 years, ≥ 70 and < 80 years, ≥ 80 years) on outcome;
- The outcome of patients admitted to the ICU within 7 days before stroke;
- The association between indication for mechanical ventilation and outcome;
- The prevalence of seizures/status epilepticus and their effect on outcome;
- The effect of invasive intracranial pressure monitoring and electroencephalogram monitoring on outcome;
- The prevalence of decisions to withhold or withdraw care and their effect on outcome;
- The prevalence of major systemic complications (i.e., infections, sepsis, cardiovascular complications) and intracranial complications (i.e., seizures, cerebral edema, hemorrhagic transformation, hydrocephalus) and their effect on outcome;
- The prevalence of neurological/neurosurgical consult and other specialists in the ICU and their effect on outcome;
- The prevalence of brain death and subsequent organ donation;
- The kinetics of recovery (mRS shift) in different stroke subtypes;
- The impact of specific interventions (i.e., craniectomy and thrombectomy) on outcome of acute ischemic stroke patients;
- The impact of specific interventions (i.e., hematoma evacuation, anticoagulation reversal) on outcome of ICH patients;
- The impact of specific interventions (i.e., endovascular and/or surgical aneurysm treatment) on outcome of SAH patients.

Discussion

This is the first study prospectively investigating care pathways of acute stroke patients requiring invasive ventilation and their functional outcomes at 1 year. Major therapeutic changes have occurred over the past years, mainly in the acute ischemic stroke field with the advent of mechanical therapy [18]. Data from this large prospective multicenter cohort of consecutive stroke patients requiring invasive mechanical ventilation in the ICU will provide a unique description of patients' characteristics, acute phase management strategies, resource use, and their correlation with long-term outcomes [19, 20]. This cohort will also provide an accurate description of non-atherosclerotic causes of strokes that can be observed in ICU patients [21]. Moreover, data on infectious complications and their association with long-term outcomes will be investigated [22, 23].

The prognosis based on different stroke subtypes will be studied, as well as, decisions to withhold or withdraw care at the acute phase and their impact on outcomes. We will obtain longitudinal data on functional outcomes at different predefined time points (i.e., 3 months, 6 months, and 1 year after ICU admission). Care pathways will be evaluated including the facilities, where the patients will be discharged and when they will return home if they do so. Also, health-related quality of life will be studied. The results generated from this study will complement other large registries focusing on mechanical ventilation in stroke patients and will allow the determination of prognostic factors for patients who may benefit from prolonged intensive care and rehabilitation. Collected data will delineate human resources and facilities needs for adequate management of acute stroke patients requiring mechanical ventilation. ICU end-of-life practices in

critically ill stroke patients have not been properly reevaluated in the last 10 years [15, 24], and the results generated from this study will reappraise these practices in the light of an evolving legislative and societal environment [25]. The observational design and the consequent difficulty to explore causality is the main limitation of the study.

Dissemination

Data will be made available to the scientific community through abstracts submitted to scientific societies and by original articles submitted to peer-reviewed journals. The SPICE scientific committee will consider any request on data sharing, and decisions will be made concerning these requests by the principal investigator once the first multicenter manuscript will have been published. A writing committee, composed in part of the scientific committee members (RS, MM, SR, JFT, IC, FW), will draft the work and all the scientific committee members will be authors of the manuscript. For each center, an investigator will be mentioned as co-author for any patient enrolled. All co-authors will approve the final manuscript before submission. All the participating centers will be recognized as contributors in the group authorship 'SPICE collaborators.'

Study Status

The study is currently in progress. At the time of manuscript submission, 371 patients have been included in the 34 participating centers. The last patient's 1-year follow-up is planned at the end of October 2019. The final database should be completed by the end of 2019.

Conclusion

The SPICE multicenter study will investigate 1-year outcomes, ethical issues, as well as care pathways of acute stroke patients requiring invasive ventilation in the ICU. Gathered data will delineate human resources and facilities needs for adequate management. The identification of prognostic factors at the acute phase will help to identify patients who could benefit from prolonged intensive care and rehabilitation.

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RS, MM, JFT, IC, and FW designed the work. All investigators were involved in patients' recruitment and data collection. SR is responsible for data management and statistical analyses. RS and MM wrote the manuscript. JFT, EG, FF, IC, and FW revised the manuscript. All authors read and approved the final manuscript.

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Data Statement
The raw/processed data required to reproduce these findings cannot be shared at this time as the data also form part of an ongoing study.

Conflicts of interest
The authors declare that they have no conflict of interest.

Ethical approval
The whole protocol has been reviewed and approved by the *comité de protection des personnes sud méditerranée 1* (ID RCB 2017-A02452-51).

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