


BMJ Open Do neurocritical care units improve outcomes for brain-injured adults: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Neurocritical care is a rapidly developing subspecialty within intensive care medicine which aims to improve outcomes of critically ill neurological patients. This has inspired the formation of specialised intensive care units or services to provide dedicated care of brain-injured patients, as well as new training pathways for physicians. However, expansion has been variable worldwide and it is yet to be determined if there are clear benefits in regard to patient outcomes. We are planning a systematic review with meta-analysis to assess whether the introduction of neurocritical care units or services, or neurointensivists have favourable effects on survival.

Methods and analysis We will include all observational and interventional studies comparing specialised neurocritical care units or services with general or non-specialised units in the care of acutely brain-injured adults. The primary outcome will be all-cause mortality at the longest follow-up, and secondary outcomes will be intensive care unit and hospital length of stay, and functional outcomes. All relevant studies will be identified through database searches. All study selection and data extraction will be conducted by two independent reviewers. We will conduct a random-effects meta-analysis to synthesise evidence for all outcomes. In addition, we will perform a subgroup analysis by disease process. We will assess confidence in the cumulative evidence using the Grading of Recommendations, Assessment, Development and Evaluations framework.

Ethics and dissemination This systematic review and meta-analysis does not require ethical approval. We will publish findings from this systematic review in a peer-reviewed scientific journal and present these at conferences. It will be included in the primary author's higher degree research thesis.

PROSPERO registration number CRD42020177190.

INTRODUCTION

Neurocritical care is an emerging subspecialty that is dedicated to the care of critically ill patients with neurological disease, including devastating acute brain injuries. This has led to the development of subspecialty training pathways and neurocritical care centres in some countries. However, the introduction of specific neurocritical care services,

Strengths and limitations of this study

- This systematic review will evaluate the association between neurocritical care units, services or neurointensivists, and clinically important outcomes in acutely brain-injured adults.
- A systematic review will be conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines, searching three electronic databases, with two independent reviewers evaluating studies and extracting data.
- A meta-analysis will assess the primary outcome of all-cause mortality at longest reported follow-up and secondary outcomes of intensive care unit and hospital length of stay, and patient functional outcomes.
- Where possible, subgroup analyses will evaluate outcomes by disease processes.
- The limitations of studies will be addressed with the Grading of Recommendations, Assessment, Development and Evaluations framework.

particularly specialised intensive care units (ICUs), is an expensive and resource-intense intervention, and there remains no definitive evidence that providing such subspecialised care improves patient outcomes.

The cohorting of patients under a specialised multidisciplinary team is not without precedent. The development of a stroke care unit has been associated with improved healthcare delivery and outcomes.¹ Similarly, the implementation of specialised ICUs dedicated to the care of critically ill brain-injured patients has been reported to improve outcomes. A systematic literature review by Kramer and Zygun in 2011, and updated in 2014, found that dedicated neurointensive care units lowered mortality and improved neurological outcomes.^{2,3} In their review of ICU processes of care, the 2014 International Multidisciplinary Consensus Conference on Multimodality Monitoring also concluded that specialised neurocritical care units can have positive impacts on patient outcomes.⁴

However, several questions remain regarding neurocritical care. There is no standard definition, and significant heterogeneity exists in the structure of individual neurocritical care units. As such, the dominant driving mechanism(s) behind the reported improved patient outcomes are not clear. It may reflect the clinical expertise of the medical and nursing team under the leadership of a neurointensivist(s) in recognising and managing neurological injuries and their sequelae. A specialty multidisciplinary team incorporating physiotherapy⁵ and nutrition⁶ may also enhance patient recovery after neurological injury. The introduction of a neurocritical care unit or service also typically involves the addition of advanced multimodal neuromonitoring to provide new insights into the injured and recovering brain. Management may also be refined by the institution of standardised neurocritical care protocols.

Furthermore, the outcomes of specific neurological conditions require review. Acute brain injuries such as ischaemic and haemorrhagic stroke and traumatic brain injuries have a significant mortality and morbidity, given their propensity to affect those of any age, as well as limited curative therapies. It is paramount therefore, to determine if neurocritical care improves the outcomes of patients with acute brain injuries, in order to better allocate resources and develop models of care that improve patient outcomes. As such, a protocol for a systematic review and meta-analysis is proposed to explore the impact of neurocritical care delivery in critically ill adults with acute brain injuries.

OBJECTIVE

To assess whether the introduction of a neurocritical care unit, neurocritical care service or neurointensivist improves outcomes in critically ill adult patients with acute brain injuries, by examining mortality, length of stay (LOS) and functional outcomes.

METHODS

Study design

To address the above objective, we will perform a systematic review and meta-analysis of the existing literature. This protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guideline⁷ (online supplemental 1). In addition, this systematic review has been submitted for registration in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020177190). The results of this study will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Eligibility criteria

Types of studies

There are multiple barriers limiting the feasibility of randomised controlled trials on this topic. As such, we

will include all peer-reviewed, English-language observational and interventional studies published as full articles. Studies analysing subgroups derived from previously published data will be excluded. There are no limitations on year of publication.

Types of participants

The study population will be adult patients, defined to be aged 18 years or older, in critical care units for an acute brain injury. Studies that included a minority of patients aged <18 years, or defined their population from aged 16 years or older will be included. Acute brain injuries include ischaemic stroke, intracerebral haemorrhages, subarachnoid haemorrhages and traumatic brain injuries. Studies that examine all neurologically ill patients, not limited by diagnosis will be included. However, studies that limit the admitting diagnosis to specific neurological conditions not involving acute brain injury, will be excluded. Data will be analysed according to the relevant condition(s) in studies with different subgroups of patients.

Types of interventions

Interventions of interest will be the introduction of a neurocritical care unit, neurocritical care consulting service or neurointensivist. The detailed definition of a neurocritical care unit will vary between centres but should primarily represent an ICU unit that is dedicated to the care of neurologically injured patients, who are exclusively managed by this specialised unit excepting logistical circumstances. A neurocritical care consulting service is defined as a specialised multidisciplinary team that provides advice on management for critically ill neurological patients and works in conjunction with the primary treating team. The team leader of such consulting services should be a neurointensivist. A neurointensivist is a physician who is accredited in neurocritical care, who is ideally board certified or nationally recognised, although not all included manuscripts may provide this level of detail.

These interventions should be compared with care provided by general ICUs or another non-neurocritical care unit. These comparisons may occur concurrently or as before-after studies. We will exclude studies examining the introduction of standardised management protocols for neurocritical care conditions.

Types of outcome measured

The primary outcome of interest is all-cause mortality at the longest follow-up within 6 months. Secondary outcomes will include ICU LOS, hospital LOS and functional outcomes at the longest follow-up within 6 months, at or after hospital discharge. Functional outcomes will be categorised dichotomously as favourable or unfavourable. Favourable outcomes are defined as a Glasgow Outcome Scale >3, an Extended Glasgow Outcome Scale >4 or a Modified Rankin Scale (mRS) <4.

Data sources

Searches for published studies will be undertaken in the following electronic databases: Ovid MEDLINE and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions; Embase Classic+Embase and Cochrane Central Register of Controlled Trials. Previous systematic reviews will be screened for relevant citations. The search strategies for each database are presented in online supplemental 2.

Data collection and analysis

Study selection process

Studies identified through the search strategy and citation chaining will be uploaded to Covidence and duplicates removed. Two authors will independently review abstracts and categorise as 'exclude', 'include' and 'maybe', with the latter two progressing to the next stage of screening. Disparities will be assessed independently by a third author. Full texts of the remaining studies will be obtained and uploaded to Covidence for the second stage of screening by the two authors, with disagreements resolved by the third author. The final included studies will be collated for further analysis.

Data collection process

Two authors will extract data independently from the eligible studies using a data extraction form. The form will aim to capture information on study characteristics, including study design, methodology and participant characteristics. The resulting data will be compared and disparities resolved through discussion between the two reviewers, or if required, a third reviewer will be consulted.

As the population of each study is likely heterogeneous depending on underlying disease process, commonly used and reported general participant characteristics were chosen for review, including age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, APACHE III score, admission Glasgow Coma Scale and pre-admission mRS. In addition, the following participant characteristics will be included for each disease process: National Institute of Health Stroke Scale on admission for stroke, intracerebral haemorrhage (ICH) score on admission for ICH, Hunt and Hess score on admission for subarachnoid haemorrhage, World Federation of Neurological Surgeons scale on admission for subarachnoid haemorrhage and the Injury Severity Score on admission for traumatic brain injury.

Outcome data

To assess the primary outcome of mortality, we will extract the number of participants in the control and interventions groups and the number that deceased at the longest follow-up period reported in the study. To assess ICU and hospital LOS as secondary outcomes, we will extract the means and SD, or medians and IQR, for each participant group. To assess functional outcome as a secondary outcome, we will extract the number of participants with a

favourable outcome, as defined previously, at the longest follow-up reported in the study.

Risk of bias assessment

The Risk of Bias in Non-randomised Studies of Intervention (ROBINS-I) tool designed by members of the Cochrane Bias Methods Group will be used for quality assessment of each study.⁸ Two authors will independent assess the risk of bias of studies and disagreement will be resolved with discussion, or the inclusion of a third author. The following domains will be assessed in keeping with the ROBINS-I tool: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. The risk of bias of each domain will be classified as low risk, moderate risk, serious risk or critical risk available. The risk of bias of each study will be classified in accordance with the ROBINS-I tool as follows:

- ▶ Low risk of bias: all domains are listed as low risk.
- ▶ Moderate risk of bias: all domains are listed as low or moderate risk.
- ▶ Serious risk of bias: at least one domain has a serious risk of bias but no domains have a critical risk.
- ▶ Critical risk of bias: there is a critical risk of bias in at least one domain.

Data synthesis

Descriptive analysis

Descriptive statistics will be generated for the included studies. These will include study characteristics such as year of publication, study design, population size, population characteristics, type of intervention and comparators and the overall risk of bias.

Statistical analysis

For dichotomous data, that is, mortality outcomes and functional outcomes, we will calculate a pooled estimate of risk ratio with 95% CI using a random-effects model according to the Mantel-Haenszel method. This will be graphically represented using forest plot graphs.

For continuous data, that is, LOS outcomes, we will calculate a pooled estimate of mean difference (MD) with 95% CI using a random-effects model. MD is used as ICU and hospital LOS would be calculated across all publications with the same unit, that is, days.

We will conduct subgroup analyses for the primary outcome, stratified by the following population disease process: subarachnoid haemorrhages, intracerebral haemorrhages, ischaemic stroke, and traumatic brain injuries.

The Paule and Mandel method will be used to estimate the between-study variance, and the CIs will be calculated using the Q-profile method.^{9 10} The homogeneity assumption will be measured by the I^2 , which describes the percentage of total variation across the studies due to heterogeneity rather than chance. I^2 will be calculated

from the basic results obtained from a typical meta-analysis as $I^2=100\% \times (Q-df)/Q$, where Q is the Cochran's heterogeneity statistic. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity. All analyses will be conducted in R V.4.0.2 (R Foundation), and a p value <0.05 will be considered statistically significant.¹¹ Publication bias will be evaluated by visual inspections of funnel plots.

Sensitivity analyses

We will perform the following sensitivity analyses to evaluate the robustness of our results:

1. Analysing only studies with low or moderate risk of bias.
2. Analysing only studies that did not restrict their study population by disease process.
3. Analysing only studies with longest reported mortality beyond ICU mortality.
4. Analysing studies by geographical locations, that is, North America, Europe and rest of the world.
5. Analysing only studies with board-certified or subspecialty trained neurointensivists.

Confidence in cumulative evidence

We will assess confidence in the cumulative evidence for each assessed outcome using the Grading of Recommendations, Assessment, Development and Evaluations framework.¹²

Ethics and dissemination

This review does not require ethical approval as a systematic review of published studies. We will publish findings in a peer-reviewed scientific journal. Results from this systematic review may be presented in local academic meetings and conferences prior to full publication. The systematic review will also be included as a chapter in the primary author's higher degree research thesis. The dataset will be made available based on a reasonable request to the researchers.

Patient and public involvement

There was no patient or public involvement in the development of this manuscript.

Limitations

We acknowledge limitations to the proposed systematic review. Included studies are anticipated to be heterogeneous in nature due to variations in intervention definitions. Specifically, there may be limited information available on the structure and characteristics of neurocritical care interventions. In addition, the strength of a systematic review and meta-analysis relies in part on the strength of available studies, and therefore may be limited due to the lack of randomised controlled trials in this area. We also intend to perform subgroup analyses for disease processes. However, this may reduce statistical power in data analysis, as well as increase the likelihood of identifying statistical significance influenced by chance due to performing multiple analyses.

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Contributors XP and AU devised the study. XP drafted the protocol, with assistance from JR, ASN and AU. XP and JR will carry out the data collection and AU will assist with data collection as the third reviewer. XP will complete the data analysis with statistical assistance from ASN. XP will draft the final manuscript, which will be reviewed by JR, ASN and AU. AU will be the guarantor of the review. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work.

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