

STUDY PROTOCOL

Open Access



Brain Injury and Ketamine study (BIKe): a prospective, randomized controlled double blind clinical trial to study the effects of ketamine on therapy intensity level and intracranial pressure in severe traumatic brain injury patients

Veerle De Sloovere¹, Liese Mebis^{2,3}, Pieter Wouters^{2,3}, Fabian Guíza^{2,3}, Eva Boonen⁴, Marc Bourgeois⁵, Jasperina Dubois^{2,6}, Didier Ledoux⁷, Piet Lormans⁸, Hugues Maréchal⁹, Emmanuel Van der Hauwaert¹⁰, Bart Depreitere¹¹ and Geert Meyfroidt^{2,3*} 

Abstract

Background In severe traumatic brain injury (TBI), sedatives are often used to control intracranial pressure (ICP), to reduce brain metabolism, to allow for other treatments such as mechanical ventilation or targeted temperature management, or to control paroxysmal sympathetic hyperactivity. Prolonged sedation is often necessary. The most commonly used sedatives in TBI are propofol and midazolam, often in combination, but both have significant side effects when used at high doses for several days. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, provides sedation and analgesia with minimal respiratory depression or haemodynamic instability. However, ketamine carries a US Food and Drug Administration (FDA) precaution regarding its use in patients with pre-anaesthetic elevated cerebrospinal fluid pressure, which discourages its use in TBI patients. Several observational studies and two large meta-analyses do not suggest that the use of ketamine as an induction agent or sedative in sedated and mechanically ventilated TBI patients would increase the ICP. Off-label use of ketamine for this indication is increasing worldwide. To date, no prospective randomized clinical trial (RCT) has demonstrated the safety of ketamine in TBI patients.

Methods The Brain Injury and Ketamine (BIKe) study is a prospective multicentre double-blind placebo-controlled RCT, to evaluate the safety, and effect on therapeutic intensity to reduce ICP, of ketamine as an adjunct to a standard sedation regimen in patients with severe TBI. Adult TBI patients, admitted to the intensive care unit (ICU), requiring sedation and ICP monitoring within 72 h of admission, will be randomized to ketamine or placebo. The study drug will be started within 6 h of randomization. The dose of the investigational medicinal product (IMP) is 1 mg/kg/h, by continuous infusion. The IMP will be stopped when the last ICP control sedative is discontinued. Data collection will stop when the patient is discharged from the ICU. All patients will be followed for 6 months post-trauma. The study is powered for the safety endpoint of detecting a clinically relevant increase of two episodes in the median

*Correspondence:

Geert Meyfroidt

geert.meyfroidt@uzleuven.be

Full list of author information is available at the end of the article



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

number of episodes of high intracranial pressure episodes per ICU stay. A total of 100 patients are required to meet these objectives. We hypothesize a clinically relevant reduction in the therapeutic intensity level (TIL) score of at least 3 points.

Discussion This study is the first prospective RCT to investigate the safety of ketamine as an adjunct to a standard sedation regimen in TBI patients.

Trial registration ClinicalTrials.gov NCT05097261. Registered on October 28, 2021.

Keywords Brain injury, Traumatic wounds, Ketamine, Cranio-cerebral trauma, Central nervous system, Analgesics

Introduction

Background and rationale {6a}

Patients with severe traumatic brain injury (TBI) are not only sedated for general indications such as pain relief, or anxiety control. In these patients in particular, sedatives are used for specific therapeutic indications and potential neuroprotective effects: reduction of brain energy expenditure, reduction of ICP, control of seizures, targeted temperature control, control of PaCO₂ by mechanical ventilation; or to treat paroxysmal sympathetic hyperactivity [1, 2]. Midazolam and propofol are the most used sedatives in TBI, but both have major drawbacks with prolonged use at higher doses [2]. Midazolam has antiepileptic properties and reduces cerebral metabolism and intracranial pressure (ICP), but to a lesser extent than propofol. With long-term use, the kinetics of midazolam become unpredictable, leading to delayed awakening, which complicates early neurological assessment [2, 3]. In addition, benzodiazepines are associated with an increased incidence of brain dysfunction and delirium with prolonged infusion [4]. In comparison, propofol has a more predictable pharmacokinetic profile, but causes profound adverse haemodynamic effects at higher doses and can lead to the often fatal propofol-related infusion syndrome (PRIS) [2, 5].

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that produces sedation with minimal respiratory or haemodynamic effects. In the early 1970 s, ketamine was banned for use in TBI, following the publication of two small, non-randomized case series that observed an increase in cerebrospinal fluid pressure after ketamine injection in spontaneously breathing patients [6, 7]. A systematic review examined the effect of ketamine on ICP in TBI patients and found “Oxford level 2b, GRADE C evidence that ketamine does not increase ICP in severe TBI patients who are sedated and ventilated, and may even decrease ICP in selected cases” [8]. Several clinical and experimental studies have suggested the potential neuroprotective effects of NMDA receptor blockade with ketamine. First, it could reduce the

excitatory amino acid response, and decrease glutamate excitotoxicity, which may prevent calcium-mediated neuronal cell death [9, 10]; second, cortical spreading depolarizations, a pathological electrical activity indicative of energy failure in the cerebral cortex, can be stopped by ketamine administration [11, 12]; third, ketamine has been shown to reduce neuroinflammation [13]. Currently, off-label use of ketamine in TBI patients is widespread [1], although to date, there has been no prospective randomized clinical trial (RCT) demonstrating the safety of ketamine use in TBI patients.

The Brain Injury and Ketamine (BIKe) trial is the first prospective placebo-controlled RCT to investigate the safety and effect on therapeutic intensity for ICP control of using ketamine as an adjunct to a standard sedation strategy in TBI patients.

Objectives {7}

The primary objective of the BIKe study is to demonstrate the safety of ketamine as an adjunct to a standard sedation regimen in patients with severe TBI. The null hypothesis is that the addition of ketamine to a standard sedation regimen in severe TBI will not increase ICP and will reduce the therapeutic intensity of ICP-lowering treatment. The safety endpoint is the number of episodes of intracranial hypertension, defined as ICP elevations > 22 mmHg for > 25 min. The ICP threshold 22 mmHg is in accordance with the current guidelines of the Brain Trauma Foundation [14]. The duration of 25 min is derived from the data of the study of Guiza et al. that demonstrated that an ICP above 22 mmHg, for longer than 25 min is associated with a worse GOS score at 6 months [15].

The efficacy endpoint will be measured by the therapeutic intensity level (TIL) score, based on the highest score in each item per day until study drug discontinuation. The clinical significance of a 3-point reduction in the TIL score is a reduction in the sedation score of the TIL score [16].

Secondary objectives are specified below and include duration and dose of sedation, incidence of ICU delirium,

incidence of PRIS, duration of mechanical ventilation and need for tier 3 therapies (barbiturate coma, secondary decompressive craniectomy or hypothermia) [17] for elevated ICP. Subgroup analyses are performed for centre effects, radiological lesion types defined by the Marshall score, isolated TBI versus polytrauma and age with sample mean as cut-off.

Trial design {8}

The BIKe study is a phase 4, multi-centre, prospective, randomized, placebo-controlled double-blind clinical trial to evaluate the safety of ketamine as an adjunct to a standard sedation regimen in TBI patients conducted in Belgium. This is the first study to evaluate the safety and efficacy of adding ketamine to a standard sedation regimen for severe TBI. The safety endpoint is the number of episodes of elevated ICP, and the efficacy endpoint is the TIL score. Both endpoints will be collected and analysed on a daily basis, until the end of ICP monitoring and treatment. The study drug will be discontinued when all sedatives for ICP treatment are discontinued. Our hypothesis is that in the intervention group (ketamine group) there will be a decrease in the sedation score and no increase or possible decrease in ICP.

Patients will be randomized 1:1, in blocks of 4 patients, with one stratification per centre. Physicians, nurses, families and patients will be blinded to the treatment allocation.

Methods: participants, interventions and outcomes

Study setting {9}

The study is conducted in 8 Belgian hospitals, both university and non-university hospitals. The participating study centres are listed on clinicaltrials.gov (NCT05097261).

Eligibility criteria {10}

Inclusion criteria:

All adult TBI patients (> 18 years of age) admitted to the ICU with ICP monitoring (parenchymal probe, external ventricular drain or both), requiring sedation within 72 h of initial hospital admission.

Exclusion criteria:

- Known pregnancy and/or lactation
- Imminent or actual brain death upon inclusion
- Allergy or intolerance to the study medication
- Pre-existing neurocognitive disorders, pre-existing congenital or non-congenital brain dysfunction
- Inability to obtain informed consent

- Inclusion in an IMP-RCT of which the PI indicates that co-inclusion specifically in the BIKe study is prohibited
- Therapy restriction code upon inclusion
- Porphyria
- Glaucoma

Who will take informed consent? {26a}

Written informed consent will be obtained by the principal investigator, sub-investigator or their designee (ICU physician) after admission to the ICU within 48 h of meeting the inclusion criteria. Consent to participate in the study will be obtained from a legal representative/close relative, as the patient is unable to give consent. The consent form includes a summary of the study in layman's terms, the study design, procedures, additional surveys (questionnaire 6 months after TBI), risks, benefits, and information about the study medication (side effects), ... as well as details about data management, ethics committee approval, insurance and contact details of the investigators. This form will be explained to the patient's next of kin before it is signed. The informed consent form (ICF) includes an opt-out option to be confirmed when the patient regains consciousness and mental capacity and does not wish to participate. A copy of the ICF is given to the next of kin.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

No additional laboratory tests outside the clinical routine will be performed. No other investigations will be carried out.

Interventions

Explanation for the choice of comparators {6b}

The comparator in this double-blind, randomized trial is a placebo. We chose sodium chloride 0.9% solution (NaCl 9 mg/ml). This is an inactive substance that is commonly used as a placebo and has no systemic or neurological effects that could influence the outcome of this trial. NaCl 9 mg/ml is indistinguishable from ketamine: it is colourless and odourless and has no distinguishing features compared to ketamine.

Intervention description {11a}

After obtaining informed consent, patients are randomized to the intervention (ketamine) or placebo

group. Within 6 h of randomization, study medication is started at 1 mg/kg/h (ketamine) or 0.02 ml/kg/h (placebo), with a maximum dose of 120 mg/h or 2.4 ml/h. Ketamine is administered undiluted, by continuous infusion; as is the placebo, both at the infusion rate of 1 mg/kg/h or 0.02 ml/h in both randomized arms. The study drug is prepared by healthcare professionals who are not involved in the care of the study patients. Study medication will be stopped when the last sedative to control the ICP is discontinued. No open-label use of ketamine is allowed during the study, i.e. until discharge from hospital.

Criteria for discontinuing or modifying allocated interventions {11b}

The study drug is discontinued when all sedatives for ICP control are discontinued. If a combination of sedatives is used, the study drug is stopped when the last sedative for ICP control is discontinued. If the study drug is stopped and the patient requires re-sedation for ICP control or other indications, the study drug will not be restarted.

The study drug will always be discontinued in the following circumstances:

- If a barbiturate coma is induced.
- If the therapy restriction code is initiated.
- If liver failure occurs, without a clearly identifiable cause and/or if metabolism of the IMP is likely to be impaired.
- If haemorrhagic cystitis (cystitis with macroscopic haematuria) occurs.
- If a serious adverse event or serious adverse reaction occurs, the sponsor will evaluate causality. If causality is established, the study drug will be stopped.
- If a patient withdraws consent for this study after regaining the capacity to consent, data collection will be stopped. The data collected to date will be retained and used for data processing, as an informed consent has been obtained from the next of kin since the start of the study. These patients will not be replaced. If the next of kin wishes to withdraw a patient who has previously consented before the end of the intervention, all data collection will be stopped, and the patient will be replaced.

The termination of the study will be justified and documented in the electronic case report form (eCRF) and source documents.

Strategies to improve adherence to interventions {11c}

All ICU nurses and ICU physicians have received additional training specifically for this study. All study medication will be administered by trained ICU nurses. The compliance to the study protocol is monitored daily by clinical trial assistants (CTAs).

Relevant concomitant care permitted or prohibited during the trial {11 d}

The use of open-label administration of ketamine is not allowed during the course of the study, i.e. until discharge from hospital. A warning will be included in each study patient's electronic health record.

Provisions for post-trial care {30}

If the null hypothesis is accepted, ketamine can be used safely as part of a sedation regimen in patients with TBI. Ultimately, this may lead to a reconsideration of the precautions and warnings for the use of ketamine in patients with increased cerebrospinal fluid pressure. Further clinical studies will be needed to investigate a potential clinical benefit or neuroprotective effect. In accordance with Belgian and European legislation, the sponsor has a liability insurance covering all damages suffered by patients as a result of their participation in the study and directly or indirectly related to their participation in the study.

Outcomes {12}

The primary efficacy outcome is a clinically relevant reduction in the TIL score of at least 3 points. The primary safety outcome is the observation of a clinically relevant increase in the median number of episodes of high intracranial pressure per ICU stay by two episodes compared to the control group.

The study drug will be discontinued when all sedatives for ICP treatment are discontinued.

Secondary endpoints include:

The mean of each hour validated ICP (mmHg), measurements per 24 h

Total duration of the initial period of sedative treatment, defined as the start of the first infusion of propofol, midazolam and/or dexmedetomidine until the cessation of the last continuous infusion of either propofol, midazolam, opioids and/or dexmedetomidine, last sedative to control ICP

Total duration of mechanical ventilation (days), defined as all types of ventilation where positive end

expiratory pressure is applied, expressed in cmH₂O (5 cmH₂O minimum)

Total dose of propofol in mg per 24 h

Total dose of midazolam in mg per 24 h

Length of stay in ICU (days): end of stay is defined as application for discharge in the hospital medical record system

Length of stay in hospital (days) defined as day of discharge in the hospital

Mean daily Richmond Agitation-Sedation scale (RASS)

Number of delirium-free days, assessed 3 times daily with the Intensive Care Delirium Screening Checklist (ICDSC) score or Confusion Assessment Method for the ICU (CAM-ICU)

Extended Glasgow Outcome Scale (GOSE) 6 months after TBI onset

ICU mortality

In-hospital mortality

Incidence of barbiturate coma, duration of barbiturate coma and daily dose barbiturates (mg)

Incidence of decompressive craniectomy

Incidence of PRIS documented and diagnosed by the attending physician and defined as:

- Cardiac manifestations, not explainable by a coronary ischemic event:

- ✓ Acute refractory bradycardia leading to asystole, or

- ✓ Electrocardiogram (ECG): widening of QRS-complex, or Brugada-syndrome:

Patterns (particularly Type 1: Coved ST-segment elevation > 2mm in > 1 of V1-V3 followed by a negative T wave), or ventricular tachy-arrhythmias

- Combined with one or more of the following features:

- ✓ Unexplained metabolic acidosis (base deficit > 10 mmol/L)

- ✓ Rhabdomyolysis (creatinine kinase at least five times the upper limit of normal)

- ✓ Hyperlipidaemia (triglyceride levels > 150 mg/dl)

- ✓ Enlarged or fatty liver, apparent on CT or echography

- All occurring in patients receiving propofol for > 24 h

- Diagnosed by the attending physician

Participant timeline {13}

	Within 72 h of admission to the hospital	Within 48 h after screening	Continuously until end of sedation	Daily during ICU admission	6 months (± 1 month) post TBI onset
Screening for inclusion/exclusion criteria	X				
Informed consent		X			
randomization and start of study intervention					
Administration of IMP			X		
Collecting clinical and biochemical data				X	
GOSE questionnaire					X

Sample size {14}

The power calculations of this study are based on two previous studies of similar patient populations [18, 19] in which TIL distributions in 31 and 21 patients respectively had maximum and average daily TIL scores (mean ± standard deviation) of 9.9 ± 3.7 and 10.2 ± 3.9 , and on the large multi-centre study [15] of similar patient populations in which the number of high intracranial pressure episodes per ICU stay was 1–5 (median–interquartile range).

As some correlation might exist between the primary efficacy and safety endpoints, a Bonferroni adjustment for multiple testing would be too strict. We therefore use the multiple testing adjustment via the step-down Holm method. In this scenario for two endpoints, the endpoint with the smallest *p* value test statistic is compared against a 2.5% alpha level, while the remaining endpoint is compared against a 5% alpha level.

Regarding the primary safety endpoint, to detect a clinically relevant increase of two (2) episodes in the median number of high intracranial pressure episodes per ICU stay from the 1–5 (median–interquartile range) baseline, with 80% statistical power and 2.5% alpha level, 45 patients per randomization arm are necessary. To account for potential lack of compliance, the sample size in each arm is further adjusted and increased to 50 patients, resulting in 84.9% statistical power at a 2.5%

alpha level. At a 5% alpha level, this would result in a statistical power of 91%.

Regarding the primary efficacy endpoint, with these 50 patients per randomization arm at an alpha level of 5%, a clinically relevant decrease of at least 3 points in the mean of the daily TIL scores during the study period from 10 ± 4.5 to 7 ± 4.5 can be determined with 95.4% power. At a 2.5% alpha level, this number of patients would result in 91.5% power. Here a slightly larger standard deviation of 4.5 was assumed. In addition, due to the sample size required to demonstrate the safety endpoint, the study also has statistical power above 86% at either 2.5% or 5% alpha level to investigate a TIL score change of 3 points in either direction (as evaluated with a two-sided test).

For both primary endpoints reported power calculations are for one-sided Student *t*-tests, where a log transform was used for the comparison of medians in the safety endpoint as described in [20].

Recruitment {15}

All adult TBI patients requiring sedation and intracranial monitoring are screened for eligibility upon ICU admission up to 72 h after initial hospital admission.

Assignment of interventions: allocation

Sequence generation {16a}

The randomized numbers were generated by computer by the data manager. This process was blinded to the investigators responsible for the conduct of the study.

Concealment mechanism {16b}

After informed consent has been obtained, patients are randomized by the investigator, sub-investigator or their designees using a central computerized randomization tool with restricted access. This generates the treatment number, which corresponds to a sealed envelope containing the information about the allocated treatment arm.

Implementation {16c}

The sealed envelope will be opened by a designated member of the study team, who is not involved in the patient's care. This person will also prepare the study medication. IMP labels are provided by the sponsor (University Hospital Leuven). The label will contain the randomization number, which will be needed in case of emergency unblinding. Access to the study medication (i.e. ketamine and placebo) will be controlled by the local hospital pharmacies. All study drugs will be stored according to local regulations and guidelines of the Summary of Product Characteristics (SmPC) guidelines.

Assignment of interventions: blinding

Who will be blinded {17a}

All persons involved in the daily care of the study patient are blinded to the intervention arm of the study. The patient and family are also blinded to the study arm.

Procedure for unblinding if needed {17b}

In an emergency, patients may be unblinded by the treating physician. Sealed unblinding envelopes with the randomization number on the outside, indicating the patient's allocation to the study arm, will be available in the ICU for this purpose.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data will be collected daily from each hospital's electronic medical record (EMR) by trained clinical Trails assistants (CTAs) and entered into an electronic case report form (eCRF). This system is centrally installed and accessible via a login for each participating centre. Laboratory data are electronically imported in the eCRF. The GOSE follow-up 6 months after TBI onset will be conducted by the CTAs or the treating physician, who will be unaware of the patient's treatment allocation. Patients or their next of kin will be contacted by telephone to complete the questionnaire.

Plans to promote participant retention and complete follow-up {18b}

If a patient withdraws consent for this study after regaining the capacity to consent, data collection will be stopped. The data collected to date will be retained and used for data processing, as informed consent has been obtained from the next of kin since the start of the study. These patients will not be replaced. If the next of kin wishes to withdraw consent before the end of the study, data collection will be stopped, and the patient will be replaced. Due to the nature of the study, loss to follow-up for the primary endpoint (reduction in cumulative TIL score) and safety endpoint (number of intracranial pressure episodes) is expected to be minimal. All patients will be contacted by CTAs or physicians by telephone for the 6-month follow-up visit to complete the GOSE.

Data management {19}

All data is stored in an eCRF, enabling secure and General Data Protection Regulation (GDPR) complaint handling of complaint data. The trial data manager performs extensive consistency checks on the data received. An independent data monitoring committee oversees the trial. Due to the nature of the disease (life-threatening disease, high risk of disability) and the patient population

(patients are unable to consent to the trial), an interim analysis of the safety and efficacy endpoints will be performed by the data monitoring committee after the 50 th patient is discharged from the ICU. All original records, such as consent forms and relevant correspondence, are archived at the participating centres in accordance with local regulations.

Confidentiality {27}

The investigator and the participating site shall treat as confidential all trial-related information and data disclosed to the participating site and/or the investigator during the trial and shall not disclose such information to any third party or use such information for any purpose other than the conduct of the trial. The collection, processing and disclosure of personal data, such as patient health and medical information, will be subject to compliance with the applicable personal data protection and the processing regulations of personal data (the Regulation (EU) 2016/679 also known as the General Data Protection Regulation (“GDPR”). The database is user ID/password protected, with logged access control set at network, directory and database level. The database is stored on secure servers within UZ/KU Leuven, and maximally protected by firewalls and login procedures with daily backups. All study data will be pseudonymized. The research team is obliged to protect the data from disclosure outside the research in accordance with the terms of the research protocol and the informed consent document. The subject’s name or other identifier will be stored separately (site file) from their research data and replaced with a unique code to create a new identity for the subject.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

The trial will not collect and/or store of biological samples for genetic or molecular analysis.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The database will be closed 9 months after inclusion of the last patient. The screening and inclusion lists will be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram. Discrete variables will be presented as percentages and frequencies (ICH episodes), while continuous variables will be presented as means, medians with standard deviation. Discrete variables will be summarized by frequencies and percentages and analysed by (exact) chi-square test or logistic

regression analysis. Continuous variables will be summarized using of means and standard deviations (SD) or medians and interquartile ranges as appropriate and as frequencies (%) N (%) for qualitative variables, and compared using Student’s t -test, Mann–Whitney U test, or chi-squared testing as appropriate. Odds ratios will be estimated using multivariate logistic regression analysis to determine prognostic factors affecting patient outcome. ICU and hospital length of stay, duration of mechanical ventilation, sedation, vasopressor or inotropic support and survival will be assessed by analysis of variance or by Kaplan–Meier analysis and log-rank (Mantel–Cox) significance test, as appropriate. All outcomes will be analysed in an uncorrected manner as well as (jointly) corrected for risk factors (GCS, age, ... risk scores). A priori defined subgroup analyses will be performed for patients after traumatic brain injury (TBI).

Interim analyses {21b}

Due to the nature of the disease (life-threatening medical condition, high risk of disability) and the patient population (patients are unable to consent to the trial), an independent data monitoring committee (DMC) will be established. The members of this committee will not be involved in any aspect of the trial. They will receive blinded safety information. An interim analysis of the safety and efficacy endpoints will be performed by the DMC after discharge of the 50 th patient from ICU.

Methods for additional analyses {20b}

The trial was not powered for any of the secondary endpoints or for subgroup analyses. Therefore, the results of these analyses should be interpreted with caution. The study was designed to ensure complete data collection for the primary endpoints, so imputation for missing values will not be required. There will be subgroup analyses by centre, Marshall score, isolated TBI versus polytrauma and age with the sample mean as the cut-off.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

If a patient withdraws consent for this study after regaining the capacity to consent, data collection will be stopped. The data collected to date will be retained and used for data processing, as informed consent was obtained from next of kin since the start of the study. These patients will not be replaced. If the next of kin wishes to withdraw a previously consented patient before the end of the study, data collection will stop,

and the patient will be replaced. All primary endpoints and all but one secondary endpoint will be collected during hospitalization. Some secondary endpoints may be missing due to slight differences in the standard of care between the participating hospitals. The 6-month follow-up questionnaire will be administered at the follow-up visit with the treating physician. If there is no follow-up visit at 6 months, the patients and/or their relatives will be actively contacted by the CTAs by telephone.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

Data sharing will only be considered only on the basis of collaboration with the PIs, after evaluation of the proposed study protocol and statistical analysis plan.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5 d}

The Study Steering Committee with representation from each participating centre is responsible for the conduct of the BIKe study. In each centre, one lead investigator per unit is responsible for the training of bedside physicians and nurses and for the training and supervision of the CTAs. The CTA team in each centre ensures daily follow-up of patient screening and enrolment, protocol compliance and outcome data collection. In the coordinating centre, the database manager is responsible for maintaining the database and performing data quality checks. Information technology (IT) specialists are responsible for maintaining the patient data management system. Regular meetings are held with the principal investigators and CTAs to discuss the progress of the RCT.

Composition of the data monitoring committee, its role and reporting structure {21a}

An independent data monitoring committee (DMC) will be established due to the nature of the condition: a life-threatening condition with a high risk of disability, and patients are not able to give consent for this clinical trial. The committee will consist of 3 members, all clinicians with experience of clinical trials and traumatic brain injury. The members of the DMC will not be involved in any aspect of this clinical trial. An interim analysis of the safety and efficacy endpoints will be performed by the DMC after the 50 th patient is discharged from the ICU. Blinded safety information will be available for review by the DMC.

Adverse event reporting and harms {22}

TBI is an inherently high morbidity and mortality condition where adverse events may occur. The time frame for collecting adverse events (AEs) is from the first study drug administration to 4 h after the last study drug administration. Serious adverse events (SAEs) will be collected until discharge from the ICU. AEs and SAEs will be reported by the investigator in the eCRF. In the case of an SAE, the reporting investigator completes the SAE form in the eCRF within 24 h of learning of the event and notifies the sponsor of the event by mail within the same timeframe. The causality of each SAE will be assessed by the reporting investigator.

The predictability of each related SAE will be assessed by the sponsor. If the event is considered a suspected unexpected serious adverse reaction (SUSAR), it will be reported to the Ethics Committee, the National Competent Authority and the participating sites in accordance with the applicable legislation.

Following events will be reported as AE or serious adverse reaction (SAR):

- Mortality.
- Acute renal failure: defined by the KDIGO criteria: AKI 3 on serum creatinine level.
- Fulminant liver failure defined according to Hy's Law as jaundice (bilirubin ≥ 2 upper limit of normal (ULN)), ALT and/or AST $\geq 3 \times$ ULN, without findings of cholestasis defined as serum alkaline phosphatase activity less than 2 times the upper normal, and no underlying chronic liver disease; in addition, we will register whether hepatic encephalopathy (if detectable) and/or coagulopathy (INR > 1.5) are present at the same time.
- Ventriculitis: defined by Lozier criteria: organisms cultured from cerebrospinal fluid (CSF), in combination with pathologic cytological and biochemical CSF analysis (leucocytosis, high levels of proteins and/or low levels of glucose) and treated with antibiotics. This will be monitored until ICU discharge.
- Exposure during pregnancy, exposure during lactation, occupational exposure and reportable instances of lack of effect are also defined as serious adverse event.

Following events are not considered adverse events, as they are recorded as secondary endpoints:

- Barbiturate coma
- Decompressive craniectomy
- Intracranial hypertension
- Propofol-related infusion syndrome

The IMP (ketamine) is an authorized drug and therefore reactions and events listed in the current SmPC do not need to be reported.

All serious adverse events must be reported to the sponsor immediately upon first knowledge, except for those for which immediate reporting is not required by the protocol or the current SmPC. The immediate report must be followed by a detailed written report. The immediate report and the follow-up report shall identify the trial subjects by code numbers. The reports should be submitted to the regulatory authorities on request.

Frequency and plans for auditing trial conduct {23}

A designated member of the sponsor's trial staff is assigned to source data monitoring at each centre after the first patient is enrolled. For this purpose, the sponsor and principal investigators will provide direct access to the eCRF, source data and study master file for monitoring. During the trial, additional monitoring will be performed at appropriate times to confirm proper informed consent procedures, compliance with protocol procedures, proper adverse event reporting and follow-up, accuracy of data collected in the eCRF, and study drug information. The supplier of the IMP, ketamine (Pfizer®), will be informed annually.

Plans for communicating important protocol amendments to relevant parties {25}

Substantial changes to the protocol will be submitted as an amendment to the Ethics Committee and the competent authorities. This includes changes that may affect the conduct of the trial or the safety of the patients. This will be communicated to the participating centres.

Dissemination plans {31a}

The results of the study will be published in a multi-centre joint publication in a peer-reviewed scientific journal with data from all clinical sites involved in the study.

Discussion

Sedation is one of the key elements in the management of TBI and prevention of secondary injury, although it has significant side effects [2]. Ketamine was banned from the neuro ICU for decades after the publication of two small, observational studies and remains under FDA precaution for the use in patients with elevated cerebrospinal fluid pressure, despite increasing clinical and experimental evidence of its potential neuroprotective effects [6–9]. The BIKe trial will randomize 100 severe TBI patients to either ketamine (50) or placebo (50) as an adjunct to a standard sedation regimen. All adult TBI patients, requiring sedation and ICP monitoring within 72 h of admission, are eligible for inclusion. This will

allow us to include patients, whose clinical situation deteriorates in the first days after hospitalization. Enrolment will be carried out by the investigators, sub-investigators or their deputies at the central and participating hospitals after elimination of exclusion criteria. After enrolment, patients will be randomized using a computerized application hosted by the central hospital and accessible to local research staff. Access to the blinded randomization code will be restricted. IMP will be started within 6 h of randomization, by ICU nurses blinded to the randomization. IMP will be stopped when the ICP control sedative is discontinued. A comprehensive Glasgow Outcome Scale will be obtained from the patient approximately 6 months after the start of the TBI.

As these patients are unable to give their consent to this study, consent will be given by proxy. This may result in a delay in obtaining consent and includes the possibility that the patient, when awake, may wish to withdraw and not participate in the study. We have an opt-out procedure for this situation. The data collected will be retained, as consent was given during the collection period.

The second limitation is the 72-h randomization window. This time window allows us to include patients with initial moderate TBI who have progressed to severe TBI. However, this delays the start of the study medication.

Thirdly, TBI is a very heterogeneous disease, ranging from an acute subdural haematoma, to diffuse axonal injury and contusions. This results in a variable course of the disease with variable duration of sedation: from 24 h up to more than a week. In the majority of TBI patients, the course of the disease and outcome are unpredictable.

Previous prospective clinical trials have used ketamine as one of the two main anaesthetic agents for sedation, at anaesthetic doses [8, 9, 21]. In our study, ketamine is added to a standard sedation regimen at a sub-anaesthetic dose, which may not be sufficient to have an effect on the TIL score.

Finally, the follow-up of TBI patients can be difficult due to the status in which they leave the hospital: return home, rehabilitation or coma clinic.

In conclusion, this is the first placebo-controlled study to investigate the safety of ketamine in TBI patients. This study may open up possibilities for the use in other brain injured patients.

Trial status

Protocol version 1.5 date 03–05–2021.

The first patients were enrolled at the central hospital in September 2021. In the following year, the 7 participating sites were gradually started separately. An 8th centre was recently added. Currently 50 patients are enrolled. The study is expected to take a further 36 months to complete.

Abbreviations

AE	Adverse event
Alk Phos	Alkaline phosphatase
ALT	Alanine transaminase
AM	After midnight
AST	Aspartate aminotransferase
BIKe	Brain Injury and Ketamine
BMI	Body mass index
BTF	Brain Trauma Foundation
BUN	Blood urea nitrogen
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CSF	Cerebrospinal fluid
CTA	Clinical trial assistant
CT scan	Computer tomography
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMR	Electronic medical record
ESICM	European Society of Intensive Care Medicine
GABA	Gamma-aminobutyric acid
GCS	Glasgow coma scale
GOSE	Extended Glasgow Outcome Scale
ICF	Informed consent form
ICDSC	Intensive Care Delirium Screening Checklist
ICH	Intracranial hypertension
ICP	Intracranial pressure
ICU	Intensive care unit
IMP	Investigational medicinal product
INR	International normalized ratio
KDIGO	Kidney disease: improving global outcome
MAP	Mean arterial pressure
µg	Microgram
mg	Milligram
ml	Millilitre
NaCl 0.9%	Sodium chloride
NMDA receptor	N-methyl-D-aspartate-receptor
PaCO ₂	Partial pressure of carbon dioxide
PaO ₂	Partial pressure of oxygen
PRIS	Propofol-related infusion syndrome
PT	Prothrombin time
RASS	Richmond Agitation-Sedation scale
RCT	Randomized controlled trial
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SUSAR	Severe unexpected adverse reaction
TBI	Traumatic brain injury
TIL	Therapy intensity level
ULN	Upper limit of normal
UZ	Universitaire Ziekenhuizen Leuven

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-025-08835-5>.

Supplementary Material 1. Appendices.
Supplementary Material 2. SPIRIT checklist.

Acknowledgements

We thank the following individuals and groups for invaluable contributions to this study.

- The patients and their families who consented to participate in the trial.
- The ICU nurses and physicians responsible for patient care in all participating centres.
- The members of the data safety and monitoring committee for their valuable guidance.
- Professor Giuseppe Citerio (San Gerardo Hospital, Monza, Italy) for initiating the discussion that led to the conception of this trial.

Authors' contributions {31b}

Concept, study design, funding and supervision: GM. Study protocol: VDS, LM and GM. eCRF: PW. Randomization tool: PW. Manuscript draft: VDS. Manuscript writing: GM, LM, VDS. All authors approved the final version of the manuscript.

Funding {4}

Pfizer, Pfizer Grant 53234057, Geert Meyfroidt, Established Investigator Award 2016, European Society of Intensive Care Medicine, Universitaire Ziekenhuizen Leuven, KU Leuven, Clinical Council for Research, Veerle Tineke De Sloovere, Education (KOOR), Veerle Tineke De Sloovere, Fonds Wetenschappelijk Onderzoek, Senior Clinical Investigator Grant 1843123 N.

- Established Investigator Award 2016, European Society of Intensive Care Medicine, to Prof. Dr. G. Meyfroidt.
- Departmental funding, Department of Intensive Care Medicine, University Hospitals Leuven, to Prof. Dr. G. Meyfroidt.
- Klinisch Onderzoeksfonds, University Hospitals Leuven to Dr. V. De Sloovere.
- The investigational medicinal product, ketamine (Ketalar®) is provided by Pfizer®, via Pfizer Global Medical Grants (Pfizer Grant 53,234,057).

Data availability {29}

The first patients were enrolled at the coordinating hospital in September 2021. In the following year, the 7 participating sites were gradually started separately. An 8th centre was recently added. Currently 70 patients are enrolled. At the current rate of enrollment, the study is expected to be completed in 2027.

Declarations

Ethics approval and consent to participate {24}

The protocol and informed consent forms have been approved by the Research Ethics Committee of the UZ/KU Leuven, acting as the central ethics committee, and by the local ethics committees of all participating centres for local participation. An annual progress report will be submitted to the Ethics Committee and the National Competent Authority, including an update on the number of participants enrolled in each centre, and an overview of serious adverse events.

Consent for publication {32}

Written informed consent was obtained from the patient's next of kin for all study patients.

Competing interests {28}

None.

Author details

¹Department of Anesthesiology, University Hospitals Leuven, Leuven, Belgium. ²Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium. ³Department of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium. ⁴Department of Anesthesiology and Intensive Care Medicine, Turnhout, Turnhout, AZ, Belgium. ⁵Department of Anesthesiology and Intensive Care Medicine, Sint-Jan Brugge-Oostende AV, Brugge, AZ, Belgium. ⁶Department of Anaesthesiology and Intensive Care Medicine, Jessa Hospital, Hasselt, Belgium. ⁷Department of Intensive Care Medicine, CHU de Liège, Liège, Belgium. ⁸Department of Intensive Care Medicine, AZ Delta, Roeselare, Belgium. ⁹Department of Intensive Care Medicine, CHR La Citadelle Liège, Liège, Belgium. ¹⁰Department of Intensive Care Medicine, AZ Imelda, Bonheiden, Belgium. ¹¹Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium.

Received: 2 February 2024 Accepted: 6 April 2025

Published online: 28 May 2025

References

- Godoy DA, Badenes G, Pelosi P, Robba C. Ketamine in acute phase of severe traumatic brain injury "an old drug for new uses?". *Crit Care* 2021.
- Opdenakker O, Vanstraelen A, De Sloovere V, Meyfroidt G. Sedatives in neurocritical care: an update on pharmacological agents and modes of sedation. *Curr Opin Crit Care*. 2019;25(2):97–104.

3. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus non-benzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2013;41:30–8.
4. Zaal IJ, Devlin JW, Hazelbag M, et al. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med*. 2015;41:2130–7.
5. Krajcova A, Waldauf P, Andel M, Duska F. Propofol infusion syndrome: a structured review of experimental studies and 153 published case reports. *Crit Care*. 2015;19:1–9.
6. Gardner AE, Olson BE, Lichtiger M. Cerebrospinal-fluid pressure during dissociative anesthesia with ketamine. *Anesthesiology*. 1971;35:226–8.
7. Shapiro HM, Wyte SR, Harris AB. Ketamine anaesthesia in patients with intracranial pathology. *Br J Anaesth*. 1972;44(11):1200–4.
8. Zeiler F, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP in traumatic brain injury. *Neurocrit care*. 2014;21:163–73.
9. Hudetz JA, Pagel PS. Neuroprotection by ketamine: a review of the experimental and clinical evidence. *J Cardiothorac Vasc Anesth*. 2010;24(1):131–42.
10. Bell JD. In vogue: ketamine for neuroprotection in acute neurologic injury. *Anesthesia Analgesia*. 2017;24(4):1237–43.
11. Hertle DN, Dreier JP, Woitzik J, Hartings JA, Bullock R, Okonkwo DO, et al. Effect of analgesics and sedatives on the occurrence of spreading depolarizations accompanying acute brain injury. *Brain*. 2012;135(8):2390–8.
12. Sakowitz OW, Kiening KL, Krajewski KL, Sarrafzadeh AS, Fabricius M, Strong AJ, et al. Preliminary evidence that ketamine inhibits spreading depolarizations in acute human brain injury. *Stroke*. 2009;40(8):e519–22.
13. Ward JL, Harting MT, Cox CS, Mercer DW. Effects of ketamine on endotoxin and traumatic brain injury induced cytokine production in the rat. *J Trauma*. 2011;70(6):1471–9.
14. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6–15.
15. Guiza F, Depreitere B, Piper I, Citerio G, Chambers I, Jones PA, Milly Lo T, Enblad P, Nilsson P, Feyen B, Jorens P, Maas A, Schuhman MU, Donald R, Moss L, Van den Berghe G, Meyfroidt G. Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. *Intensive Care Med*. 2015;41:1067–77.
16. Maas AI, Harrison-Felix CL, Menon D, Adelson PD, Balkin T, Bullock R, Engel DC, Gordon W, Langlois-Orman J, Lew HL, Robertson C, Temkin N, Valadka A, Verfaellie M, Wainwright M, Wright DW, Schwab K. Standardizing data collection in traumatic brain injury. *J Neurotrauma*. 2011;28:177–87.
17. Hawryluk GWJ, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Med*. 2019;45(12):1783–94.
18. Zuecher P, Groen JL, Aries MJ, Steyerberg EW, Maas AI, Ercole A, Menon DK. Reliability and validity of the therapy intensity level scale: analysis of clinimetric properties of a novel approach to assess management of intracranial pressure in traumatic brain injury. *J Neurotrauma*. 2016;33(19):1768–74.
19. Fletcher JJ, Wilson TJ, Rajajee V, Davidson SB, Walsh JC. Changes in therapeutic intensity level following airway pressure release ventilation in severe traumatic brain injury. *J Intensive Care*. 2018;33(3):196–202.
20. O'Keeffe AG, Ambler G & Barber JA. Sample size calculations based on a difference in medians for positively skewed outcomes in health care studies. *BMC Med Res Methodol*. 2017;17:157.
21. Gregers MCT, Mikkelsen S, Lindvig KP, Bröchner AC. Ketamine as an anesthetic for patients with acute brain injury: a systematic review. *Neurocrit Care*. 2020;33(1):273–82.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.