EFFICACY OF PROPRANOLOL IN TRAUMATIC BRAIN INJURY PATIENTS ADMITTED TO THE ICU: A PROSPECTIVE, RANDOMIZED, TRIPLE-BLIND STUDY (ProP TBI in ICU).

First Protocol date: April 28, 2025

Last protocol modification: November 11, 2025

Protocol version: V.1

CÓDIGO: Prop-TBI 04-2025

Nº EUCT: 2025-524194-17-00

IRB approval at the meeting held on January 28, 2026.

AEMPS approval (Agencia Española de Medicamentos y Productos Sanitarios) (AEMPS) April, 14th, 2026

Beta-blockers have shown promise as a treatment to improve patient prognosis following traumatic brain injury (TBI), although the exact mechanism by which they might confer this benefit remains unknown.

At the clinical level, several retrospective cohort studies, prospective cohort studies, small prospective clinical trials, and various reviews and meta-analyses suggest that beta-blockers may be associated with an improved prognosis in patients with TBI. Furthermore, the optimal timing, dosage, and duration of beta-blocker treatment remain uncertain. This means there is still uncertainty regarding the overall efficacy of beta-blockade in patients with TBI, as well as the specifics of patient selection, drugs, dosages, routes of administration, and physiological targets.

In summary, the use of beta-blockers in patients with TBI appears to be associated with reduced mortality at the time of ICU discharge, as well as better long-term functional outcomes. However, the lack of high-quality scientific evidence clearly limits the ability to make a generalized recommendation regarding the use of beta-blockers in these patients. Therefore, further clinical trials are needed to analyze the effect of beta-blockers on mortality and short- and long-term functional outcomes in patients with TBI admitted to an Intensive Care Unit (ICU).

HYPOTHESIS

The hypothesis of this clinical trial is that 14-day treatment with propranolol can reduce in-hospital mortality in patients with traumatic brain injury admitted to the ICU.

DESIGN

The Prop-TBI in ICU trial is a prospective, randomized, multicenter, triple-blind clinical trial with two parallel treatment groups, designed to evaluate the efficacy of propranolol versus placebo in patients with traumatic brain injury (TBI) requiring ICU admission.

A randomized, triple-blind, multicenter, two-arm clinical trial (propranolol versus placebo) has been designed with an adaptive feature allowing the study to continue in the subgroup of patients who required intracranial pressure (ICP) monitoring. To this end, an interim analysis will be conducted approximately two years after the start of the study. This interim analysis will include an overall futility analysis. Also in this interim analysis we will perform a comparison between both groups in those patients with ICP monitoring.

If significant differences are observed between the subgroups, the sample size would be recalculated based on the data obtained, with a modification of the inclusion criteria to include only patients from the subgroup showing the greatest response, while continuing the study with the same general structure.

PRIMARY OBJECTIVE

To compare in-hospital mortality in patients with traumatic brain injury (TBI) requiring ICU admission after receiving 14 days of treatment with propranolol versus placebo.

SECONDARY OBJECTIVES

-To compare the percentage of patients with traumatic brain injury (TBI) showing a good outcome (Extended Glasgow Outcome Scale score ≥5) after receiving 14 days of treatment with propranolol versus placebo, at 1 month and 6 months post-injury.

-Compare the occurrence of adverse effects between the two groups during the 14-day treatment period.

SELECTION OF SUBJECTS.

The study will be conducted at six Spanish hospitals: Hospital Son Espases (Palma de Mallorca); Hospital 12 de Octubre (Madrid); Toledo University Hospital; Burgos University Hospital; Hospital Arnau Vilanova (Lleida); and Hospital Germans Trias i Pujol (Badalona).

Patients with TBI admitted to these hospitals who meet the inclusion/exclusion criteria will be randomized to receive propranolol or placebo, administered orally or via nasogastric tube.

The propranolol dosages used are those typically employed in the ICU: treatment begins with an initial dose of 10 mg every 6 hours (40 mg/day), which may be increased to a maximum of 40 mg every 4 hours (maximum 240 mg/day) based on blood pressure and heart rate parameters.

Inclusion criteria:

Patients eligible to participate must meet the following inclusion criteria:

-Patients aged 18 to 80 years (inclusive) who have sustained a moderate or severe traumatic brain injury (GCS 3–13) and require ICU admission.

-Signing of the informed consent by the patient or their legal representative, in the event that the patient is unable to do so.

-Before starting the trial, the patient must be hemodynamically stable, defined as having a systolic blood pressure (SBP) of 110 mmHg or higher, a cerebral perfusion pressure (CPP) of 60 mmHg or higher (for patients with ICP monitoring), and a heart rate (HR) of 60 beats per minute or higher. Patients meeting these hemodynamic parameters while receiving a noradrenaline dose lower than 0.10 µg/kg/min may be included.

-Initiation of the study within the first 96 hours following the trauma.

Exclusion criteria:

-Age 17 years or younger, or 81 years or older (inclusive)

-Hemodynamically unstable patients, defined as having a systolic blood pressure of 109 mmHg or less, a cerebral perfusion pressure of 59 mmHg or less (in patients with ICP monitoring), and a heart rate of 59 beats per minute or less, and requiring a noradrenaline dose greater than 0.10 µg/kg/min.

-Lactic acid >2 mmol/L at the time of randomization.

- Patients with a TBI of more than 96 hours' duration

-Polytrauma patients with an extracranial Injury Severity Score greater than 18 points or an extracranial AIS score of ≥4 in any region.

-Patients with penetrating traumatic brain injury.

-Pre-existing heart disease that contraindicates beta-blockers, such as first-, second-, or third-degree heart block without a permanent pacemaker; heart failure defined as an ejection fraction of less than 40%.

-Patients receiving home treatment with digoxin, diltiazem, or verapamil.

-Patients treated with beta-blockers prior to admission

-Pre-existing asthma or bronchospasm

-Patients with spinal cord injuries

-Patients with both dilated pupils upon admission

-Patients with a poor prognosis and a life expectancy inferior to 24 hours

-Pregnant or breastfeeding women (a pregnancy test is required before inclusion in the clinical trial)

-Patients with intolerance to any of the excipients contained in the propranolol or placebo capsules: lactose, calcium carboxymethylcellulose, gelatin (E441), magnesium stearate, hypromellose (E464), glycerol (E422), titanium dioxide (E171), carmine (E120), or sodium carboxymethylcellulose.

-Patients for whom follow-up at one month and six months cannot be guaranteed.

- Patients unable to take medication orally due to swallowing difficulties, and for whom the placement of a nasogastric tube is not indicated.

- Patients enrolled in another clinical trial

PROCEDURES

Once it has been verified that the patient meets all inclusion criteria and none of the exclusion criteria, and after informed consent has been signed by the patient or their next of kin, the physician responsible for the patient will assign a treatment kit to the patient in sequential order. The study may begin as soon as the patient meets all inclusion criteria, but always within the first 96 hours following the trauma.

The initial dose of propranolol will be 10 mg every 6 hours (minimum 40 mg per day), administered orally or via nasogastric tube. Patients will be re-evaluated every 24 hours to adjust the dose based on blood pressure and heart rate. The propranolol/placebo doses may be increased in an attempt to achieve a heart rate between 60 and 100 bpm and a systolic blood pressure between 110 and 160 mmHg. The maximum dose may be up to 40 mg every 4 hours (maximum 240 mg per day). Treatment with propranolol/placebo will last for 14 days or until hospital discharge or patient death, whichever occurs first.

The patient's heart rate, systolic blood pressure, and cerebral perfusion pressure will be recorded prior to the administration of the propranolol/placebo dose. Criteria for withholding the medication include a heart rate of 59 bpm or lower, systolic blood pressure of 109 mmHg or lower, or cerebral perfusion pressure of 59 mmHg or lower. If, after being enrolled in the study and receiving a dose of the study medication, the patient has required the initiation of vasoactive medication, the next dose of propranolol/placebo may be administered provided the previously described hemodynamic parameters are met and the dose of noradrenaline is less than 0.1 µg/kg/min.

If the patient requires further treatment to control blood pressure and/or heart rate, a protocol is attached to standardize treatment across the various hospitals (Figure 1).

After the 14-day treatment completion, if the patient exhibits tachycardia and/or hypertension, this protocol may be continued. The decision to initiate a beta-blocker is left to the discretion of each investigator. Administration of the drug will be recorded even if the 14-day study period has concluded.

Patients will be followed up at one month and six months post-injury. This follow-up will be conducted by the neuropsychologist hired for the study, who will ask the necessary questions over the phone to obtain the Extended Glasgow Outcome Scale (GOSE) score. The study concludes at the six-month follow-up visit or upon the patient's death, whichever occurs first.

RANDOMIZATION AND BLINDING

A randomization list will be prepared for each hospital. The randomization code will be known only to the Pharmacy Department of Son Espases Hospital.

The Son Espases Pharmacy Service will be responsible for preparing and packaging the propranolol/placebo capsules—sufficient for a 14-day treatment course—for all the hospitals. The containers of propranolol/placebo will be shipped from the Son Espases Pharmacy Service to the pharmacy departments of the hospitals participating in the clinical trial. Each hospital will have a limited, numbered supply of treatments, which will be used in sequential order.

The preparation and packaging of capsules will be carried out in accordance with the standard operating procedures of the pharmaceutical technology laboratory and its quality controls, as previously authorized by the Spanish Medicines Agency in the study's technical dossier.

Blinding will be maintained throughout the study for the researchers, the patients, and the individuals responsible for performing the statistical analysis.

Once it has been verified that the patient meets all inclusion criteria and none of the exclusion criteria—and after informed consent has been signed by the patient (if conscious) or by the next of kin (if the patient is unconscious)—the physician responsible for the patient will be in charge of randomizing the patient.

ADVERSE EVENTS

An adverse event is any undesirable experience occurring in a subject during a clinical trial, whether or not it is considered related to the investigational products.

An adverse event is considered serious if it:

- results in the subject's death

- is life-threatening

- causes permanent or persistent disability

- results in hospitalization or prolongs an existing hospitalization.

Adverse events must be recorded by the trial investigator, describing them in terms of duration, intensity, frequency, and the causal relationship between the treatment and the adverse event.

STATISTICAL ANALYSIS

A descriptive analysis of baseline variables will be conducted for each treatment group, and their comparability will be assessed. Intention-to-treat and per-protocol analyses will be performed.

Despite randomization, logistic regression will be used to estimate the effect of propranolol and placebo on mortality and on the GOSE score at 1 and 6 months, dichotomized into poor outcome (GOSE 1–4) and good outcome (GOSE 5–8). Subsequently, the results will also be analyzed using the "sliding dichotomy" approach, adjusting for prognostic variables such as age and baseline Glasgow Coma Scale score.

Given that the initial severity of the injury will significantly determine the patient's final outcome—regardless of any treatment—the efficacy of propranolol will also be assessed using the "sliding dichotomy" approach. According to this analysis, patients with a less severe initial injury should experience a better recovery than those with a more severe initial injury. For instance, moderate disability in a patient for whom only death or severe disability was expected might be considered a good outcome; conversely, moderate disability in a patient with an excellent initial prognosis might be considered a poor outcome. The aim of using this type of statistical method is to increase the sensitivity of the analysis, and it has already been employed in neurotraumatology clinical trials (Skolnick BE; NEJM 2014; Wright WE; NEJM 2014).

An interim futility analysis will be conducted on patients enrolled during the two years; if the upper limit of the 95% confidence interval for the difference in the proportion of deaths between the groups is less than 6%, and the calculated conditional power—indicating the probability of obtaining a p-value < 0.05 by the end of the study—is low (<20%), consideration will be given to stop the study for futility.

This interim analysis will also examine the treatment response within the subgroup of patients who required ICP monitoring. If a significant difference is detected between the two groups (propranolol vs. placebo), a new sample size calculation based on data from the subgroup showing the greatest response will be proposed; the study would then continue under the same general terms, but with inclusion criteria limiting the sample to the type of patients who benefited the most. The final decision will be made by the Data Monitoring Committee, which will carefully consider the decision, taking into account how the termination criteria behaved over time and considering all aspects of the study, including adverse events and other endpoints.

SAMPLE SIZE

We estimate that a sample of 536 patients, randomized 1:1, would be required to detect a 33% reduction in hospital mortality—estimated at 20%—with 80% power, assuming a two-tailed Type I error rate of 5%. This accounts for a 10% inflation due to non-adherence (withdrawal of consent, loss to follow-up, or change in treatment) and an interim futility analysis.

PROJECT PHASES

-Define the protocol (March–April 2025)

-Obtain approval from the European Medicines Agency (May–August 2025)

-Obtain approval from Ethics Committees (September–November 2025)

-Apply for the SEMICYUC grant (February 2026)

-Patient recruitment and simultaneous clinical data collection (June 2026–June 2028). Principal investigators at each hospital will be responsible for explaining the study at participating centers, performing randomization, obtaining informed consent, and prescribing the treatment. Participating hospitals will oversee the study.

-Interim futility analysis (June 2028). This analysis will be conducted by the statistician at Hospital Son Espases (Dr. G. Frontera). The final decision to stop the trial will be made by the Data Monitoring Committee.

-Preparation of the blinding materials (medication/placebo) will be carried out by the Hospital Son Espases Pharmacy Department (Dra. L. Periañez and an hourly-contracted pharmacy technician), who will supply the necessary treatments to each hospital.

-A person will be hired to act as data manager for the collection and handling of the large volume of data to be generated. This individual will also perform monitoring and pharmacovigilance tasks.

-Assessment of GOSE scores at 1 month and 6 months post-TBI: these will be conducted by the neuropsychologist included in the project.

PROP-TBI in ICU treatment protocol

Treatment group:

Propranolol 10 mg/6 H po/NG tube (40 mg/day)

Increase the dose to achieve a heart rate of 60–100 bpm and a systolic blood pressure of 110–160 mmHg, up to a maximum propranolol dose of 40 mg every 4 hours via oral/nasogastric tube (maximum daily dose: 240 mg).

Placebo group:

1- Heart rate, blood pressure, and cerebral perfusion pressure will be recorded before administering the dose of propranolol/placebo.

2- Parameters for NOT administering the medication include:
HR ≤59 bpm; SBP ≤109 mmHg; CPP ≤59 mmHg

3- Therapeutic targets for increasing medication doses:
Heart rate between 60–100 bpm and systolic blood pressure between 110–160 mmHg.

4- If, after being enrolled in the study, the patient requires vasoactive support (norepinephrine dose <0.1 µg/kg/min) and meets the hemodynamic parameters described above prior to the administration of propranolol/placebo, the study medication may be administered

1) If HR >100 bpm and SBP >160 mmHg persist, the following may be used:

Dexmedetomidine ev: 0,4-1,2 micrograms/kg/hour

Clonidine 0,15 mg/12 h po/NG tube

2) If only SBP >160 mmHg persists, the following may be used:

Amlodipine 5-10 mg/12-24 H po/NG tube

Captopril 25-50 mg/6 H po/NG tube

Perfusions of urapidil o clevidipino

3) If only HR >110 bpm persists, the following may be used:
Ivabradine 5-7,5 mg/12 H vo/SNG

1) If HR >100 bpm and SBP >160 mmHg persist, the following may be used:

Dexmedetomidine ev: 0,4-1,2 micrograms/kg/hour

Clonidine 0,15 mg/12 h po/NG tube

2) If only SBP >160 mmHg persists, the following may be used:

Amlodipine 5-10 mg/12-24 H po/NG tube

Captopril 25-50 mg/6 H po/NG tube

Perfusions of urapidil o clevidipino

3) If only HR >110 bpm persists, the following may be used:
Ivabradine 5-7,5 mg/12 H vo/SNG

* If, after completing the 14-day study treatment, the patient presents with tachycardia and/or arterial hypertension, this protocol may be continued, and the initiation of a beta-blocker is left to the discretion of each investigator. Its administration shall be recorded in the data collection form, even if the 14-day study period has concluded.