Prospective Randomized Evaluation of Decompressive Ipsilateral Craniectomy for Traumatic Acute Epidural Hematoma (PREDICT-AEDH): study protocol for a randomized controlled trial

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Abstract

Background: Expeditiously surgical evacuation of acute epidural hematoma (AEDH) is an attainable gold standard and is often expected to have a good clinical outcome for patients with surgical indications. However, controversy exists on the optimal surgical treatment for AEDH, especially for patients with brain herniation. Neurosurgeons are confronted by the decision to evacuate the hematoma with decompressive craniectomy or craniotomy. Here, we present the protocol for a randomized controlled trial targeted at comparing the outcome and economic benefits of decompressive craniectomy versus craniotomy for the treatment of traumatic brain injury (TBI) patients with cerebral herniation undergoing evacuation of AEDH.

Methods/design: Patients of both genders, aged from 18 to 65 years, presenting to the emergency room with a clinical and radiological diagnosis of AEDH with herniation, comply with other inclusion and exclusion criteria are enrolled. Clinical information, including diagnosis of AEDH, clinical radiological information and treatment procedures, follow-up data of 1, 3 and 6 months post injury are collected on 120 eligible patients, randomized into groups of decompressive craniectomy versus craniotomy in a 1:1 ratio among 51 centers. The primary outcome is the Glasgow Outcome Score-Extended (GOSE) at 6 months post-injury. Secondary outcomes include incidence of post-operative cerebral infarction, incidence of additional craniocerebral surgery, and other evaluation indicator within 6 months post-injury.

Discussion: This study is expected to help neurosurgeons make a better decision to evacuate the epidural hematoma with or without a DC, especially for patients with brain herniation, and improve current situation of lack of general evidence.

Trial registration: Clinicaltrials.gov: NCT 04261673 (Registration date: 04 February 2020)

Background

Traumatic brain injury (TBI) remains one of the most challenging global public health care problems, and more than 50 million people suffer a TBI each year worldwide [1, 2]. As a common type of TBI, the incidence of epidural hematoma (EDH) among all TBI is reported to be in the range of approximately 2% – 4% [3–5], but account for a significant proportion of fatal head injuries with mortality rates ranging from 1.2 to 33%. EDH occurs more frequently in young people, with a mean age between 20 and 40 years. Elderly people rarely suffer from AEDH but have significantly higher mortality.

As the leading cause of TBI, vehicle-related accidents are also the most common cause of EDH, accounting for 53% (range, 30–86%) of all EDH. Other causes include falls, assaults, sports injuries, et al. have been shown in numerous studies.

Epidural hematoma is caused by bleeding between the skull and outer coverings of the brain, an accompanying raised intracranial pressure (ICP) will result in midline shift and direct or indirect compression of the brainstem, which is a potentially life-threatening problem and is badly need of a

neurosurgical emergency. Wide availability of CT examination makes the rapid diagnosis of EDH and monitoring EDH progression visible. Expeditiously surgical evacuation of EDH is an attainable gold standard and is often expected to have a good clinical outcome. Indeed, the treatable nature of EDH has led some authors to suggest that “toward zero mortality” is an achievable target with respect to this condition.

Ordinary treatment strategies principally aim to decrease ICP quickly and promote the repositioning from herniation, if concurrent [3]. The Brain Trauma Foundation (BTF) has produced informative guideline on the management of EDH but no specific surgical options [3]. Although craniotomy for acute EDH is conventionally employed in practice, some patients suffered from clinical deterioration after an initial hematoma evacuation craniotomy by secondary injuries, including fatal cerebral infarction (CI), especially in case combined with preoperative herniation. An initial hematoma evacuation with additional DC in these cases might effectively prevent and/or alleviate postoperative CI. However, relatively low incidence of postoperative CI caused by AEDH leads to less surgeon choose to remove the bone flap for the majority of patients with AEDH. In addition, lack of high-quality evidence leading to indefinite indications for adopting decompressive craniectomy in AEDH, results in broad practice variation between hospitals, countries and even between surgeons within a hospital. Other critical issues such as association between timing of surgery and outcome, and identification of subgroups that do not benefit from DC needs further investigation. So far, no specific evaluation of decompressive craniectomy for AEDH patients with herniation was investigated in prospective clinical trials.

Therefore, we present a randomized controlled trial of multicenter prospective interventional cohort study of surgical strategies for AEDH, which called Prospective Randomized Evaluation of Decompressive Ipsilateral Craniectomy for Traumatic Acute Epidural Hematoma (PREDICT-AEDH). The aim of this study is to compare the outcome and cost-effectiveness of decompressive craniectomy versus craniotomy for the treatment of TBI patients with cerebral herniation undergoing evacuation of an acute epidural hematoma.

Methods And Design

Study design

This is randomized, multicenter, clinical controlled, exploratory trial. Patients allocated to both craniotomy and decompressive craniectomy groups are followed for a total of 6 months. This multicenter design is essential to ensure the required number of patients with different surgical treatment strategies for AEDH with cerebral herniation from 51 hospitals. To fully reflect the population more objectively, recruitments of patients will conduct for 2 continuous years in all centers. Follow-up data and clinical information relating to the participants, including diagnosis of AEDH, clinical radiological information and treatment procedures, are collected in details, and the data are then analyzed statistically. A concise flow chart of the entire study is shown in Fig. 1. Time schedule of enrolment, interventions, assessments, and visits for participants are shown in Table 1.

Table 1
Time schedule of enrolment, interventions, assessments, and follow up for participants.

	Enrollment	Operation and treatment	Follow up			Adverse effects and other operation
Timepoints	Day 0	Day 0 to discharge At discharge	1 month post-injury	3 month post-injury	6 month post-injury	Within 6 month post-injury
Informed Consent	X					
Eligibility	X					
Information of enrollment	X					
Patient Information	X					
Medical history	X					
Randomization	X					
Surgery notes		X				X
Physical and neurological examination	X	X X	X	X	X	
Imaging	X	X X	X	X	X	X
ICP management		X				
GOSE		X X	X	X	X	
LOS		X X	X	X	X	
Treatment cost		X X	X	X	X	
MMSE			X	X	X	
EQ-5D-5L			X	X	X	

Participant selection

The study will recruit patients for two years between 1 September 2020 and 31 August 2022. The last half a year follow-up assessment will stop on 1 March 2023. Patients of both genders presenting to the emergency room of participating centers with a clinical and radiological diagnosis of AEDH are eligible for inclusion. Only patients who has an eligibility determined by participating senior neurosurgeon of the center can be recruited in the trial.

Inclusion Criteria:

- Aged from 18 to 65 years (18 and 65 are included);
- With informed consent;
- Clear medical history of traumatic brain injury;
- Within 12 hours after injury;
- Supratentorial acute epidural hematoma on CT scan with midline shift, which is the leading cause of operation, despite associated other lighter intracranial injury (e.g., subarachnoid hemorrhage and contusion);
- The admitting neurosurgeon considers that the epidural hematoma needs to be evacuated with a craniotomy or decompressive craniectomy.
- Unilateral mydriasis or bilateral mydriasis before the operation.

Exclusion Criteria:

- Previous intracranial surgery prior to trauma;
- Patients with a score of 3 on the GCS, with bilateral fixed and dilated pupils, bleeding diathesis or defective coagulation, or other injuries that were deemed to be unsurvivable;
- Patients who had injury of the oculomotor nerve;
- Patients are considered to be operated mainly by following pathological change on CT: subdural hematoma, intracerebral hemorrhage, large size infarction, et al., but not because of epidural hematoma;
- Severe pre-existing disability or severe co-morbidity which would lead to a poor outcome even if the patient is supposed to a good recovery from the TBI;
- Pregnant female.

Sample size calculation, Randomization and allocation

Previous retrospective study and our data reported that patients who received a synchronous decompressive craniectomy had a GOSE of 6.63 ± 1.27, which was better than patients received craniotomy with a GOSE of 5.78 ± 1.58.[6] We calculate a sample required in this clinical trial with a significance level of 5% (two-sided) and a power of 80% to demonstrate a 20% difference, in a 1:1 randomization ratio basis, with an assumption that 10% of the patients would be lost during follow-up. Ultimately, considering the quality of the study, the sample size is enlarged to 120.

Patients fulfil all the eligibility criteria and provide written informed consent are randomly allocated to groups of craniotomy or decompressive craniectomy by the central randomization management information systems, a 24-hour central web-based software designed by Clinical Research Institute, Shanghai Jiao Tong University School of Medicine. Investigators of different centers will record clinical information of patients, and generate subject identification number of eligible study patients. At the same time, central randomization management can assure concealment of the allocation list and information of patients.

In consideration to patients' conditions deteriorate which have to adopt decompressive craniectomy as lifesaving action, patients who is randomly allocated to craniotomy group but receive decompressive craniectomy finally during the operation will be rejected in this trial. And detailed data of these patients will be recorded as information of observation study, but eliminated in our randomized controlled trial.

Since the intervention is surgical procedure and decompressive craniectomy will result in skull defect, patients and investigators cannot be blinded for allocation. Assessors involved in this study and investigators who are responsible for the analysis of outcomes are blinded for the treatment groups.

Treatment Interventions

The randomization process allocates eligible patients to either one of two surgical treatment groups. Surgical strategies according to guidelines for the surgical management of AEDH consists of evacuation of the hematoma with a craniotomy, or with additional decompressive craniectomy, defined as hematoma evacuation with leaving a large bone flap [3, 7]. However, the bone flap must be replaced and fixed with fixation system (plates and screws) for patients received a craniotomy. All treatments for surgical management of AEDH are essential to be consistent for two groups, including preoperative preparation and anesthesia, except for removal or replacement of bone flap. Above surgical techniques have been well established and unification with a standardized surgical treatment is the essential aim. The operation will be performed by qualified senior neurosurgeons with sufficient surgical skills of each participating centers.

Normal management process and medical decision of subjects will not be affected by recruiting into the PREDICT study. All patients received the postoperative care management according to guidelines and intensive care protocols, and examination e.g., radiographic or biochemical examination is proceeded generally according to management protocol. Normally, cranioplasty is recommended to reconstruct the skull for patients who adopted DC. Treatment for complications will differ considerably between patients, e.g., epilepsy or cerebral infarction and late complications e.g., hydrocephalus will accept appropriate treatment according to patients' clinical characteristics.

Aims and Outcomes

The aims of the trial are to evaluate the surgical treatments for AEDH from views of efficacy, economic benefits and complications between craniotomy and decompressive craniectomy. The endpoints have been divided into primary and secondary endpoints. Primary endpoint is the Glasgow Outcome Score-

Extended (GOSE) at 6 months post-injury, the most commonly used prognostic evaluation scale in TBI, which is indicated by the long-term functional outcomes, including overall mortality and morbidity rates [8, 9]. Additional, following secondary endpoints are intended to be investigate as supplementary of functional and cognitive measures:

(1) The incidence of post-operative cerebral infarction within 6 months post-injury, which was primarily diagnosed by independent radiologists with CT or MRI examination;

(2) The incidence of additional craniocerebral surgery, as a result of clinical deterioration after initial surgical treatment of AEDH, within 6 months post-injury;

(3) The incidence of serious adverse events (SAE) within 6 months post-injury, and SAE is defined as an untoward occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is otherwise considered medically significant by the investigator.

(4) The length of patient's stay in ICU and hospital after initial surgery within 6 months post-injury.

(5) Detailed economic evaluation, as the total medical expense related to treatment of AEDH, including the costs of operations, hospitalization and rehabilitation within 6 months post-injury.

(6) Quality of life at 6 months post-injury with the score of 5-level EuroQol five dimensions questionnaire (EQ-5D-5L). The EQ-5D is a generic instrument for describing and valuing health which comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

(7) MMSE (mini-mental state examination) scores at 6 months post-injury.

Data collection

Once patients are enrolled in the study, data relating to demographic and clinical information including hospital admission, treatment process and follow-up will be collected by the local investigators and recorded on the CRF. Detailed data consist of neurological condition, timing of injury (also the ER, initial CT and surgical operation), radiographic abnormalities, operation data, postoperative care management (including ICP management and pharmacological data). Post-operative CT scan is performed routinely on the 1st, 3rd and 7th day post initial surgery. Cerebral infarction is initially detected on post-operative CT image depicting a low-dense area and the blood supply of involved lobes are further detected by transcranial doppler sonography (TCD) and/or MRI, related radiographic data and neurological condition will be recorded, and cerebral infarction is primarily diagnosed by independent radiologists with CT or MRI examination. Follow-up visits in the outpatient department are scheduled at 1, 3 and 6 months after

injury, data will be collected and recorded. Information recorded on CRFs will entered into an electronic data collection (EDC) database by a designated person at each participating center, EDC are developed and maintained by investigator independent of study in the Clinical Research Institute, Shanghai Jiaotong University School of Medicine.

Data management

All Investigators participating this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information. Access to collated participant data will be restricted to approved individuals involved in treating process and representatives of regulatory authorities. Computers used to input the data will set up user names and passwords with limited-access measures. Published results will not contain any personal data that could allow identification of individual participants.

All data will be collected and recorded using CRFs and the EDC, a data management committee (DMC, located at Clinical Research Institute, Shanghai Jiaotong University School of Medicine) is established to supervise data and established clinical research associate (CRA) will regularly visit each participating center to ensure that all contents of the research program are strictly followed. If not, the CRA promptly submits information to the investigators. Throughout the project process, a research summary conference will be held every 6 months to discuss progress and arise problems' solutions. All study documents will be kept for a minimum of 5 years, and documents will not be destroyed without permission from the sponsor when the minimum retention period has elapsed.

Data analysis

Patient characteristics and variation in both treatment and outcome variation will be described using descriptive statistics. Continuous variables were described as mean and standard deviation (SD) or as median and interquartile range (IQR). To assess differences between cohorts, appropriate tests will be employed according to distribution and scale of measurement. Student's t-tests or Mann-Whitney U tests are used for continuous variables, X^2 tests or Fisher's exact test are used for categorical variables. The analyses for better characterization of AEDH will be exploratory, aiming to better understand the complexity of the disease and to discover new associations. In addition to standard statistical descriptive, multivariable regression models or other analyses maybe used as appropriate. $P < 0.05$ will be considered to indicate statistical significance.

Ethics and dissemination

The study protocol has been approved firstly by ethics committee and institutional review board of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (KY2020-038), research sponsored center. Other participating centers are accessed separately from each ethics committees or institutional review boards. During the process, the study investigators will strictly follow the Declaration of Helsinki and Human Biomedical Research Ethical Issues. Any modifications of protocol will be firstly submitted to the review board that might approve it before putting into practice. The normal management process and

medical treatment of enrolled participants will not be affected by recruited into the PREDICT study. Besides, if suppose participant dies or serious adverse events occur, detailed record will be reported to ethics committee and institutional review board of sponsored center or participating centers and be investigated.

All enrolled participants are asked to provide a signed informed consent to produce documentary evidence that they have received enough information about the clinical trial, the study interventions, participants' rights, and voluntary wishes of participation.
Meanwhile, participants are also informed that they could withdraw consent and quit at any moment during the course of trial, without affecting their treatment process, only by communicating this decision with investigators firstly.
All patients or the public were not directly involved in the design or conduct of the study. The patient and their caregivers will be told that this study will take about 4 years to complete and the developments of the study will be informed. The results of trial will be disseminated through academic conferences, and published in peer-reviewed journals. After the results of the study are published, investigators will inform patient and their caregivers by telephone or e-mail immediately.

Discussion

To the best of our knowledge, this study will be the first randomized controlled trial designed to evaluate the benefit of DC on traumatic AEDH patients with brain herniation [10, 11]. Specifically, two different treatment methods, decompressive craniectomy and craniotomy, with remarkable difference of leaving a large bone flap or not, are compared. Result of study will be helpful for further clarifying indications of decompressive craniectomy and surgical planning decision-making in management of AEDH.

There is controversy with regard to the initial neurosurgical management of AEDH [4, 12, 13]. Neurosurgeons are confronted by the decision to evacuate the hematoma with or without a DC in some cases, especially for patients with brain herniation [6, 14]. The BTF recommends that all patients with an EDH volume of greater than 30 cm^3 should undergo surgical evacuation of hematoma regardless of Glasgow Coma Scale [3]. Although no sufficient data support certain surgical treatment method, craniotomy provides a more complete evacuation of the hematoma [3]. However, there is a set of patients who experience clinical deterioration after an initial hematoma-evacuation craniotomy, as a results of secondary brain injuries with increased ICP [10, 15–18]. Additional, incidence of post-traumatic cerebral infarction secondary to AEDH was reported to 18.2%, which was even higher among patients with high risk factors e.g., transtemporal location, preoperative shock for longer than 30 min, bilateral mydriasis, preoperative brain herniation and so on [3, 6, 19]. While decompressive craniectomy has shown potential in controlling raised ICP, and which is recommended as soon as possible in case of serious post-traumatic cerebral infarction secondary to AEDH [6, 10, 15, 17–19]. DC seems to be a better surgical management of AEDH in some cases. However, previous clinical practice indicates the removal of the bone flap is not always essential in many patients with EDH [5, 20]. DC performed inappropriately with initial hematoma-evacuation might lead to unavoidable complications, such as abnormal

hemodynamics, subsequent cerebral necrosis and infarction as well as a need for cranioplasty [15, 21]. Inappropriate management with undefined surgical indications can lead to unnecessary death and disability, which may against possibly achievable target of “toward zero mortality” in management of AEDH. Although there is no consensus on if and when to proceed with the decompressive craniectomy in management of AEDH with brain herniation, also the specific surgical techniques, concerns regarding the application of decompressive craniectomy deserves more investigation, such as proposals for randomized controlled trials [10].

China is a large country with a wide population distribution, widespread primary hospitals remain the main battleground of TBI, peculiarly in management of AEDH, with characteristics of relatively high incidence and likely rapid deterioration. Fast accurate diagnosis, correct and effective management of AEDH is principal for medical workers of primary hospitals. Therefore, there is a clinical rationale to investigating DC in management of AEDH in current surgical practice patterns, and to improve current situation of lack of general evidence. This study is expected to help neurosurgeons make a better decision to evacuate the epidural hematoma with or without a DC, especially for patients with brain herniation, and will provide a strong level of evidence for surgical management of AEDH.

Trial status

Recruitment started in September 2020 and is planned to end in October 2023, with 120 patients randomized. Fellow-up will finish in May 2024. The current protocol version is 1.0, dated 8 February 2021.

List Of Abbreviations

AEDH: Acute epidural hematoma; TBI: Traumatic brain injury; GOSE: Glasgow Outcome Score-Extended; DC: Decompressive craniectomy; RCT: Randomized controlled trial; EDH: Epidural hematoma; ICP: Intracranial pressure; BTF: Brain Trauma Foundation; CI: Cerebral infarction; SAE: Serious adverse events; EQ-5D: EuroQol five dimensions questionnaire; MMSE: Mini-mental state examination; ER: Emergency room; TCD: Transcranial doppler sonography; EDC: Electronic data collection; DMC: Data management committee; SD: Standard deviation; IQR: Interquartile range;

Declarations

Ethics approval and consent to participate

The study protocol has been approved firstly by ethics committee and institutional review board of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (KY2020-038). All enrolled participants will provide signed informed consent.

Consent for publication

This manuscript does not contain individual personal data from patients.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CY: Protocol development. XJH: Protocol development, trial coordination. JFF: Proposal and protocol development. LX: Protocol development and trial coordination. JYH: Protocol development and acquiring of data. WPL: Proposal and trial coordination. JYJ: Principal Investigator. All authors read and approved the final manuscript.

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Figures

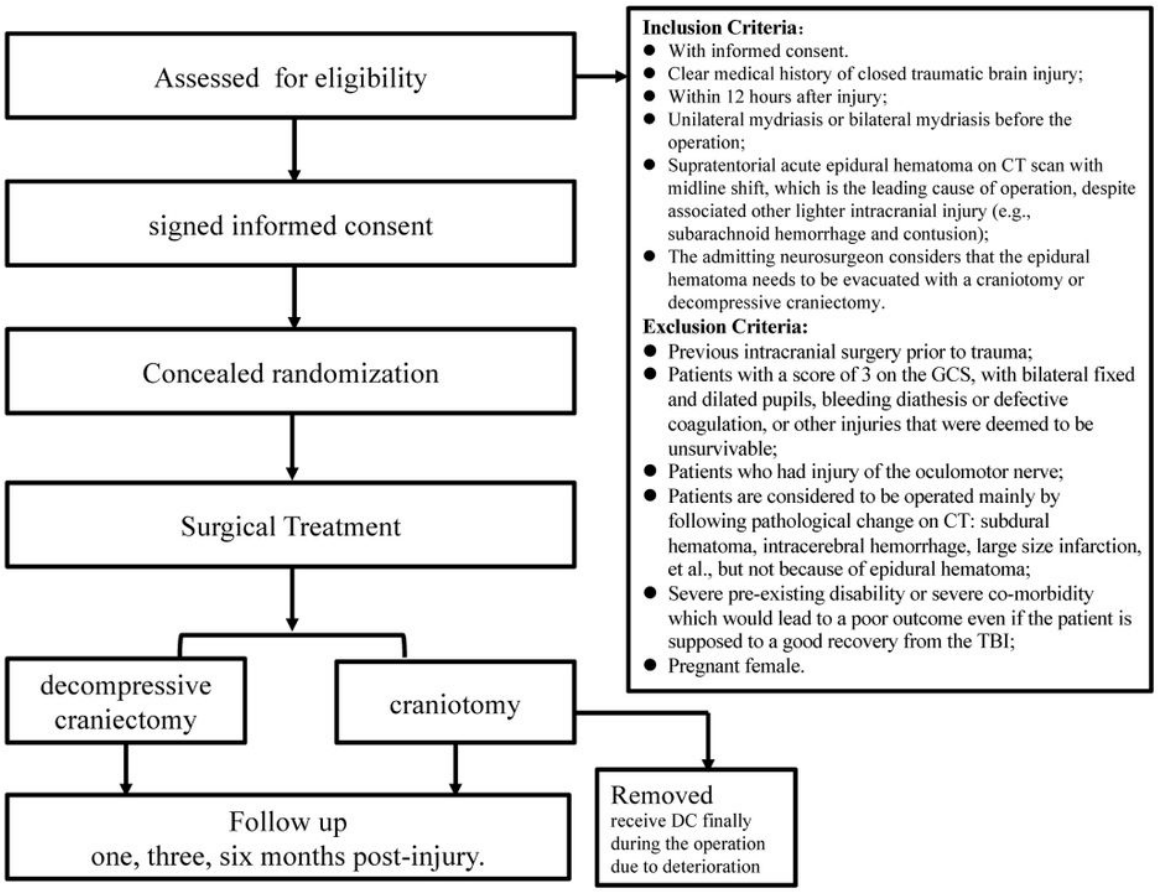

Figure 1

Study flow chart

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