DEXAMETHASONE FOR THE TREATMENT OF TRAUMATIC BRAIN INJURED PATIENTS WITH BRAIN CONTUSIONS AND PERICONTUSIONAL EDEMA: STUDY PROTOCOL FOR A PROSPECTIVE, RANDOMIZED AND TRIPLE BLIND TRIAL. (DEXCON TBI TRIAL)

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BACKGROUND

Traumatic brain injury (TBI) is defined as an alteration in brain function caused by an external force. It is usually classified according to the neurological examination obtained by the Glasgow coma scale exam (GCS) in mild TBI (GCS 14-15 points), moderate (GCS 9-13 points) or severe (GCS less than 8 points). TBI is a global public health problem as there are more than 50 million cases of TBI per year wordlwide (1), and it is one of the main causes of death and disability secondary to trauma, causing a great emotional and economic burden for the patients themselves, their families and society in general. Data published by Eurostat from 24 European countries show that in 2012 there were 1.5 million hospital discharges and 57,000 deaths attributable to TBI (2). In 2010, the costs associated with TBI in Europe were estimated at 33 billion euros (3). In addition, the incidence of TBI has increased in recent years due to the use of motor vehicles in developing countries and the increase in casual falls in an increasingly aging population in developed countries (1).

In recent years, the prognosis of this type of patients has not varied substantially (4). Various explanations for this observation have been described. One reason could be the increase in age in patients with TBI. Older patients are more likely to have complications and therefore these complications could mask an improvement in the management of this type of patients and therefore the prognosis (5). In addition, head trauma is a complex and heterogeneous pathology, and these are two of the reasons why the vast majority of clinical trials have not shown beneficial results of drugs so far (1,6), except the CRASH-3 trial with tranexamic acid (7). The most cited reasons for this failure in clinical trials (1,6,8) include the heterogeneity of this pathology; the absence of analytically valid biomarkers or surrogate variables, and the lack of variables or study methods sensitive enough to detect differences between groups.

Among the drugs that have been tested in clinical trials in patients with TBI are corticosteroids. Based on the results of the MRC CRASH study (9), the current Clinical Practice Guidelines (10) do not recommend the administration of high doses of methylprednisolone to improve the prognosis for patients with TBI. However, due to the experience of dexamethasone in patients with brain tumors, this glucocorticoid is still used in neurosurgical patients with various pathologies and its role is currently being reassessed in patients with TBI and chronic subdural hematomas (11,12).

In daily clinical practice, patients with TBI and cerebral contusions developing and area of pericontusional edema are among the patients who are occasionally given dexamethasone on the belief that this edema is similar to that of tumors. Clinically, the beneficial effect of dexamethasone in patients with tumors and peritumoral edema, which is primarily vasogenic, has been well demonstrated (13).

Cerebral edema is classified as cytotoxic and vasogenic. Cytotoxic edema is primarily intracellular and appears after ischemic insults. In vasogenic edema, however, water has an extracellular location and appears when there is a disruption or an abnormal increase in the permeability of the blood brain barrier (14). Published studies have described the presence of a mixed component (vasogenic and cytotoxic) in patients with TBI and cerebral contusions (15,16). Experimental studies have shown that the alteration of the blood brain barrier is biphasic. There is a rapid initial opening phase after the trauma that occurs in the first hours. Subsequently, a second opening phase of the blood brain barrier occurs, which usually begins between 3-7 days after the trauma (17). At the clinical level it has been proven that can take days or weeks for the blood brain barrier to return back to normal (17,18). For this reason it is possible that there is a therapeutic window for corticosteroids in this type of patients. However, it is well known that corticosteroids have a beneficial effect on vasogenic edema (as in patients with tumors) but none on cytotoxic edema.

Using diffusion tensor magnetic resonance imaging (DT-MRI), our group has shown that the radiological characteristics of the vasogenic edema in patients with brain tumors and cerebral contusions are similar. Specifically, the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were similar in both groups of patients (19). We have also observed, using DT-MRI, in a group of 30 patients with TBI, cerebral contusions and pericontusional edema, that the use of dexamethasone at low doses was associated with a reduction in the volume of cerebral edema and improvement in radiological parameters (ADC and FA). (author´s unpublished data).

For this reason, and taking into account the preliminary results mentioned in the previous paragraph, it is intended to conduct a clinical trial to assess the effect of dexamethasone on the prognosis of TBI patients with brain contusions and pericontusional edema. The idea of guiding the treatment of patients with TBI and

cerebral contusions depending on the type of edema can be very useful and a novel way of designing this clinical trial.

To conclude and as described in the third paragraph, the current Clinical Practice Guidelines (10) do not recommend the administration of high doses of methylprednisolone to improve the prognosis for patients with TBI. In our opinion this does not mean that the effect of low doses of dexamethasone (maximum dose of 16 mgr per day) should not be studied in a short and descending course to a selected group of patients such as patients with cerebral contusions and pericontusional edema. This dose is the usual one in neurooncology and there is an extensive experience in its use. In addition, two clinical trials with dexamethasone at these doses are already being conducted in patients with TBI but with chronic subdural hematomas (11,12).

OBJECTIVE

To estimate the efficacy of dexamethasone, with respect to placebo in patients with TBI and brain contusions.

METHODS, DESIGN, DISCUSSION

Overview

The DEXCON TBI trial is a multicenter, pragmatic, randomized, triple-blind, placebo controlled trial to quantify the effects of the administration of dexamethasone on the outcome of TBI in TBI patients with brain contusions and pericontusional edema.

Pragmatic design and the uncertainty principle

The design will allow us to find out how effective the treatment actually is in routine everyday practice. Ethically, this randomized controlled trial can only be undertaken if there is collective scientific uncertainty about which of the interventions being compared is more likely to benefit patients. However, for an individual clinician to be able to recommend enrolment of a patient into a trial, they must be substantially uncertain about the appropriateness of the trial treatment in that particular patient. The eligibility criteria for the DEXCON trial are based on this uncertainty principle. A patient can be enrolled only if the responsable clinician is substantially uncertain as to which of the trial treatments would be most appropriate for that particular patient. Using the uncertainty principle should allow the process of this trial to be closer to what is customary in normal medical practice.

Eligible patients

Adults with TBI who fulfill the following inclusión criteria are eligible:

-Patients who have suffered a head injury and have one or more cerebral contusions with visible pericontusional edema in the CT scan.

-Patients with brain contusions in whom non-sugical treatment has been selected initially.

-Age 18 or over and under 85

-Signing of informed consent by the patient or by his legal representative.

The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use dexamethasone in a particular patient with TBI. This pragmatic approach will allow us to see whether the intervention improves patient outcomes under real-life conditions.

The exclusion criteria are the following:

-Patients with TBI and brain contusions who have required surgery to evacuate the cerebral contusion before randomization.

-Patients with TBI who have required a craniotomy before randomization for any other reason: evacuation of subdural, epidural hematoma or depressed skull fracture.

-Patients with an extracranial Injury Severity Score greater than 18 points.

-Patients in whom the use of corticosteroids is contraindicated.

-Patients who take oral corticosteroids chronically.

-Patients included in another clinical trial.

-Known intolerance or hypersensitivity to dexamethasone.

-Patients with allergy or intolerance to the following excipients contained in dexamethasone / placebo capsules: lactose, corn starch or microcrystalline cellulose.

-Patients with a history of psychotic disorders.

-Patients with inability to take medication orally due to swallowing problems in which it is not indicated to place a nasogastric tube.

-Pregnant or breastfeeding patients.

-Patients in a GCS 3 points situation with bilateral dilated pupils.

-Patients with associated spinal cord injuries.

-Patient with any systemic condition that contraindicates the use of corticosteroids.

Randomization

To ensure a balanced sample size across groups over time, the statistician of the study will apply the block randomisation method with a block size of 2 (two possible sequences: AB and BA) and will be generated with the statistical package R, version 3.5.3, a list for each hospital. A limited number of treatments will be available in each

hospital, sent from the Pharmacy Department of Son Espases Hospital, which will be numbered, and will be assigned in a correlative manner.

Patients, clinical staff, evaluators of the results as well as the statistical team will be blinded to the assignment of medications.

Only the pharmacist, who masks the capsules and labels the containers, will know the assignement of the codes, and will keep them blind until the last phase of the study, after the main statistical analysis, or when unmasking is required.

Once it is verified that the patient meets all the inclusion criteria and none of the exclusion criteria, and after signing the informed consent by the patient himself or by the closest relative, the doctor responsible for the patient will correlatively assign the number to the patient.

Settings

Initially, the study will be carried out in Son Espases Hospital (Palma de Mallorca) and 12 de Octubre Hospital (Madrid). During the first year, all possible patients will be tried to be recruited. A minimum of 60 patients are expected between the two hospitals.

If after the first year interim analysis the Trial Steering Committee (TSC) decides to continue the trial, recruitment will begin in the hospitals included in the Spanish National Registry of Traumatic patients in the ICU (RETRAUCI Network) which includes 56 public hospitals.

Outcome measures

After a patient has been randomized, the outcome will be collected even if the trial treatment is interrupted or is not actually given

Primary outcome

The primary outcome is the functional status (outcome) of TBI patients one and six months after the trauma according to the Glasgow Scale Outcome Extended (GOSE).

Secondary outcomes (Supplemental data)

-Number of episodes of neurological deterioration in both groups of patients during the 12 days of treatment.

-Symptoms associated with TBI in both groups of patients during the 12 days of treatment.

-Volume of pericontusional edema before and after 12 days of treatment in both groups of patients.

-Presence of adverse events between the two groups during the 12 days of treatment.

-Neuropsychological tests between the two groups of patients one month and 6 months after the TBI.

Estimated event rate

In our previous studies we have described that among TBI patients with brain contusions not treated with dexamethasone, the proportion of patients with good recovery (GOSE 7 and 8) was 50%.

Sample size and treatment effect size that should be detectable

Since the data available in this type of patients with this treatment is scarce and inconclusive, we will perform a randomized, triple-blind, placebo controlled trial with an interim futility analysis (interim analysis). The primary endpoint for the DEXCON TBI trial is the good recovery (GOSE 7-8) one month after the TBI.

A study with 600 patients would have about 80% power (two sided alpha=5%) to detect a 12% absolute increased (from 50% to 62%) in good recovery (GOSE 7-8). It includes an inflation of 10% due to non-adherence (withdrawal of consent, loss to follow-up, cross-over or change of treatment).

Recruitment of collaborating investigators

The trial will recruit hospitals from Spain. Suitable collaborating hospitals and investigators will be assessed in terms of the trauma service that they provide and their ability to conduct the trial.

Before the trial can begin at any site, the local Principal Investigator must agree to adhere to Good Clinical Practice Guidelines and all relevant national regulations. In addition, all relevant regulatory and ethics approvals should be in place before the trial starts at a site.

Ethical considerations, information giving and written informed consent

The GCS score is a method of assessing the level of consciousness in TBI patients. Patients with a GCS score of 15 are generally considered fully conscious, but those with a GCS score of 14 or less may not be fully conscious and would not be mentally capable of giving informed consent to participation in a clinical trial. Besides, a brain contusion is a clinical sign indicating significant brain injury, and patients with this diagnosis would not be physically or mentally capable of givin informed consent to participation in a clinical trial.

Therefore, given that patients are eligible for inclusión in the DEXCON TBI trial if they have a TBI and have a brain contusion on a CT scan, in most cases they will, by default, be physically or mentally incapable of giving consent.

Prior information giving to the patient´s relatives

If relatives are present, they will be provided with brief information about the trial. Specifically, the responsible doctor will explain to the relatives that the patient will receive the usual treatments for traumatic brain injury but that, in addition to these, the patient has been enrolled in a research study that aims to improve the treatment of patients with this condition.

It will be explained that the study is being done to see whether using a drug called dexamethasone will help patients with head injury by reducing the amount of edema and inflammation into the brain, therefore preventing further brain damage. The relative will be informed that the patient will be given a treatment over 12 days of either dexamethasone or a dummy medicine (a capsule which does not contain dexamethasone). The doctor will explain that dexamethasone has been shown to improve outcome in patients with other types of brain injuries, such as tumors, and that, whilst we hope that it will also improve recovery after head injury, at present we cannot be sure about this. If requested, a brief information sheet will be provided. If relatives object to the inclusion of the patient in the trial, their views will be respected. If no relatives are present, the patient can not be included in the study.

Treatment

Dexamethasone will be compared with matching placebo.

Dose selection

Dexamethasone doses are those commonly used in neurooncology and there is an extensive experience in its use. It will be a short and descending course: 4mg/6 hours (2 days); 4 mg/8 hours (2 days); 2 mg/6 hours (2 days); 2 mg/8 hours (2 days); 1 mg/8 hours (2 days); 1 mg/12 hours (2 days).

Drug manufacture, blinding and supply of trial treament

Dexamethasone (Fortecortin®) will be acquired from ERN, SA. Laboratories (Barcelona, Spain). The Son Espases Pharmacy Department will be in charge of developing and conditioning the 4mg, 2mg and 1mg dexamethasone / placebo capsules needed for 12 days of treatment, keeping the researchers blind.

The preparation and conditioning of the capsules will be carried out following the standardized work procedures of the pharmaceutical laboratory and its quality controls, previously authorized by the Agencia Española del Medicamento (AEMPS).

The Son Espases Pharmacy Department will be responsible for identifying the containers and sending them by courier to the participating hospitals. A record of the dispensing of test samples will be kept and will be sent in acknowledgment of receipt for control.

Patients, clinical staff, evaluators of the results as well as the statistical team that will perform the analysis will not know the assigned treatment. A randomization list will be created for each hospital. The randomization sequence will only be known by the Pharmacy Department of Son Espases Hospital.

Administration of trial treatment

Each patient will receive 3 containers with the correspondingly identified doses, and an information sheet explaining dose and frequency for proper oral administration.

Other treatments for traumatic brain injury

There is a wide spectrum of treatments for TBI. As the trial will be conducted in Spain, each participating site should follow its own clinical guidelines for the treatment of TBI patients. There is no need to withhold any clinically indicated treatment in this trial.

Dexamethasone or placebo would be provided as an additional treatment to the usual management of TBI.

Safety and Adverse events

Dexamethasone has a well documented safety profile. Nevertheless, data on adverse events, such as infectious complications, hyperglycemia, gastro intestinal bleeding or appearance of psychotic symptoms will be collected as secondary outcomes and will be presented to the independent Data Monitoring Committee (DMC) for blinded review.

Definitions

Adverse events (AE): Any undersirable and unintended medical occurrence affecting a trial participant during the course of a clinical trial.

Serious adverse events (SAE): A serious adverse event (experience) is any undersirable medical occurrence that results in death or is life-threatening or requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

Reporting of adverse events for this trial

Death, life-threatening complications, and prolonged hospital stay which is attributable to the adverse event are pre-specified outcomes to be reported in this trial. This clinical trial is being conducted in an emergency condition using a drug in common use. It is important to consider the natural history of the critical medical event affecting each patient enrolled, the expected complications of this event, and the relevance of the complications to dexamethasone.

Adverse events to be reported using an adverse event reporting form will be limited to those trial outcomes that might occur and be reasonably attributable to the trial drug. Events that are part of the natural history of the primary event of TBI or expected complications of TBI should not be reported as adverse events.

If an SAE occurs, a written report must be submitted within 24 h. The Trial Steering Committe (TSC) will coordinate the reporting of all SAEs to all relevant Regulatory Agencies, Ethics Committees and local investigators as per local legal requirements.

Unblinding

In general there should be no need to unblind the allocated treatment. Unblinding should be done only in those rare cases when the clinician believes that clinical management depends importantly upon knowledge of whether the patient received dexamethasone or placebo. In those few cases when urgent unblinding is considered necessary, a 24-h telephone service will be available. The caller will be told whether the patient received dexamethasone or placebo.

Data collection and management

This trial will be coordinated from Son Espases Hospital. Data will be collected at each site by local investigators and sent to the TSC. These data will be collected from the patient's routine medical records and no special tests will be required.

All data on adverse events, including those routinely collected as outcomes, will be collected and reported as recquired by the relevant authorities.

Data will be collected by the investigator on the paper Case Report Forms (CRFs) and transmitted to the TSC through the Research Electronic Data Capture (REDCap). REDCap is a secure web application for building and managing online surveys and databases. Original paper CRFs will remain at each trial site. The data will be used in accordance with local law and ethics committee approval.

Monitoring

The intervention with dexamethasone has marketing authorization in Spain and has been in clinical use for decades. Its safety profile is well established and no significant serious adverse events associated with its use have been identified. The trial will routinely collect data on adverse events which may theoretically be associated with this product and the condition under investigation, and these will be reviewed by the independent DMC.

The trial procedures are based on routine clinical procedures and include (1) the oral administration of the trial drug using routine clinical use; (2) collecting routine clinical information from the medical records; and (3) informed consent. There are no complex procedures or interventions for the participants or investigators in this trial. Clinical management for underlying conditions will remain as per each hospital's standard protocol.

Investigators/institutions are required to provide direct access to source data/documents for trial related monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents must be kept for at least 5 years after the end of the trial.

End of trial for participants

For the recruited patients the trial ends at death or at 6-month follow-up, whichever occurs first. If during the treatment phase a patient develops an adverse event, the trial drug should be stopped, the patient treated in line with local procedures, and then followed up.

The trial may be terminated early by the Trial Steering Committee (TSC). The independent DMC may give advice/recommendation for the early termination of the trial but the TSC is responsible for the final decision.

Analysis

The primary analysis will compare all patients allocated to dexamethasone versus those allocated to placebo, on an ‘modified intention-to-treat’ basis. Modified intention-to-treat basis, which will include all patients who were randomly assigned, except those who withdrew consent, those who were lost the follow up or had protocol violations. Protocol violations corresponded to those patients who did not complete the 12-day treatment duration. A descriptive analysis of the baseline variables will be made for each treatment group, followed by a comparison between both groups.

In the secondary analysis a logistic regression model will be built to estimate the effect of dexamethasone and placebo on the patient´s functional status measured with the GOSE at one month and at 6 months. The scale will be dichotomized in unfavorable outcome (GOSE 1-6) and favorable outcome (GOSE 7-8). In this analysis the primary outcome will be adjusted by age, pupil reactivity, blood pressure and GCS. To choose a model, the adequacy and goodness of fit will be measured.

Since the severity of the initial injury will significantly determine the final outcome of the patient, regardless of any treatment, the results of this study will be analyzed using the 'sliding dichotomy'. According to this analysis, patients with a less severe initial injury should have a better recovery than those with a severe initial injury. For example, a moderate disability in a patient for whom no more than death or severe disability could be expected is considered a good outcome, and vice versa, consider a moderate disability in a patient with excellent initial prognosis as poor outcome. Patients with a

severe initial injury (GCS score of 4 to 5 or, or with a GCS motor score of 2 to 3) will be considered to have a favorable outcome if the 6-month GOS-E score is 3 or higher. Patients with a moderate-to-severe initial injury (GCS score of 6 to 8 or, GCS motor score of 4 to 5) will be considered to have a favorable outcome if the 6-month GOS-E score is 5 or higher, and those with a less initial injury (GCS score of 9 to 12, GCS motor score of 6) will be considered to have a favorable outcome if the 6-month GOS-E score is 7 or higher.

The purpose of the sliding dichotomy approach is to increase the sensitivity (to lower the false negative rate) of the analysis. All these variables will also be analyzed in a pre-specified subgroup analysis comparing patients with a pericontusional edema volume of more than 10 mL in the pre-inclusion computed tomography (CT) scan in the study with those who have less than 10 mL of edema volume in the same CT study.

Interim analysis

Since the data available in this type of patients receiving this treatment are scarce and inconclusive as to the primary outcome variable, we will perform an interim analysis. A statistician (Dr G Frontera) will blindly perform an interim analysis calculating the conditional power, an approach that quantifies the probability of obtaining a significant result at the end of the study given the data available after one year enrolling patients.

Since the probablilty chosen for futility in this trial is very small (< 0,15), it can be concluded that it would be useless to continue the trial. This interim analysis will be performed at the end of the first year since the inception of the trial, when it is estimated that about 100 patients will have been recruited. At the same time, a safety analysis will be also perfomed, focused on the adverse effects collected during the first year.

The results will be assessed and discussed by an independent Data Monitoring Committee, formed by one statistician and two experts in TBI, who will inform and make recommendations to the Trial Steering Committee, which will finally make the decisions.

Follow-up

No extra tests are required for the trial but a case report form should be completed at the end of the 12- day treatment, or at death or hospital discharge if either happens sooner. The GOSE and the neuropsychological evaluations will be performed one month and 6 months after the TBI. Both evaluations will be performed by clinical

neuropsychologists, and the protocol used will always follow the same process. The neuropsycological tests that will be performed are described in the Supplemental data

Sponsorship and trial management

This research project has no sponsor.The trial will be coordinated by the Trial Steering Committee (TSC).

Indemnity

This project has been listed as a ``low intensity clinical trial´´ by the Agencia Española del Medicamento (AEMPS). In this scenario, the damages on the patient that could result from taking part in this trial do not need to be covered by an specific insurance contract if they are covered by the individual or collective professional civil liability insurance or equivalent financial guarantee of the health trust where the clinical trial is carried out.

Protocol development

The Protocol Committee consists of the following investigators who are responsible for the development of, and agreeing to, the final protocol. Subsequent changes to the final protocol will require the agreement of the TSC.

Clinical experts: Dr Jon Pérez Bárcena, Dra Ana María Castaño León, Dr Alfonso Lagares Gómez-Abascal, Dr Jesús Barea Mendoza, Dr Javier Ibañez Domínguez.

Statistician and Trial management: Dr Guiem Frontera

Independent Data Monitoring Committee (DMC)

Dr Pedro Delgado MD. Servicio de Neurocirugía. Hospital Universitario de Burgos. Spain.

Dr Marcelino Sánchez Casado MD, PhD. Servicio de Medicina Intensiva. Hospital Virgen de la Salud. Toledo. Spain

Dr Carlos Campillo Artero MD; PhD. Servei de Salut de les Illes Balears, Palma de Mallorca, Spain, CRES/BSM Universitat Pompeu Fabra, Barcelona Spain.

To provide protection for study participants, an independent DMC has been appointed for this trial to oversee the safety monitoring. The DMC will review, after the first year, accumulating data from the ongoing trial and advise the TSC regarding the continuing

safety of current participants and those yet to be recruited, as well as reviewing the validity and scientific merit of the trial. The statistician (Dr G Frontera) will provide (in a blind manner) the analysis service required by the DMC.

Standard operating procedures

The DMC has the responsibility for making recommendations to the TSC, while randomization is in progress, to unblind the results. The DMC they will do this if, and only if, the following two conditions are satisfied: (1) the results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of participants in terms of the major outcome; and (2) the results, if revealed, would be expected to substantially change the prescribing patterns of clinicians who are already familiar with any other trial results that exist. Exact criteria for “proof beyond reasonable doubt” are not specified by a purely mathematical stopping rule, but they are strongly influenced by such rules.

Trial steering committee (TSC)

Dr Jon Pérez Bárcena. Intensive Care Department. Son Espases Hospital. Palma de Mallorca.

Dra Ana María Castaño León. Neurosurgery Department. 12 de Octubre Hospital. Madrid.

Dr Alfonso Lagares Gómez-Abascal. Neurosurgery Department. 12 de Octubre Hospital. Madrid.

Dr Jesús Barea Mendoza. Intensive Care Department. 12 de Octubre Hospital. Madrid.

Dr Javier Ibánez Domínguez. Neurosurgery Department. Son Espases Hospital. Palma de Mallorca.

Dr Guillem Frontera. Research Unit. Son Espases Hospital. Palma de Mallorca.

The role of the TSC is to provide overall supervisión of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC will take responsibility for: a) major decisions such as a need to change the protocol for any reason; b) monitoring and supervising the progress of the trial; c) reviewing relevant information from other sources; d) considering recommendations from the DMC.

When outcome data are available for the participants included during the first year, the TSC will review the rate of recruitment into the trial and the overall event rates. The TSC will consider the extent to which the rate of recruitment and the event rates correspond to those anticipated before the trial and will take whatever action is needed in light of this information.

Collaborators´responsibilities

If after the first year interim analysis the TSC recommends to continue the trial, recruitment will begin in the hospitals included in the Spanish National Registry of Traumatic patients in the ICU (RETRAUCI Network). This network involves 56 public hospitals that are already actively collaborating. The coordinating center for the DEXCON Trial will be Son Espases Hospital (Palma de Mallorca, Spain).

Coordination within each participating hospital will be through a local Principal Investigator whose responsibility will be detailed in an agreement in advance of starting the trial and will include: ensure all necessary approvals are in place prior to starting the trial; delegate trial-related responsibilities only to suitably trained and qualified personnel; train relevant medical and nursing staff who see TBI patients and ensure that they remain aware of the state of the current knowledge, the trial and its procedures; agree to comply with the final trial protocol and any relevant amendments; ensure that all patients with TBI are considered promptly for the trial; ensure consent is obtained in line with local approved procedures; ensure that the patient entry and outcome data are completed and transmitted to the TSC in a timely manner; ensure the Investigator's Study File is up to date and complete; be accountable for trial treatments at their site; ensure the trial is conducted in accordance with Good Clinical Practice Guidleines and fulfils all national and local regulatory requirements; allow access to source data for monitoring, audit and inspection; be responsible for archiving all original trial documents, including the data forms, for 5 years after the end of the trial.

Contacting the Trial Coordinating centre in an emergency

For urgent enquiries, adverse event reporting and unblinding queries, investigators can contact the 24-h telephone service provided by the TSC. A central telephone number is given in the Investigator's Study File.

Publication and dissemination of results

All efforts will be made to ensure that the trial protocol and results arising from the DEXCON TBI trial are published in an established peer-reviewed journal. At least one

publication of the main trial results will be made. The success of the trial will be dependent entirely upon the collaboration of the nurses and doctors in the participating hospitals and those who hold key responsibility for the trial. Hence, the credit for the study will be assigned to the key collaborator(s) from each participating site, as it is crucial that those taking credit for the work have actually carried it out. The results of the trial will be reported first to trial collaborators.

Financial support

The Sociedad Española de Medicina Intensiva Y Unidades Coronarias (SEMICYUC) is funding the run-in costs for this trial and up to 100 patients´recruitment. Full funding is being sought from public and private funding organizations for the main trial. Funding for this trial covers dexamethasone acquisition, pharmacy expenses and central organizational costs only. The design and management of the study are entirely independent of the manufacturers of dexamethasone or the funders. Review by each Ethics Committee and the Agencia Española del Medicamento (AEMPS) would create a substantial financial burden which could limit the conduct of the trial. We request that payment for review of the protocol by each Committee be waived or set at a reasonable rate to reflect the actual cost of reviewing the trial protocol.

Trial status

Ethics approval obtained from Comité de Ética de la Investigación de las Islas Baleares (CEI-IB) and from Comité de Ética de la investigación del Hospital 12 de Octubre have been obtained. The trial has also been approved by the AEMPS, which is a public agency depending on the Health Ministry of the Spanish government.

Patient recruitment is planned to take place during the first year in Hospital Son Espases (Palma de Mallorca, Spain) and Hospital 12 de Octubre (Madrid, Spain), and is active starting August 2020.

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FIGURE 1. TRIAL OVERVIEW

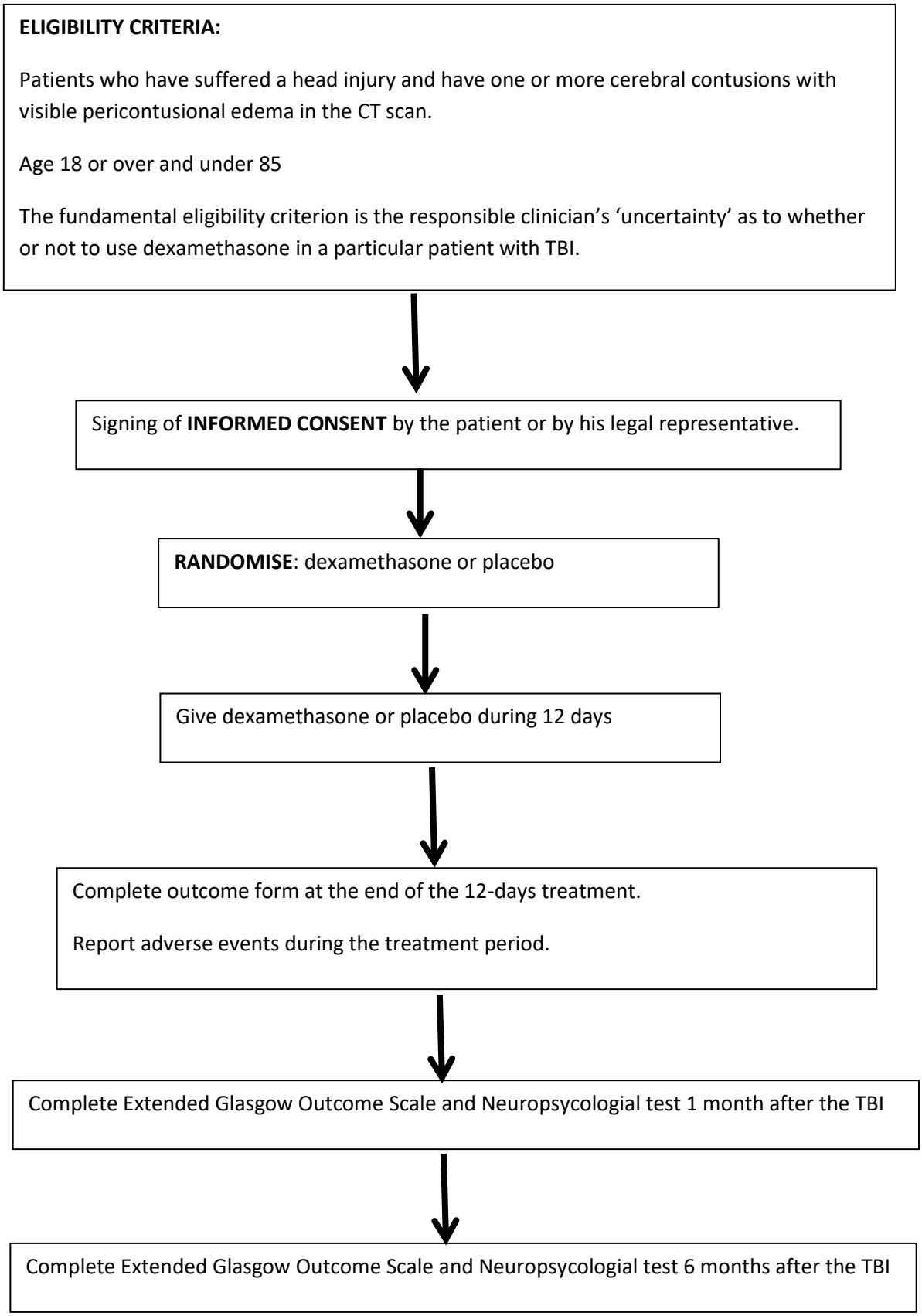
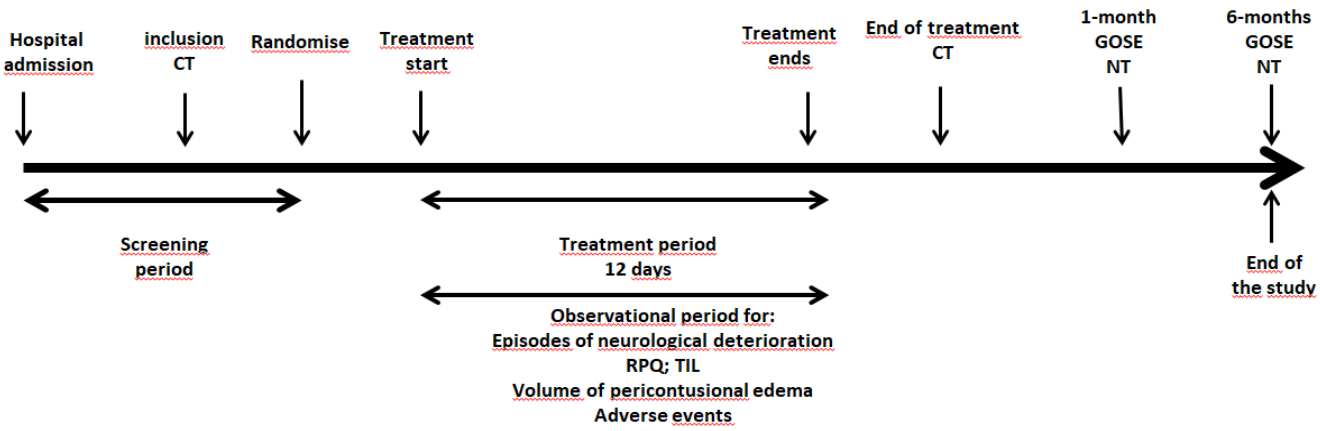


FIGURE 2. MEASURES OF OUTCOME DURING THE TRIAL



Inclusion CT: CT performed in the previous 24 hours before randomisation
End of treatmen CT: CT performed in the following 48 hours after treatment period
GOSE: Glasgow Outcome Scale Extended
RPQ: Rivermead post-concussion symptoms questionnaire
TIL: Therapy Intensity Level
NT: Neuropsycological tests: QLIBRI, MOCA, RAVL-T, Coding WAIS IV, CPT, STROOP, TOLDX, Digit span WAIS IV

SUPPLEMENTAL DATA 1.

Primary Outcome measurement

The primary outcome is the Glasgow Scale Outcome Extended (GOSE) performed one month and 6 months after trauma. This scale will be dichotomized in favorable outcome (GOSE 7-8 points) and unfovable recovery (GOSE≤6 points)

Secondary Outcome measurements

-Compare the number of episodes of neurological deterioration in both groups of patients during the 12 days of treatment.

The number of episodes of neurological impairment will be detected by the Glasgow coma scale and the abbreviated NIHSS scale, during the 12 days of treatment.

An episode of neurological impairment is defined as a worsening of at least 2 points on the Glasgow coma scale or the NIHSS scale, which lasts at least 2 hours, and which cannot be fully attributed to other causes other thanthat cerebral edema. In order to rule out other causes of neurological deterioration, complementary tests will be performed according to the protocol of action of each hospital. Among these tests are an arterial blood gas analysis, blood test with blood count and biochemistry, electroencephalogram and a cranial CT scan.

Baseline scores to compare subsequent neurological examinations will be performed 30 minutes before starting the study medication. Subsequently, the reference scores will depend on the patient's clinical evolution. After sustained episodes of improvement or worsening in the patient's clinical situation, the baseline scores will be recalculated to reflect the best score of the Glasgow coma scale and the NIHSS before a possible episode of neurological impairment. In those patients in whom it is not possible to perform neurological examinations, the reason will be collected in the Investigator’s Study File.

The neurological exams will be performed 3 times per day during the 12 days of treatment.

-Compare the symptoms associated with TBI in both groups of patients during the 12 days of treatment.

The symptoms associated with TBI will be studied daily through the Rivermead Post Concussion Symptom (RPQ) scale. The RPQ is a questionnaire that measures the severity of symptoms associated with TBI. The questionnaire contains 16 symptoms and the patient is asked to quantify these symptoms during the past 24 hours.

In each case, the symptoms are compared with the severity of these symptoms before the trauma. The symptoms range from 0 to 4 points: 0: it has not presented such a symptom; 1: it has not been a bigger problem than before the TBI; 2: slight problem; 3: moderate problem; 4: serious problem.

The RPQ scale will be performed once daily during the 12 days of treatment.

-Compare the volume of pericontusional edema before and after 12 days of treatment in both groups of patients.

In each center, researchers will record the volume of the lesions including the hemorrhagic portion and the pericontusional edema using the ABC / 2 methodology. In the case of multiple contusions, each of them will be measured separately up to a number of 3, starting with the largest.

The image will be analyzed using a standard window for all cases (window level 60 and width of 100 UH), thus ensuring a similar gray scale in the different centers. A measurement of the largest diameter (A) will be made in each contusion, followed by the largest perpendicular diameter to A (B) and the number of cuts in which the contusion (hyperintense area and perilesional hypodense area) can be identified (C). The total volume of the bruises will be equal to the sum of the individual volumes of each one, whose volume results from multiplying the three diameters and dividing them by two. Once this process has been carried out, a measurement will only be made of the hyperdense portion of the contusions to establish the volume of the edema:

Edema volume = total volume-volume hyperdensity.

This procedure will be performed again centrally in the 12 de Octubre hospital, Madrid. Previously, the patient's data will be anonymized and the images will be sent through a web platform with a secure server for review. In a central way, the total volume of the contusion will be established as well as the volume of the edema by means of a semi-automatic method using the Analyze software (vesion 10.0; Analyze Direct, Stilwell, Kansas, USA) of which a license is available. The method consists of a semi-automatic analysis in which in each axial section a central voxel is selected and thanks to the density selection, voxels with similar density characteristics are selected.

The performance of measurements in each hospital and subsequent centralization of the images will allow to establish the interobserver and intermethod reproducibility of the measurement of the edema associated with the contusions, in addition to estimating in two ways the difference of measurements at two time points throughout the study and after an intervention.

-Compare the presence of adverse events between the two groups during the 12 days of treatment.

Those adverse effects that have special interest and serious adverse effects will be collected. Side effects of special interest are:

-Metabolic: Hyperglycemia will be especially monitored. The the maximum value of capillary glycemia will be recorded daily. The amount of daily insulin that the patient needs to control de glucose level will also be collected.

-Psychiatric: presence of psychotic symptoms using the Confusion Assessment Method (CAM).

-Digestive: Episodes of gastro intestinal hemorrhage; Episodes of epigastric pain, vomiting or reflux symptoms.

-Infectious: Presence of new infectious episodes. Infectious episode will be confirmed in accordance with the Centers for Disease Control (CDC) criteria and mainly based on microbiological criteria.

- Compare the results of the neuropsychological tests between the two groups of patients one month and 6 months after the TBI.

Two neuropsychological evaluations will be performed: 1 month and 6 months after the TBI. Both evaluations will be performed by clinical neuropsychologists, and the protocol to be used will always follow the same procedure and tests. The tests that integrate this protocol are described below:

-The MOCA (Montreal Cognitive Assessment): originally designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.

- Rey Auditory Verbal Learning Test (RAVLT) is one of the most widely used word learning tests in clinical research and practice. Five presentations of a 15-word list are

given, each followed by attempted recall. This is followed by a second 15-word list (list B), followed by recall of list A, and delayed recall and recognition are also tested.

- Coding (WAIS-IV Battery subtest): essentially aims to assess processing speed, associative memory, graphomotor speed.

- Computerized Continuous Continued Test (CPT) The CSAT-II RESEARCH VERSION: this version is used to evaluate sustained attention, discrimination, types of errors made, motor response style and response speed during the task.

- Stroop test: This is a psychological test linked especially to neuropsychology that measures measuring the level of interference generated by automatisms in the performance of a task.

- Digit Span (WAIS-IV Battery subtest): essentially measures auditory working memory and your ability to record, maintain and manipulate auditory information consciously.

- Test Tower of London-Drexel University version test (TOLDX): measures executive planning ability in subjects with frontal lobe injury. Traditionally used as a planning and problem-solving measure.

- Quality of Life after brain injury (QOLIBRI) Spanish version: to measure quality of life after TBI. Through these scales and questionnaires, what is intended is to obtain information obtained, preferably, from the patient himself and simultaneously from a family member or friend (proxy) in order to corroborate the information provided by the patient himself.