

Study Design

Cognitive rehabilitation after traumatic brain injury: study protocol for a randomized, sham controlled, multicenter trial

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Abstract

Background and Aim: According to the World Health Organization, 10 million people are affected annually by traumatic brain injury (TBI), worldwide. It is a major cause of disability, being cognitive impairment the main issue that compromises quality of life. Phase II, open label studies suggested that cognitive rehabilitation therapy (CRT) might help improving cognitive performance in military personnel after TBI. However, there is no evidence that these effects are not due to placebo effect or to natural history of the disease and that are not limited to that specific population. Our proposed study will test the hypothesis that CRT improves cognitive performance of adult patients with TBI compared to a sham intervention.

Methods: This will be a randomized, sham-controlled, single-blinded with a third blinded rater, multicenter trial involving eight tertiary care hospitals in Brazil, Colombia, Germany and USA. In total, 160 patients will be stratified by TBI severity and country and randomized with concealed allocation to receive: 1) standard rehabilitation therapies + CRT or 2) standard rehabilitation therapies + sham intervention. The primary outcome is the difference in cognitive improvement compared to baseline, measured by Wechsler Memory Scale (WMS) at 12 months. The main secondary outcome is patients' performance in Wisconsin Card Sorting Test (WCST), and Benton Visual Retention Test (BVRT) at 12 months. Other outcomes are: performance on the same tests at 6, 18 and 24 months, return to prior activity in 24 months, well-being according to WHO-5 score and functional status according to SF-36 at 12 and 24 months.

Conclusion: Cognitive impairment after TBI is a major cause of disability and requires specific rehabilitation. Currently, there are no published randomized clinical trials, with a blinding strategy, to establish the efficacy of CRT compared to a sham intervention in the recovery of TBI patients.

Key-Words: Traumatic brain injury, cognitive rehabilitation therapy, adults, cognitive scales, well-being, functional status, study protocol, study design.

Trial registration: This trial will be registered at www.clinicaltrials.gov

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Aims of the study

In this trial we will evaluate adult patients who have suffered an acute traumatic brain injury (TBI) within the last 3 months, and have a documented cognitive deficit. We will compare the effect of standard therapy plus CRT versus standard therapy plus a sham intervention on patients' cognitive improvement up to one year after recruitment. Cognitive status will be measured by application of three neurocognitive scales (Wechsler Memory Scale IV, Wisconsin Card Sorting Test and Benton Visual Retention Test).

The study will test the primary hypothesis that CRT improves cognitive performance of adult patients with TBI compared to a sham intervention, measured by performance in WMS IV cognitive test as the main outcome. Secondary outcomes will include performance at the other two scales (WCST and BVRT) at 12 months. Since cognitive deficit after TBI may compromise different aspects of functioning and quality of life that might change with time, we will assess other outcomes such as: performance on the three tests (WMS IV, WCST and BVRT) at 6, 18 and 24 months, return to prior activity in 24 months, well-being according to WHO-5 score and functional status according to SF-36 at 12 and 24 months.

Methods

Study design

We will conduct a randomized, sham-controlled, single-blinded with a third blinded rater, multicenter trial involving eight tertiary care hospitals in Brazil, Colombia, Germany and USA to assess whether CRT is superior to sham interventions in improving cognitive performance in patients with TBI and cognitive deficit in a period of 12 months.

Eligibility

Our study population will comprise of both male and female adult patients aged between 18 to 59 years. We have excluded pediatric patients and those aged 60 years or more because cognitive processes in children and in the elderly are subject to changes caused by other factors rather than by the intervention itself; this could possibly lead to bias and might require trials specifically designed for this population.

Inclusion Criteria

- Patients aged 18-59 years;
- Patients who sustained acute TBI in the past three months, classified as mild, moderate or severe, according to the Glasgow Coma Scale (GCS) and with a documented cognitive deficit;
- Patients with blunt TBI;
- Patients will only be included after giving informed consent on their own or by a legal representative.

Exclusion criteria

- Non-traumatic brain injury;
- Penetrating brain injury;
- Prior history of any known traumatic brain injury;
- Unstable clinical condition including, but not limited to, a) the likely need for immediate surgery, b) hemodynamic instability, c) organ failure, d) the need for inotropic or ventilator support, e) delirium, f) uncontrolled/refractory seizures;
- Inability to complete the CRT protocol due to: a) Karnofsky Performance Scale (KPS) \leq 40, b) Inability to complete cognitive tests, c) Lack of productive verbal communication, d) Other factors determined by evaluating team
- Formal diagnosis of any psychiatric disorder (including anxiety, mood, psychotic, personality and neurodevelopmental disorders, intellectual deficit, dementia and substance abuse disorders). Psychiatric patients will be excluded due to the possibility of presenting unusual cognitive styles and deficits in executive functioning, and also the need to take psychotropic drugs;
- No evidence of cognitive deficit on baseline tests;
- Any other pathologic condition at the research team's discretion;
- Participation in another simultaneous trial.

Sampling

The sample for the study will be obtained from 8 tertiary public and private hospitals, from 4 different countries (Colombia, Brazil, Germany and the USA). These countries were selected on the basis of their reported incidence of TBI, their policies on addressing TBI as a public health issue and their official commitment to rehabilitation of disabled patients with sequelae from TBI and their reintegration to society.

Since TBI is an acute injury, convenience sampling will be used for this trial.

Recruitment

Recruitment period will last 16 months. All patients meeting eligibility criteria will be invited to enroll in the study. A team member at each center will personally invite inpatients; patients who have already been discharged at the time of recruitment will be invited through a letter or a telephone call. All patients (or legal representatives) will then be informed about the trial and asked to sign the informed consent form.

Strategies to enhance adherence

The following strategies were designed to increase patients' adherence to the research protocol and prevent high drop-out rates: research coordinators will give an initial talk with subjects and relatives regarding the importance of the knowledge that will be obtained with this study.

-Periodic reassurance encounters will be done by research assistants and rehabilitation team to assess patient's compliance and to resolve doubts or inconveniences that might be elicited by patients.

-All patients enrolled will receive state-of-the-art standard therapy that will be covered by the trial.

-Patients will receive financial aids for parking, transportation, children care and snacks during the time of the study.

Randomization and allocation concealment

In each center, stratified computer assisted randomization will be used according to TBI severity, which will be defined by patient's initial GCS scoring after brain injury, as follows: Mild (13-15), Moderate: (9-12), and Severe (3-8). We will also stratify by country, since some differences are due to socio-cultural factors, education level and access to health care facilities are expected.

TBI is more prevalent among men, so it is high likely to have a tendency of male predominance in each stratum. However, it is important to measure the effect of CRT in cognitive performance of both men and women. In order to control for imbalances between genders, a blocked randomization at a 1:1 ratio will be introduced in each stratum. Allocation to each stratum and block will be concealed.

Blinding

Patients will be blinded to the treatment received: cognitive rehabilitation versus sham intervention. The rehabilitation team that will provide the treatment will not be blinded, but they will be instructed not to reveal the specific type of therapy they will provide. The rater neuropsychologist will be blinded when assessing results of neuropsychological evaluations. Patients will be instructed not to discuss the intervention with the rater.

Data analysis will also be blinded. Adequate measures will be taken to minimize any possible bias in the study. IRT (Interactive Response Technology) will be used to randomize patients to the treatment arms. For the sponsor, those responsible for analysis and interpretation of the results (i.e. the clinical team, statisticians) will remain blinded to data that would systematically unblind patient treatment assignments. The BIRC (Blinded Independent Review Committee) will also be blinded to treatment.

As mentioned above, the team responsible for applying the treatments will need to be unblinded to the type of treatment each patient is receiving. However, they will be blinded to data collection during and after treatment, and will not participate in any step of data analysis. Moreover, randomization data will be kept strictly confidential for the Sponsor Trial Team until the time of treatment unblinding.

In rare cases, when unblinding occurs because of emergency patient management, the actual treatment arm will not be communicated to any of the sponsor employees

involved in running the trial in order to remain blinded. The patient will be withdrawn from the study treatment. An independent statistical group external to the sponsor, not involved in the trial conduct, will prepare data reports for the Data Monitoring Committee (DMC). An independent bioanalyst not involved in study conduct will be blinded to treatment assignment. An independent neuropsychologist responsible for the bioanalysis and independent statistical group for a DMC meeting will do analysis of data for patients.

The blinding assessment method will be evaluated at the end of the study. The percentage of participants in each group who believed that they have received a sham intervention or the CRT intervention will be compared using the chi-square test (8).

Intervention

All patients will receive standard therapy, including conventional physical therapy, occupational therapy and speech/language therapy.

After consenting, patients will be allocated to one of the arms (CRT or placebo) and will undergo a baseline cognitive evaluation to confirm eligibility. Patients initially enrolled but without evidence of cognitive deficit at baseline tests will be excluded after concealed allocation to prevent selection bias.

Once eligibility is confirmed, the following interventions will be initiated:

Treatment Arm: Cognitive Rehabilitation Therapy (CRT)

CRT will incorporate basic tools to daily life challenges based on training subjects in abstract thinking abilities that are achieved by competences in attention, integration and innovation. Some of the strategies will include strategic learning, visual selective learning task and pictures analogies task.

Patients in this arm will receive CRT therapy for 3 to 6 months, depending on patient's cognitive status, divided in four phases:

1-Pre-training phase (2 sessions).

2-Training phase (12 sessions, administered twice a week in the first 5 weeks and once a week in the rest of training).

3-Post training phase, (2 sessions, starting after two weeks of training phase).

4-Delayed post training phase, (2 maintenance sessions three months after training phase).

Placebo Arm: Sham Therapy

Participants in this group will perform playful activities mimicking therapy without structured cognitive therapy. These activities will include reading texts, watching computer images and looking at random pictures.

Sample Size Calculation

The calculation of the sample size was performed using G*Power 3.1 software. We stipulated an alpha error

probability of 0.05, a power of 0.8, and an effect size of 0.5. The sample size was adjusted for a dropout rate of 25%. The final sample size should be 159 patients. To obtain an even number of subjects in each group, we used a total of 160 subjects; 80 subjects in each treatment arm. Each of the four countries will recruit 40 patients.

Assessment

Primary endpoint of the trial will be the average in performance in Wechsler Memory Scale IV cognitive test in patients receiving standard therapy plus cognitive rehabilitation therapy versus standard therapy plus sham intervention after 12 months from baseline. WMS IV will be evaluated by the 5 combined index scores: Auditory Memory Index (AMI), Visual Memory Index (VMI), Visual Working Memory Index (VWMI), Immediate Memory Index (IMI) and Delayed Memory Index (DMI) (9).

The following results will be analyzed as secondary endpoints:

- Cognitive performance in WCST and BVRT at 12 months;
- Difference in cognitive improvement, on the three tests (WMS IV, WCST and BVRT) after 6, 18 and 24 months;
- Return to work (or previous activity), defined as taking over a full-time or part-time job or study. Assessment will be done quarterly (every three months) until 24 month from baseline and will be evaluated in a time-to-event analysis;
- Well-being according to WHO-5 score after 12 and 24 months from baseline, evaluated as ordinal data;
- Functional status according to SF-36 questionnaire after 12 and 24 months from baseline, evaluated as ordinal data.

Pre-specified subgroup analysis:

- Subgroup analysis on all endpoints determined by country, severity of TBI (mild, moderate, severe) and gender;
- Subgroup analysis by socio-economic status using the Kuppaswamy scale that includes three variables: income level, educational level and occupation (10).

Data collection

Data collection will be via electronic data capture system. All captured data will be stored in a locked database, reports will be forwarded to the statisticians for data analysis, as per statistical plan.

Registry will be web-based. The principal investigator and the contribution of several sites will provide participants of this study content of the website.

The registry will be hosted in a secure server (www.crtinbraintrauma.us), hosted in USA. All data stored on the server will be encrypted and will be held in Boston (USA) and will follow the USA privacy and security laws. When accessing the website, all traffic will be encrypted via secure sockets layer (SSL). Only the principal investigator and authorized research coordinators will have the access.

The entry point into the registry will be through the website www.crtinbraintrauma.us, using a specific program password for data entry. A code and date of birth will be used to identify each patient. Patient data will be kept confidential and be entered by a member of the team from each participating program.

Statistical Analysis Plan

Baseline Characteristics

To test balance between groups, baseline characteristics (gender, age, evolution time, type of trauma, and severity of trauma) will be compared. For variables expressed as mean ± standard deviation and that have a Gaussian distribution, comparison between groups will be made by using the Student t test and, for those who do not have a Gaussian distribution, the Mann Whitney test. For variables expressed in frequency, comparison between groups will be made by using the chi-square test, or its exact version when more than 20% of cells have expected frequencies less than 5.

Outcomes

The Table 1 summarizes the statistical tests that will be applied to each outcome according to the type of variables.

Table 1. Statistical tests plan per outcome

Endpoint	Statistical test
WMS IV (12 months)	Student t-test
WMS IV (other time points)	Student t-test
WCST/BVRT	Student t-test
Return to work (or previous activities)	Kaplan Meier and log-rank test
WHO-5 (well-being)	Wilcoxon rank sum test
SF-36 (functional status)	Wilcoxon rank sum test
Confounders	ANCOVA

Multivariate analysis

Any “significant improvement” (yes or no), specified at the assessment section of this protocol will be considered as a binary outcome for multivariate analysis. A multivariate model and relative risks with 95% confidence interval will be calculated to examine the strength of association between each independent variable and the occurrence of “significant improvement”. Multivariate analysis will be conducted employing a Poisson regression model with (log-linear) robust variance. Poisson regression is selected as it provides a better estimate of relative risk, which in turn represents the most significant way for effect measures in longitudinal studies (11).

The level of significance will be set at p-value <0.05 and 95% confidence interval.

Intention-to-treat analysis

Results will be analyzed with an intention-to-treat (ITT) approach, preserving the original groups created by randomization. Patients randomized to each arm will be analyzed as the initially intended treatment (CRT vs placebo).

Missing data

As mentioned at the sample size calculation section, we have estimated a drop-out rate of 25% throughout the duration of the trial. Missing data will be assumed as missing at random (MAR) and will be handled with the multiple imputation (MI) method.

Plan for IRB submission

The IRB submission will be done locally by each site center. The research coordinator will be responsible for the IRB submission.

Registration of the trial

After approval, this trial will be registered at www.clinicaltrials.gov

Privacy & Confidentiality

All staff involved in this study will be trained and certified to protect subject private health information. Data will be de-identified accordingly in electronic forms and all other study-related material.

Discussion

Potential limitations

Informed consent: considering that the research will be conducted in patients with learning disabilities or diminished cognitive ability there may be potential problems such as understanding the purpose of the research and what will be their role in the study. Therefore obtaining informed consent can be difficult and there is need to develop appropriate strategies for communicating the implications of involvement in research. One of these strategies will be to explain the informed consent will be explained in the presence of the patient's legal representative. Moreover, the informed consent will be repeated later during the whole study, as it is expected that patient will improve and be able to fulfill sufficient competence, voluntariness and autonomy to understand the.

When able to consent, patients are enabled to be withdrawn from the trial at any moment if they decline to participate. For patients unable to consent, legal representatives can request patient's removal from the trial at any point.

An ethics monitoring committee, not related to the conduction of the research, will be formed and periodical analysis of study progress and results will be done. In any case of ethical issue or when a sufficient result power is achieved the study should be interrupted.

Potential unblinding and blinding assessment: as the intended intervention and sham intervention may present several differences, patients can start guessing in which group they were assigned and that can generate bias. It is interesting to avoid contact between subjects to preserve blinding. At the end of the study, each patient will be asked to answer a questionnaire addressing if they knew to which group they were assigned to, and statistical tests will be used to analyze success of blinding.

Group imbalances: as possible in any study, randomization may not be perfect in the end and some imbalance between groups can occur. Multivariate analysis will test the influence of simultaneous variables in the outcome and correct possible imbalances.

Future perspectives

Neurological recovery after a brain injury is a continuous process that depends on family and social interactions as well as access to multidisciplinary care. Progress in a TBI patient depends, among different factors, on the severity of the injury, anatomic distribution of the injury, and the opportunity and quality of the rehabilitation received. Considering that patient's progress is a dynamic process, improvements in performance obtained from interventions given during their participation in the present study can remain stable, improve or deteriorate due to lack of stimulation. A post-trial plan needs to be designed for maintenance of patients' achievements. This would be an ethical approach to avoid abandonment and to address patients' needs after their voluntary participation in the trial.

Addressing the need of maintenance, a strategy to be considered could be to the follow-up of patients after completion of the initial study period for an extended period of two years. No specific therapy would be administered at this stage, but patients and caregivers will be provided with orientation and support. Patients' cognitive status can be assessed periodically, taking into account that results could not be related only to initial cognitive therapy. It can be also related to the facility access from each patient, family stimulus and care, as well as the processes related to late brain plasticity.

Expected results would probably demonstrate the need for continued interventions in patients after brain trauma, or prolonged short periodical interventions according to outcomes.

Conclusion

Our proposed trial addresses a knowledge gap in the area of rehabilitation of cognitive deficits after TBI. Our multicenter, single-blinded with a third blinded rater, sham-controlled, randomized study has the potential to contribute to demonstrate the usefulness and effectiveness of CRT in the cognitive recovery of these patients, leading

to a more integral rehabilitation process. Conclusive results will strengthen evidence-based, standard treatment guidelines.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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