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ABSTRACT

Background: Severe traumatic brain injury (TBI) is associated with a high mortality rate and those that survive commonly have permanent disability. While there is a broad consensus that appropriate prehospital treatment is crucial for a favorable neurological outcome, evidence to support currently applied treatment strategies is scarce. In particular, the relationship between prehospital treatments and patient outcomes is unclear. The BRAIN-PROTECT study therefore aims to identify prehospital treatment strategies associated with beneficial or detrimental outcomes. Here, we present the study protocol. **Study Protocol:** BRAIN-PROTECT is the acronym for **BRA**in **INj**ury: **P**rehospital **R**egistry of **O**utcome, **T**reatments and **E**pidemiology of **C**erebral **T**rauma. It is a prospective observational study on the prehospital treatment of patients with suspected severe TBI in the Netherlands. Prehospital epidemiology, interventions, medication strategies, and nonmedical factors that may affect outcome are studied. Multivariable regression based modeling will be used to identify confounder-adjusted relationships between these factors and patient outcomes, including mortality at 30 days (primary outcome) or mortality and functional neurological outcome at 1 year (secondary outcomes). Patients in whom severe TBI is suspected during prehospital treatment (Glasgow Coma Scale score $\leq$ 8 in combination with a trauma mechanism or clinical findings suggestive of head injury) are identified by all four helicopter emergency medical services (HEMS) in the Netherlands. Patients are prospectively followed up in 9 participating trauma centers for up to one year. The manuscript reports in detail the objectives, setting, study design, patient inclusion, and data collection process. Ethical and juridical aspects, statistical considerations, as well as limitations of the study design are discussed. **Discussion:** Current prehospital treatment of patients with suspected severe TBI is based on marginal evidence, and optimal treatment is basically unknown. The BRAIN-PROTECT study provides an opportunity to evaluate and compare different treatment strategies with respect to patient outcomes. To our knowledge, this study project is the first large-scale prospective prehospital registry of patients with severe TBI that also collects long-term follow-up data and may provide the best available evidence at this time to give useful insights on how prehospital care can be improved

List of Abbreviations: AIS: Abreviated Injury Score; AMC: Amsterdam Medical Center (University hospital, part of AUMC); ANOVA: Analysis of Variance; AUMC: Amsterdam University Medical Centers (two main locations addressed as "VUmc" and "AMC"); CI: Confidence Interval; CT (scan): Computed Tomography scan; EMS: Emergency Medical Services; EMV: Eye Motor Verbal score; Erasmus MC: Erasmus Medical Center (University hospital); GCS: Glasgow Coma Scale; GLM: Generalized Linear Models; GOS: Glasgow Outcome Scale; GOSE: Glasgow Outcome Scale – Extended; HEMS: (Physician-based) Helicopter Emergency Medical Service; ISS: Injury Severity Score; PEARL: Pupils Equal And Reacting to

Light; Radboud UMC: University Medical Center Radboud Nijmegen (University hospital); RTS: Revised Trauma Score; SSC: Scientific Steering Committee; TBI: Traumatic Brain Injury; UMCG: University Medical Center Groningen; UMCU: University medical Center Utrecht (University hospital); VUMC: VU Medical Center (University hospital, part of AUMC); WBP: Wet Bescherming Persoonsgegevens; WMO: Wet Medisch-wetenschappelijk Onderzoek met mensen **Key words:** (MESH): air ambulances; brain injuries; traumatic; clinical protocols; emergency medical services; treatment outcome

INTRODUCTION

Severe traumatic brain injury (TBI) is a leading cause of death and permanent disability in the population under 45 years and imposes a considerable burden on society through loss of productive life years and lifetime costs of care (1–3). The tremendous impact of TBI on individual patients, as well as the socioeconomic relevance, necessitates the development of optimal treatment strategies to ensure the best possible outcomes.

Prehospital healthcare providers have the unique opportunity to treat the patient at the earliest possible moments during the so called "golden hour" of trauma care, and there is broad consensus that effective early treatment at this stage can substantially contribute to improved outcomes (4–7). The aims of prehospital management of patients with severe TBI are rapid transport to an appropriate treatment facility, while preventing and treating factors that are known to trigger secondary brain injuries, such as hypoxia, hypotension, as well as hypo- and hyperventilation (4, 6). Specific treatments, e.g., those aiming at control of intracranial pressure (e.g., mannitol) or to limit intracerebral hemorrhage (e.g., tranexamic acid), may also be administered in the prehospital setting (8, 9). However, given a large spectrum of treatment possibilities and limited evidence for any of those treatments, it is still unclear how patients should be optimally treated in the acute or prehospital setting (4, 10–13). Examples of controversial topics requiring further evidence include: optimal airway management and ventilation strategies (13, 14), how hemodynamic instability can best be treated (15), and the use of hyperosmolar drugs to reduce intracranial pressure (16, 17). Logistic and operational factors, such the mode of patient transport, distances to trauma centers or prehospital treatment times may also have a relevant influence on patient outcomes and warrant further investigation to optimize organizational aspects of prehospital trauma care.

S. M. Bossers et al.   THE BRAIN-PROTECT STUDY PROTOCOL

3

International guidelines for the management of TBI have been published by the Brain Trauma Foundation, the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (18, 19). Remarkably, the quality of evidence was considered low for all prehospital treatments, and the strength of all recommendations concerning any prehospital therapeutic intervention, treatment threshold or monitoring modality was weak (19). The bottom line is that prehospital treatment of severe TBI is currently a black box in which a spectrum of different treatment approaches is applied, but in which the effects of these treatments on outcomes remain unclear.

To address the current knowledge gaps, the BRAIN-PROTECT research consortium has set itself the goal to investigate the relationship between the prehospital treatment of patients with suspected severe TBI and outcomes. We here present the study protocol of the BRAIN-PROTECT study.

METHODS

BRAIN-PROTECT Study Objective

BRAIN-PROTECT is the acronym for **BRA**in **IN**jury: **P**rehospital **R**egistry of **O**utcome, **T**reatments and **E**pidemiology of **C**erebral **T**rauma. The main objective of this research project is to identify prehospital factors, in particular treatment strategies, associated with beneficial or detrimental outcomes in patients with suspected severe TBI. We focus on patients with severe TBI, because these patients are at high risk for impairments of vital functions and secondary brain injury, and may profit most from optimal prehospital treatment. We chose to study patients with suspected — rather than confirmed — severe TBI because prehospital treatment is based on the suspicion, not on the final diagnosis, and we wish to obtain estimates for treatment effects that are relevant to current practice in the prehospital setting. Nonetheless, the data also allow subanalyses of patients with confirmed TBI. Ultimately, the analysis of the collected data is intended to allow improvements in prehospital treatment and patient outcomes.

Design and Setting

The BRAIN-PROTECT study is a prospective, observational study of the prehospital treatment of patients with suspected severe TBI in The Netherlands. The Netherlands has a population of about 17.2 million inhabitants, with an average population density of 504 persons per square
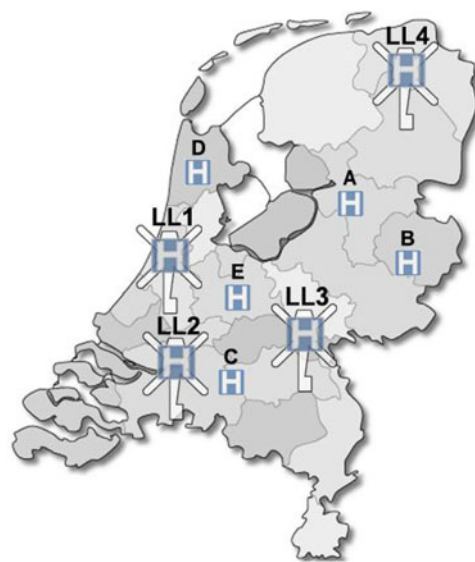
FIGURE 1. Map of the Netherlands, showing the location of the participating helicopter emergency medical services (HEMS) operators and their associated respective trauma centers (LL1–LL4; i.e., representing 4 HEMS and 4 level 1 trauma centers), as well as participating trauma centers without HEMS operation (A–E). See Table 1 for details.

kilometer (20). Prehospital trauma care is provided by 25 regional ambulance services. Generally, two ambulance vehicles, each with a qualified prehospital emergency medical nurse and a medically trained ambulance driver, are dispatched to major accidents.

Additionally, a 24/7 physician-based Helicopter Emergency Medical Service (HEMS) system is available in the Netherlands. HEMS physicians are either anesthesiologists or surgeons, all well trained in prehospital emergency procedures. Other team members include a certified flight nurse and a pilot. The four EC135 helicopters (Airbus Helicopters) of this HEMS operation are stationed in Amsterdam (callsign "Lifeliner 1"), Rotterdam ("Lifeliner 2"), Nijmegen ("Lifeliner 3"), and Groningen ("Lifeliner 4") (Figure 1). If required for logistic, technical, or meteorological reasons, the HEMS team can respond to accidents using a designated road ambulance vehicle.

The purpose of the HEMS is to complement the ambulance care by providing specific expertise, not to substitute ambulance care. Hence, HEMS teams are dispatched in addition to, rather than instead of, ground ambulance teams. Based on a catalog of dispatch criteria, a HEMS team is routinely activated for all patients with suspected severe traumatic brain injury (21). The activation threshold is low, resulting in overtriage and a substantial proportion (about 50%) of canceled missions (22). Occasionally, the trauma severity is initially underestimated by

TABLE 1. Participating HEMS and trauma centers

	Reference	Name	Location	Start prehospital inclusion
HEMS & Trauma centers	LL1*	Amsterdam UMC, location VUmc±	Amsterdam	02-2012
	LL2*	Erasmus MC±	Rotterdam	04-2014
	LL3*	Radboud UMC±	Nijmegen	11-2012
	LL4*	UMC Groningen±	Groningen	01-2013
Trauma centers	A	Isala	Zwolle	
	B	Medisch Spectrum Twente	Enschede	
	C	Elisabeth-TweeSteden	Tilburg	
	D	Noordwest ziekenhuisgroep	Alkmaar	
	E	UMCU±	Utrecht	

±University Medical Centers

*LL [number] = PHEMS in the Netherlands, referring to the number from which location it is deployed (e.g., Amsterdam, Rotterdam, Nijmegen, or Groningen).

the dispatch center. In such cases, a HEMS team can be secondarily activated by the ambulance team at the accident scene. In the majority of cases of severe TBI, HEMS teams arrive at the accident scene to treat the patient. However, if the patient is ready for transport in the ground ambulance before HEMS arrival, the ambulance and HEMS will commonly rendezvous en route to the hospital. Hence, a HEMS team is involved in the treatment of the vast majority of patients with prehospitally suspected severe TBI, with only few exceptions (e.g., unavailability of a HEMS team, scoop-and-run to a nearby hospital).

After initial prehospital treatment and stabilization, patients with severe TBI are transported to designated level 1 trauma centers. Currently, there are 11 officially appointed trauma centers with 24/7 treatment facilities for all severely injured patients, plus an additional trauma center with level 1 facilities for all adult trauma patients, but without pediatric facilities. Only in exceptional circumstances (e.g., catastrophic hemorrhage that cannot be controlled), patients are transported to the nearest regional hospital instead of a designated trauma center.

Patient Inclusion and Prospective Follow-up in Participating Centers

All patients with suspected severe TBI treated by one of the four Dutch HEMS operations are identified, based on the combination of a trauma with a prehospital Glasgow Coma Scale (GCS) (23) score $\leq$ 8 that does not consistently restore above 8 during the prehospital treatment, in combination with a trauma mechanism or clinical findings that are suggestive for head injury. Patients who were declared dead on scene as well as patients with possible brain injury but in whom traumatic head injury is not suspected, such as suffocation, drowning, or strangulation, are not considered for inclusion. No age restrictions are imposed for inclusion in the research database.

Identified patients are prospectively followed up by an independent data manager (see below) in 9 participating trauma centers for in-hospital data and outcome data until 1 year after the accident. The type of collected data is described in more detail below. Data acquisition began in February 2012 with a phased approach across the participating centers, and follow up data have been collected until December 2018. Table 1 and Figure 1 summarize the participating centers.

Scientific Oversight

A Scientific Steering Committee (SSC) was implemented to oversee the scientific activities during the study. The SSC is multidisciplinary, containing delegates from the Emergency Medical Services, HEMS, Neurosurgery, Neurology, Trauma surgery, and Anesthesiology. Most members of the SSC have an extensive academic background in (trauma related) research or a clinical background in the treatment of patients with TBI. Two members of the group hold master degrees in medical statistics and epidemiology, respectively, and contribute the respective methodologic and statistical expertise.

Ethics, Privacy and Legislation

The Medical Research Ethics Boards of the Amsterdam University Medical Center, location VUmc (at the time of approval: VU University Medical Center, reference number 2012/041) and Erasmus MC Rotterdam (reference number MEC-2012-515) reviewed the study protocol and concluded that the research is not subject to the Dutch Medical Research Involving Human Subjects Act (*Wet medisch-wetenschappelijk onderzoek met mensen, WMO*). In this observational study, patients were not subject to any treatment interventions other

than standard care, such that informed consent for treatment is not applicable. Informed consent for the inclusion of data into the research database and study participation could not be obtained at the time of the accident in the comatose patient population. As a requirement to obtain secondary informed consent from patients or relatives could cause substantial inclusion bias, a leading Dutch law firm specializing in patient privacy legislation was consulted. We adopted their suggested approach to comply with the Dutch Personal Data Protection Act (*Wet Bescherming Persoonsgegevens, WBP*), while waving the requirement for informed consent according to Dutch law: All patient data were coded and anonymized by an independent data-manager (not employed by the researchers, paid by a third party, not involved in publication of the data). This allowed us to combine anonymous prehospital, inhospital, and outcome data in the research database, while ensuring that data could not be traced back to individual patients by anyone — including the researchers — except the data-manager. All coding lists and all personally identifiable information are securely stored in the respective trauma centers at all times. Informed consent is, however, required and obtained for a telephonic interview with the patient or a proxy at one year after the accident to obtain the Extended Glasgow Outcomes Scale score. This interview is conducted by the data-manager, who is the only person who can link the patient code in the research database back to the original patient file in order to obtain contact information. Prior to the interview, patients or their relatives receive a letter in which they are informed about the ongoing study and that they will be approached for an interview on a voluntary basis.

Data Collection

Data registration is based on the Utstein template for uniform reporting of data following major trauma (24, 25), supplemented with other variables of interest. The following data are collected:

A. Prehospital Data and Suspected Injuries.

Prehospital data are collected by the four HEMS. These data include the following:

- Operational data (e.g., dispatch times and distances, type of transport).
- Demographic data (e.g., gender and age)
- Trauma mechanism and observed or suspected injuries.
- Vital parameters, routinely measured at 3 time points: on arrival at the patient, after initial stabilization, and before arrival at the hospital. Relevant vital parameters measured at other time points (e.g., nadir values to document hypotension, bradycardia, or

desaturation; or any other measurements deemed relevant) could also be entered in the database.
- Prehospital interventions (ranging from basic prehospital treatments, such as oxygen administration, type of intravascular access, or use of immobilization devices, through details of basic and advanced airway management and ventilation techniques, to advanced prehospital management such as diagnostic ultrasound or thoracostomy).
- Prehospital medications and fluids.

B. Intra-hospital Data and Confirmed Injury Characteristics.

The data-manager identifies the included patients in participating trauma centers, based on matches between prehospital information (e.g., date and time of arrival at hospital, gender, trauma mechanism and other characteristic information) and queries performed in the trauma centers. Subsequently, the data manager collects follow-up data as well as previous medical history data. These data include the following:
- Medical history, including preinjury medication.
- First vital parameters in the emergency department.
- First in-hospital laboratory values.
- First key interventions.
- Cerebral CT imaging results [observed injuries, Marshall score (26), Rotterdam score (27)].
- Other detected injuries.
- Operations in the first 48 hours.
- Revised Trauma Score (RTS) (28).
- Abbreviated Injury Scale (AIS) scores (until 2014, the 1995 version, update 1998 was used; as of 2015, the 2005 version, update 2008 was used across all trauma centers) (29).
- Injury Severity Score (30).

C. Outcome Data.

Outcome data are also mainly collected in the trauma centers, and long-term functional outcome data are obtained by a telephone interview with patients (or proxies in the case of persisting severe inabilities) who can be contacted by the data manager and who provide informed consent.

Primary outcome:
- Mortality at 30 days (binary outcome — dead versus alive at 30 days)

Secondary Outcomes:
- Survival time, mortality at discharge, at 6 months and at 1 year.
- Length of hospital stay.
- Length of intensive care unit stay.
- Days on mechanical ventilator.
- Any documented complications during hospital admission.
- Glasgow Outcome Scale (GOS) score at discharge (31).

- Extended Glasgow Outcome Scale (GOSE) score at 1 year (10–14 months) (32).

Statistical Considerations

A. Sample size, Power and Minimum Detectable Difference

The target for patient recruitment was set at 2500 patients. This sample size provides 80% power for a two-sided test to detect an absolute 5% reduction in mortality (primary outcome) for a given treatment or intervention, at a 0.05 alpha level, assuming a baseline mortality rate of 30%, and assuming an equal distribution of patients across two treatment groups. At this sample size, the expected number of deaths (625–750, assuming an overall mortality between 25 and 30%) is sufficient for liberal adjustments for potential confounding variables, without risking overfitting in multivariable regression analyses. As incomplete follow-up and missing data are inevitable in an observational study — and, as not all patients will be eligible for specific analyses (e.g., subanalyses on patients with actually confirmed severe TBI) — the actual minimum detectable difference can differ from 5%. For example, a sample size of 2000, 1500, or 1000 patients, respectively, provides 80% power to detect a 5.6%, 6.4% or 7.8% mortality reduction, respectively, and still provides ample opportunity to control for confounding.

B. Interim Analyses

No interim analyses have been planned a priori. However, data are regularly inspected and checked for the purpose of data quality monitoring and data cleaning, and a limited set of descriptive analyses are performed to inform collaborators and stakeholders on the study progress. In addition, medical students who assist in the entering of anonymized prehospital data into the database during a scientific internship are allowed to analyze parts of the data for their internship reports. Only testing of a-priori hypotheses, defined at the beginning of each internship in a formal proposal, are allowed, to avoid data dredging. None of these preliminary analyses (performed by the students themselves, therefore not always conforming to accepted statistical standards) has been or will be published or otherwise communicated to the public. Since these analyses are exclusively for training but not for inferential purposes, we are not planning to adjust subsequent inferential analyses for these preliminary analyses.

C. Statistical Analysis Plan

The distribution of continuous data is assessed by histograms, Q-Q plots, and Shapiro-Wilk tests. Descriptive statistics for demographic data, injury characteristics, treatments, as well as outcome data include means and standard deviations, medians and quartiles, or numbers and percentages as appropriate. Unadjusted two-sided between-group comparisons are performed by hypothesis tests such as Pearson's chi-square tests, Student's t-tests or analysis of variance (ANOVA), for binary and continuous outcomes, respectively. Multivariable regression models are used to obtain adjusted estimates of treatment effects of the factor under investigation (independent variable of main interest) and its statistical significance, while accounting for potential confounders (additional independent variables in the model) (33). For this purpose, Generalized Linear Models (GLM) and their extensions are used, with appropriate link functions depending on the distribution of the dependent variable of interest. For the primary outcome, a logit link function (logistic regression model) is used (33). Treatment effect estimates, such as mean differences or odds ratios, are reported including 95% confidence intervals (34).

DISCUSSION

We aim to implement a nationwide prospective database, including all patients in whom severe TBI is suspected in the prehospital setting. Inclusion of patients via the four national HEMS operators is the most feasible approach, as compared to inclusion at 25 regional ambulance services. Severe TBI is a primary deployment criterion for HEMS in the Netherlands, and so this approach should result in a high capture rate of patients with severe TBI. Nonetheless, a minority might be treated by Ambulance EMS only (e.g., scoop-and-run or unavailability of HEMS). Moreover, patients who do not appear severely injured in the prehospital setting may deteriorate in the hospital or turn out to be more severely injured than initially assumed (35). Such patients, despite having severe TBI, are not included using our approach. However, this was a deliberate choice as the study focusses on the prehospital treatment of those patients who are prehospitally assumed to have severe TBI.

Importantly, the research is subject to the inherent limitations of observational studies. Such studies generally only permit an analysis of the associations between factors of interest and outcomes, but do not support causal inferences. Nonetheless, in the absence of other high quality prehospital data, the observed confounder-adjusted associations may generate hypotheses on the optimal prehospital treatment of patients with suspected severe TBI.

To minimize selection bias, all consecutive patients who comply with the inclusion criteria are included. Information bias is minimized by the

prospective design and use of objective (e.g., blood pressure) and validated (e.g., AIS scores) data. However, in a dynamic prehospital setting where variables are repetitively observed or measured at varying intervals, standardization of measurement time points is difficult. In this study, vital parameters were routinely documented at three predetermined time points, with the possibility to add additional relevant vital parameters at other time points to document nadir values or vital parameters associated with specific events or interventions. However, measurement artifacts, oversight of brief events (e.g., brief hypotension after induction of anesthesia), deliberate nonreporting of complications, or documentation errors cannot be excluded and may bias the results.

Data cleaning techniques are used to identify implausible values for all variables in the database, which are subsequently cross checked against the original data sources by the data-manager. Implausible values that cannot be confirmed or corrected are set to missing. In particular, correct assessment of prehospital GCS scores play a pivotal role as they are, among other criteria, an inclusion criterion. HEMS physicians are competent to assess this score, which has been shown to provide excellent reliability (36). When it is not possible to perform an assessment, e.g., after induction of anesthesia, the relevant scores are routinely recorded as "not assessible" rather than assigning a score of 3. Nonetheless, we cannot exclude the possibility that GCS sores are occasionally inadvertently scored after sedative medication had been administered.

Data obtained in a physician-based HEMS environment in the Dutch setting may not necessarily readily generalize to paramedic-based systems or to countries with different demographic, geographic, or logistic characteristics (37). For all these reasons, reported results must be interpreted with care and should be confirmed in further studies.

SUMMARY AND CONCLUSIONS

Current prehospital treatment of patients with suspected severe TBI is based on marginal evidence, and optimal treatment is basically unknown. The BRAIN-PROTECT study provides the unique opportunity to evaluate and compare different treatment strategies with respect to patient outcomes. To our knowledge, this study project is the first large-scale prospective prehospital registry of patients with severe TBI that also collects long-term follow-up data, and may provide the best available evidence at this time to give useful insights on how prehospital care can be improved in the future.

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