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Evaluation of titanium mesh cranioplasty and polyetheretherketone cranioplasty: protocol for a multicentre, assessor-blinded, randomised controlled trial

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ABSTRACT

Introduction Cranioplasty is a common surgery in neurosurgery department. However, restoring the integrity of skull brings many challenges to surgeons, and the selection of ideal implant materials is throughout the history of cranioplasty. Although titanium mesh was still preferred by many neurosurgeons in cranial reconstruction, the new polyetheretherketone (PEEK) material, for example, is gaining popularity for craniofacial reconstruction today. There remain limited data that compare the outcome of PEEK cranioplasty and titanium mesh cranioplasty. It is necessary to conduct a study to compare outcome of different materials for cranioplasty.

Methods/design In this multicentre, assessor-blinded, randomised controlled study, we will randomise 140 patients in a 1:1 ratio to PEEK cranioplasty versus titanium cranioplasty. Eligible patients are adults who were diagnosed with cranial defect (due to severe traumatic brain injury, ischaemic stroke, haemorrhagic stroke, infiltrative tumour and so on), the defect size is over 25 cm^2, and they need to agree to participate in this trial. Instead of standard examinations, the enrolled patients receive neurological, motor, cognitive function and cerebral hemodynamics examinations as well as cosmetic evaluation. The procedures are repeated 3, 6 months after cranioplasty. The primary outcome, defined as infection or implant exposure after surgery, is the implant failure rate within 6 months. Secondary outcomes include postoperative complication rates, neurological outcomes, motor function, cerebral hemodynamics, cosmetic outcome and the total cost over a 6-month period.

Ethics and dissemination This trial protocol has been approved by Biomedical Research Ethics Committee of West China Hospital of Sichuan University. All patients will be fully informed the implant materials, potential complications after surgery, responsibilities during the trial, and they will sign the informed consent before joining in this trial. If the patient's cognitive function is impaired, the patient's next of kin would be carefully informed. The results will be disseminated through academic conferences, student theses and will be published in a peer-reviewed journal.

Trail registration number ChiCTR1900024625; Pre-results.

Strengths and limitations of this study

- This will be the first multicentre, randomised controlled study that assesses the long-term outcome of titanium mesh cranioplasty and polyetheretherketone cranioplasty.
- This study will help neurosurgeons choose alloplastic material especially for those patients who suffer bone resorption with autologous bone cranioplasty and require reoperation.
- Complications following cranioplasty and the relationship to timing will be detected in the study.
- Subgaleal effusion following cranioplasty, less studied in similar research, will also be investigated.
- Different medical conditions and surgeons' experiences are limitations of this study, however, personnel will be trained centrally in advance and reach uniform standard.

INTRODUCTION

Cranioplasty, dating back to 7000 BC, offers protective barrier and cosmesis benefits for patients with cranial defects following cranial surgery while relating to neurological and cognitive improvement.[1–3] Over the past half century, neurosurgical and emergency care increasingly improved, and this procedure has become a routine surgery in neurosurgery department.[4 5] However, reconstructing the cranial defect brings many challenges to surgeons, and search for ideal materials is throughout the development of reconstructive procedures.[6–9]

Ideally, the implant material should be durable, biocompatible, widely available and with low incidence of infection. Several options, ranging from autologous bone, metals, acrylics and plastic, have been used in reconstruction and reported with different success rates.[9 10] Given the low costs and the biocompatibility, autologous bone

grafts are traditionally regarded as the gold standard in cranial reconstruction. The most common complication following autologous bone transplant is bone flap resorption, which results in unsatisfactory appearance and in some cases, necessitating reoperation and replacement with alloplastic materials.[11 12] Therefore, the necessity to explore the optimal alloplastic materials for cranial reconstruction was the impetus for this study.

Nowadays, various synthetic materials have been used in cranioplasty. Polymethylmethacrylate was one of the early chosen material used for cranioplasty.[13] It is strong, heat resistant, radiolucent and inert, but the exothermic reaction may also lead to injuries to soft tissues around it.[14] Other common materials conclude hydroxyapatite and calcium phosphate, and both have positive and negative characteristics.[9 15]

More recently, titanium mesh was a popular material used in cranial reconstruction because it has good biocompatibility, low infection rate, good mechanical strength and low cost. In addition, computed-assisted three-dimensional (3D) modelling was used in titanium mesh design that results in excellent cosmesis.[16] The titanium mesh implant, however, is associated with allergic reaction, and the erosion of overlying soft tissue with incidence of implant exposure is another complication.[17 18] Besides, the titanium mesh could conduct temperature which results in scalp paresthesia.

New material such as polyetheretherketone (PEEK) implants are gaining popularity for craniofacial reconstruction today because it has proven to have advantages in a number of settings such as radiolucent, chemical inert, stiffness and sterilisations with various methods. In addition, the PEEK implants could be designed specific to patients' defect cranial with computer-assisted 3D printing technology and could also be used in complex craniofacial reconstruction.[19 20] However, the high cost of PEEK implants may place an excessive economic burden on patients and epidural effusion after cranioplasty trouble many surgeons, and some surgeons speculate that the effusion was because of allergic reactions.[21]

Despite the increasing popularity of PEEK, there is a paucity of researches comparing the outcomes of titanium mesh and PEEK cranioplasties. Therefore, the aim of this study was to compare long-term implant failure rate and aesthetic outcomes, neurological outcomes and postoperative complications rate of primary PEEK cranioplasty versus primary titanium mesh cranioplasty.

OBJECTIVE

The primary objective is to compare implant failure rates (defined as implant exposure or infection requiring removal of the synthetic material) at any time within 6 months in patients with cranioplasty. The secondary outcome evaluations include the following indications: (1) complications rates and the relationship to the timing, (2) neurological and cognitive outcome, (3) motor function, (4) cerebral hemodynamics changes and (5) cosmetic outcome.

DESIGN

The PEEK cranioplasty and titanium mesh cranioplasty (PTCP) is a multicentre, prospective, assessor-blinded, randomised controlled clinical trial from December 2019 through June 2021. The treatment schedule and flow chart of this study are shown in figure 1. A total of 15 centres from around China are included in this trial. Personnel of other centres are experienced neurosurgeons who are skilled in both neurosurgery and cranioplasty, and these centres demonstrate to have previous trial experience with high rates of follow-up. Besides, the personnel involved in this study will be trained centrally in the study requirements, surgical strategies of covered cranioplasty and embedded cranioplasty[22] and standardised measurement of neurological, motor, cognitive function as well as assessment of brain hemodynamics, resulting the information from study participants in a uniform manner. All participating hospital sites receive local ethics committee approval or obey our ethics committee review decision.

RECRUITMENT AND ELIGIBILITY

Two recruitment strategies are included in this trial. First, participants are recruited on outpatient department. Second, after reviewing patient database, those who receive craniectomy will be informed for subsequent visits. Recruitment will begin on December 2019. Each subject will receive financial compensation.

Inclusion criteria

1. Patients aged over 18 years, either sex.
2. Diagnosed with cranial defect (due to severe traumatic brain injury, ischaemic stroke, haemorrhagic stroke, infiltrative tumour and so on).
3. The defect size is over 25 cm^2.
4. Agree to participate in this clinical trial, and the informed consent was signed by patients or next of kin on behalf of the patient.

Exclusion criteria

1. Bilateral cranial defect.
2. Active smoking.
3. Diagnosed with diabetes or coronary heart disease.
4. With a history of radiation therapy.
5. With hydrocephalus or bypass surgery has been performed.
6. Previous scalp free tissue transfer.
7. A documented allergy to titanium.
8. Non-initial cranioplasty surgery.
9. With uncontrolled intracranial infection.
10. With intracranial hematoma.
11. With unhealed scalp.
12. With operative contraindications and not suitable for surgery (eg, pulmonary infection, poor general condition).

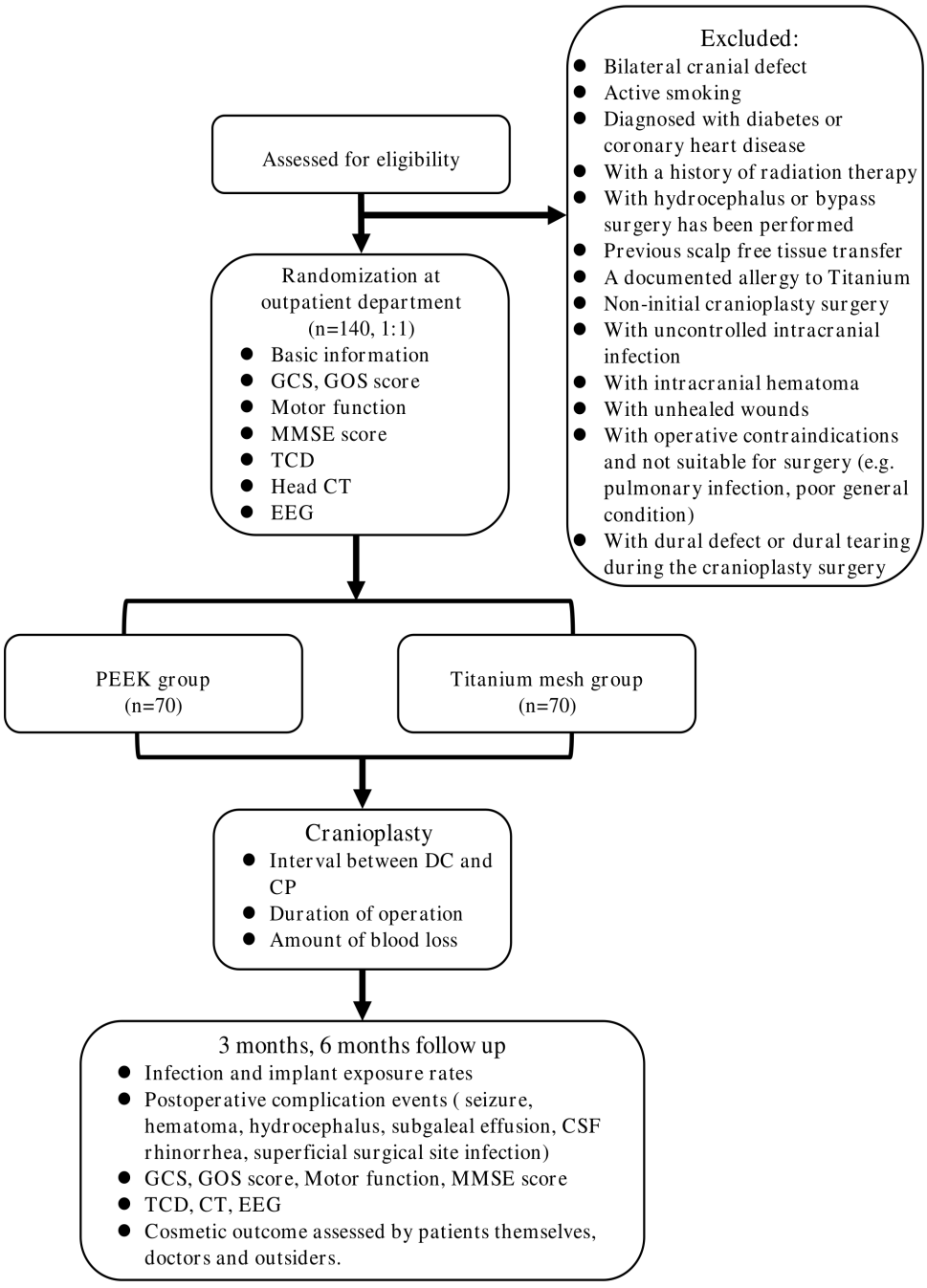

Figure 1 Flow chart of the participants (procedure) through the trial. EEG, electroencephalography; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; MMSE, Mini-Mental State Examination; PEEK, polyetheretherketone; TCD, transcranial Doppler sonography, DC, decompressive craniectomy; CP, cranioplasty; CSF, cerebrospinal fluid

13. With dural defect or dural tearing during the cranioplasty procedure.

SAMPLE SIZE

Previous studies reported that over 25% of patients had implant failure of the titanium cranioplasty, compared with a less than 10% implant failure rate of using PEEK cranioplasty.[22–24] We calculate that a sample of 120 will be required in this clinical trial with a significance level of 5% (two-sided) and a power of 80% to demonstrate a 20% difference in rates of satisfactory outcome due to implant failure. Considering the quality of the study, the sample size is enlarged to 140.

RANDOMISATION AND BLINDING

After patients give consent for participation and meet eligibility, patients will be randomised. They will be randomly allocated to PEEK cranioplasty group and titanium mesh cranioplasty group by the method of simple randomisation using randomisation software. It is impossible to blind the participant or the surgeons because

the implanted materials are clearly indentified.Therefore, patients will be informed what materials they are allocated. iIn order to ensure the quality of the study, blinding will be ensured for the assessors involved in this study, and they will not contact researcher who conducts the randomisation process.

INTERVENTION

After eligible patients are recruited in the study, the investigators will collect basic information of patients, and the informed consent will be signed. The patients will receive the surgery based on the randomisation result. Our previous study showed the surgical strategies, and personnel involved in this trial will be trained centrally to achieve unification.[22]

Manufacture of custom-made titanium and PEEK cranioplasties

With high-resolution CT scan of patients' head and computer-assisted techniques, the virtual 3D model of the skull was generated, and the titanium mesh and PEEK cranioplasties were both designed individually for every patient, which could restore structural integrity and achieve bone symmetric. Titanium meshes were generated by compression into a mould, cutting to shape with a thickness from 0.6 to 1.0 mm, while the PEEK implants were fabricated using 3D print technology in line with the model. Therefore, the range of titanium mesh is usually a bit larger than that of the cranial defect and the PEEK implant could be perfectly matched to the cranial defect.

Surgical procedure

This is a multicentre study so the personnel will be trained centrally in order to reach a standard surgical uniform. If the patient shows cerebral swelling, lumbar cistern drainage was performed until the swelling subsided, and the patient was stable. The patient's hair was completely shaved, and care was taken not to damage the scalp. Following anaesthesia, the scalp was vigorously washed and the skin preparation was applied. Care needs to be taken to avoid contamination during skin preparation. After preparation, the scalp was dissected and reflected using scissors, during the process dural tearing should be avoided to prevent postoperative CSF leakage, and bleeding on the scalp or dura was controlled by bipolar coagulator. Hydrogen peroxide was also used to wash the scalp and the dura to minimise bleeding and contamination. Next, margin of skull defect was debrided. Considering the shape of titanium mesh implant, the exposed area was 0.5–1.0 cm larger than the size of cranial defect to accommodate the required implant. Then, we use scissors to cautiously dissect the temporalis muscle and manage the muscle according to our experience.

The custom-made implant was then placed, and appropriate adjustment was made to ensure precise position intraoperatively. After dural suspension, the titanium or PEEK material was anchored using screws, then the wound drain was positioned for drainage of blood above the implant material. The galeal layer and the skin were closed respectively with sutures. The drain was left for about 3 days after cranioplasty and removed when the drainage was low.

OUTCOMES

Primary outcome

The primary outcome of this clinical study is the implant failure rate within 6 months. The implant failure was defined as infection or implant exposure after cranioplasty that removal of the implant was necessary.

Secondary outcome

The secondary outcomes include the following:

1. Complication events occurring at any time within 6 months after cranioplasty. These complications refer to postoperative new seizures, postoperative hematoma developed in the epidural or subdural space, postoperative hydrocephalus, cerebrospinal fluid rhinorrhea, subgaleal effusion and superficial surgical site infection that could be treated conservatively.
2. Neurological outcome will be assessed using Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS) scores, while the Mini-Mental State examination (MMSE) was used for cognitive evaluation. The assessment process was performed prior to surgery and 3, 6 months after surgery.
3. Motor function was evaluated using Oxford grading system, which comprises 6 grades, from 0 (no contraction) to 5 (full resistance). It was assessed before admission and 3, 6 months follow-up visits.
4. Cerebral hemodynamics was measured by transcranial Doppler sonography (TCDS) prior to and 3, 6 months after cranioplasty. Because TCDS suffers from variability in assessment between the clinicians, the involved clinicians in each centre would be trained centrally and provided uniform assessment standard.
5. Cosmetic outcome was assessed by the patients themselves and the neurosurgeon. The degree of temporal hollowing was the major concern.
6. Total costs refer to surgery expenses over a 6-month period.

DATA COLLECTION

After the patient was enrolled in the study, experienced staff at each participating centre will collect their basic data, neurological function evaluation, cognitive assessment, cerebral hemodynamics and imaging for baseline information. The follow-up data will be collected and recorded 3 months and 6 months after cranioplasty. The data collection form and the plan are shown in table 1.

Their family members will help them if they have difficulties in completing the evaluation. Data will be paper-based acquired, and the data will be anonymised by each centre. Then the data will be transferred to the assessors

Table 1 Study schedule

	Baseline	3 months	6 months
Infection/Implant exposure		√	√
Complication events		√	√
GCS	√	√	√
GOS	√	√	√
MMSE	√	√	√
Motor function	√	√	√
TCD	√	√	√
CT imaging	√	√	√
EEG	√	√	√
Cosmetic outcome	√	√	√

EEG, electroencephalography; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; MMSE, Mini-Mental State Examination; TCD, transcranial Doppler sonography.

and transmitted into the electronic database. Any adverse events occurring during the study period are documented. All the data will be recorded in the data collection form in time.

DATA AND SAFETY MONITORING

An independent data monitoring committee (DMC) will periodically monitor the safety and efficacy of this trial and identify if there is a need to make adjustments. The DMC consists of neurosurgeons, neurologists, statisticians and data analysts. Members of the DMC will assess the trial once a year to review the study data.

STATISTICAL ANALYSIS

All statistical analysis was performed using statistical software SPSS V.22 and p values<0.05 was considered to have statistical difference. Continuous variables following normal and non-normal distribution were described as arithmetic mean±SD and median (range), respectively, while median (range) was implemented to describe categorical variables.

The primary outcome of implant failure rate will be analysed by χ^2 test, so will the secondary outcome of complication rates. t-Test was used to analyse continuous parameters and if the distribution did not follow t-test applicability, a non-parameter test, such as Mann-Whitney U test, was implemented. Subgroup analysis stratified by age, with/without subgaleal effusion, location of cranioplasty, cerebral hemodynamics and neurological function is pre-planned, and regression methods will be used.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

No patient or public was involved in the design, recruitment or conduct of this research. Participants will be informed that they could contact us if they have emotional needs. Following completion of the trial, a journal manuscript will be prepared to provide feedback on the research results.

ETHICS AND DISSEMINATION

All patients will be fully informed the implant materials, potential complications after surgery, responsibilities during the trial, and they will sign the informed consent before joining in this trial. If the patient's cognitive function is impaired, the patient's next of kin would be carefully informed. Possible adverse events include infection, implant exposure, postoperative seizures, postoperative hydrocephalus, intracranial hematoma and subgaleal effusion. These are common complications after cranioplasty. All the reported complications are documented.

The results will be disseminated through academic conferences, student theses and will be published in a peer-reviewed journal.

DISCUSSION

Cranioplasty is a common surgical procedure performed with either autologous bone or implanted materials. The most commonly used alloplastic material for reconstruction has been titanium mesh. However, a number of studies have demonstrated that the use of titanium mesh is along with high rates of complications. An increasingly popular material was the PEEK, it has proven to have advantages over the titanium mesh. Search for ideal materials is throughout the development of reconstructive procedures, but the data were severely limited due to paucity of high-quality studies. The PTCP is the first multicentre, randomised controlled study to provide robust evidence by assessing the implant failure rate, complication rates and neurological improvement of different implant materials for cranioplasty. The primary outcome is implant failure rate at any time within 6 months. The secondary outcomes include complication rates and neurological improvements. This study will help neurosurgeons choose a better cranioplasty material especially for those patients who suffer bone resorption with autologous bone cranioplasty and require reoperation. A wide range of complications following cranioplasty and the relationship to timing will also be detected in this multicentre study. Subgaleal effusion was a common but less studied complication in similar publications. We will investigate the underlying mechanism and do further management. One limitations of this study are the medical conditions and surgeons' experiences which vary from centre to centre, however, personnel will be trained centrally in order to reach uniform standard.

Contributors JG conceived of the original idea for the trial, has been part of the trial design and protocol writing, edited the paper and were overall guarantors. JY obtained ethical approval and has been part of the trial design as well as drafted the protocol. TS, YY, XL and HY have contributed to the study design, interpretation of the results and commented the paper. All authors approved the final manuscript.

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Disclaimer Funding for this trial covers meetings and central organisational costs as well as a certain amount of economic compensation for patients. These funding sources have no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Competing interests For the purposes of conducting this clinical trial, Dr Junwen Guan reports three grants from Johnson (Shanghai) Medical Equipment Co., Ltd, Kontour (Xi'an) Medical Technology Co., Ltd and Medprin Regenerative Medical Technologies Co., Ltd.

Patient consent for publication Not required.

Ethics approval This study has been approved by Biomedical Research Ethics Committee of West China Hospital of Sichuan University and the review boards of other trial centres (No. 2019-384). Also, this study has been registered at the Chinese Clinical Trial Registry (ChiCTR1900024625).

Provenance and peer review Not commissioned; externally peer reviewed.

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