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ORIGINAL ARTICLE

Mild Hypothermia Versus Normothermia During Barbiturate Coma Therapy After Severe Traumatic Brain Injury: Protocol for a Randomized Controlled Trial

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Abstract: **Introduction:** Severe traumatic brain injury (TBI) is a leading cause of death and long-term disability worldwide. Therapeutic hypothermia may lower intracranial pressure (ICP) and reduce metabolic demand. This study aims to compare mild therapeutic hypothermia with controlled normothermia in adult TBI patients undergoing Barbiturate Coma Therapy (BCT), and to explore artificial intelligence (AI)-assisted prognostic models. **Methods:** This single-center, pilot, parallel-group randomized trial evaluates the feasibility and safety of adding mild hypothermia to BCT and explores early signals of benefit or harm. The primary outcome, six-month Glasgow Outcome Scale–Extended (GOSE), is reported descriptively with exact 95% confidence intervals. Secondary outcomes include Cerebral Performance Category, mortality, duration of mechanical ventilation and vasopressor use, intensive care unit (ICU)/hospital length of stay, complications, and physiological/laboratory trends. An exploratory AI-assisted substudy (using prospectively collected clinical, radiological, physiological, and laboratory data) applies LASSO regression to admission predictors of six-month unfavorable outcome and mortality.

Keywords: Brain Injuries; Traumatic; Hypothermia; Induced; Glasgow Outcome Scale; Prognosis

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1. Introduction

Traumatic brain injury (TBI) is a major cause of death and long-term disability worldwide (1-4). Severe TBI (sTBI) carries high mortality and substantial residual impairment among survivors (2, 5). Although the primary mechanical insult is irreversible (5, 6), secondary injury evolves over hours to days via raised intracranial pressure (ICP), edema, impaired perfusion, blood–brain barrier failure, mitochondrial dysfunction, excitotoxicity, inflammation, oxidative stress, and aggravators including hypoxia, hypotension, fever, and metabolic derangement (5, 6). This secondary phase is where the therapeutic window lies. If intervention is initiated early and systematically, these processes could be slowed or interrupted before neurons are lost irreversibly (6, 7).

Sustained intracranial hypertension strongly predicts poor outcome and death after sTBI (6, 8), as rising ICP lowers cerebral perfusion pressure, worsens ischemia, and increases herniation risk (6, 9). Management follows stepwise escalation, sedation, ventilatory/hemodynamic optimization, osmotherapy (including hypertonic saline) (10), cerebrospinal fluid (CSF) drainage, neurosurgery, decompressive craniectomy, and finally barbiturate-induced metabolic suppression (6, 11). Temperature control remains attractive because it simultaneously influences metabolism, perfusion, inflammation, and neuroprotection (7, 12).

Hypothermia's rationale is that lowering cerebral metabolic demand and inflammatory activity may complement thiopental-induced suppression. Animal models consistently show neuroprotection with controlled hypothermia (13, 14), and fever independently worsens outcome, supporting active temperature management even without deep cooling (7, 12).

Clinical evidence, however, has been inconsistent. Early cardiac-arrest studies suggested benefit (15, 16). TTM2 found no difference in six-month mortality or neurological outcome between 33°C hypothermia and normothermia with active fever prevention (50% vs. 48%) (17), and hypothermia carries rec-

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ognized risks: hemodynamic instability, electrolyte derangement, coagulopathy, insulin resistance, infection (16). Safe implementation requires careful monitoring and experienced teams (18).

Trials in sTBI have been similarly inconclusive: Eurotherm3235 improved ICP control but worsened six-month outcome (favorable outcomes 25.7% vs. 36.5%) (19). The POLAR trial, testing early prophylactic cooling, showed no benefit either (favorable outcomes 48.8% vs. 49.1%) (20). An umbrella review of 30 systematic reviews found conflicting mortality/outcome effects, with pneumonia, coagulopathy, arrhythmia, and electrolyte abnormalities as recurring harms (21).The field has largely responded by moving away from routine or prophylactic hypothermia toward active fever prevention and controlled normothermia as the default, reserving subnormothermic targets for carefully selected patients under close monitoring (7).

A key methodological issue is comparing hypothermia against actively maintained, not passive, normothermia, to avoid confounding by simple fever prevention (7, 12). The inconsistent results may also reflect the real costs of cooling: shivering, deeper sedation requirements, electrolyte shifts, coagulopathy, infection, hemodynamic instability, and rebound ICP during rewarming (12, 20). Negative results from broad TBI trials may also not generalize to all subgroups, since effect likely depends on injury stage, lesion type, and whether cooling is used as targeted rescue rather than prophylaxis (7, 12, 13). However, in high-risk patients, the potential costs of hypotension, vasopressor dependence, prolonged ventilation, infection, dysmotility, and loss of the neurological examination must also be considered (22, 23). In these patients, the benefit–harm balance may differ substantially: mild hypothermia could either limit ICP-driven injury or amplify arrhythmia, hemodynamic instability, coagulopathy, infection, and rebound ICP (7, 12).

Predicting outcomes in sTBI is its own challenge. Validated tools like CRASH and IMPACT have improved risk stratification by combining admission variables: age, Glasgow Coma Scale score, pupillary reactivity, hypotension, hypoxia, and computed tomography (CT) findings (24, 25). These models perform reasonably well and have been validated in diverse cohorts. But they capture a snapshot at admission and may miss the dynamic intensive care unit (ICU) story: evolving ICP trajectories, vasopressor requirements, metabolic and inflammatory changes, organ dysfunction, and treatment complications (25, 26). Machine-learning approaches using richer longitudinal datasets have shown promise for predicting mortality and functional outcome in TBI (27, 28). Yet algorithmic sophistication is not the same as predictive accuracy. Many machine-learning studies in neurocritical care suffer from overfitting, missing data, poor calibration, and lack of external validation; problems that are especially acute in single-center cohorts where the number of candidate predictors can easily outstrip the sample size (29, 30).

The TRIPOD+AI (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis + artificial intelligence) statement provides updated guidance for reporting regression- or machine-learning-based prediction models, emphasizing predictor selection, missing-data handling, calibration, validation, and interpretability (31). Embedding a prognostic substudy within a prospective trial reduces retrospective bias and enables assessment of dynamic predictors in a relatively homogeneous, high-acuity cohort (27, 31). Serial physiological/laboratory/biomarker data, vasopressor exposure, acid–base status, renal/coagulation indices, inflammatory/oxidative-stress markers, and thyroid-axis hormones may clarify how temperature modulation interacts with thiopental-induced suppression (32).

Against this background, we conducted a single-center, pilot, exploratory, parallel-group randomized trial comparing mild therapeutic hypothermia (34–35°C) with active controlled normothermia (36–37°C) in adults with sTBI requiring Barbiturate Coma Therapy. In parallel, we built an exploratory AI-assisted prognostic substudy examining whether prospectively collected clinical, radiological, physiological, laboratory, and treatment variables could provide preliminary signals for predicting in-hospital mortality and six-month unfavorable functional outcome. The trial was designed primarily to test feasibility, safety, and early effect-size signals to guide a future adequately powered multicenter study, rather than to provide a definitive efficacy verdict.

2. Methods

2.1. *Study design and setting*

This single-center, pilot, exploratory, parallel-group randomized trial compares mild therapeutic hypothermia with active-controlled normothermia in adults with sTBI requiring Barbiturate Coma Therapy as part of standard tiered management. A prospective prognostic substudy evaluating clinical, radiological, physiological, laboratory, and AI-assisted predictors of mortality and functional outcome is embedded within the therapeutic trial. A superiority-type analytical framework governs the main therapeutic comparison, but the trial is not powered for confirmatory efficacy testing, and all treatment-effect estimates are therefore interpreted descriptively and treated as hypothesis-generating rather than as a basis for clinical recommendations.

Recruitment and treatment occur in the adult ICU of Imam Reza Hospital, Tabriz University of Medical Sciences, Iran, a tertiary referral center for trauma, neurosurgery, and neurocritical care with invasive monitoring, mechanical ventilation, advanced imaging, neurosurgical capability, and prolonged critical care capacity.

2.2. *Participants*

Adults aged 18–75 with sTBI (post-resuscitation GCS ≤8), CT evidence of traumatic intracranial pathology, and a clinical indication for Barbiturate Coma Therapy arising during standard tiered management after first-tier measures (head-of-bed elevation, optimized sedation/analgesia, fever prevention, normocapnia [PaCO2 35–40 mmHg], adequate oxygenation) and, where indicated, second-tier measures (osmotherapy with mannitol [0.25–1.0 g/kg] or hypertonic saline, brief controlled hyperventilation [PaCO2 30–35 mmHg], CSF drainage, neuromuscular blockade, decompressive craniectomy) have been applied. Patients started on thiopental primarily for hemodynamic instability rather than tiered sTBI management are excluded, as are patients with pregnancy or lactation, pre-existing severe neurological disability, non-survivable injury, uncontrolled hemorrhage or severe coagulopathy, refractory hemodynamic instability despite vasopressors, severe active infection contraindicating cooling, unstable significant arrhythmia, or concurrent enrolment in an interfering interventional study.

Because eligible patients typically lack decision-making capacity, written informed consent is obtained from a legally authorized representative or first-degree relative before study procedures whenever feasible. When urgency precludes prior consent, emergency deferred consent is used where locally permitted, with representative consent sought as soon as possible; patients who regain capacity are subsequently informed and asked for ongoing consent (33).

2.3. *Randomization and allocation concealment*

Participants are randomized 1:1 to hypothermia or normothermia. An independent biostatistician, uninvolved in recruitment, treatment, or assessment, generates the sequence using variable permuted blocks (sizes 2, 4, 6) (34, 35), stratified by bilateral pupillary non-reactivity (yes/no) and post-resuscitation GCS motor score (1–3 vs 4–6), with separate sequences per stratum. Allocation is implemented via a centrally held, secure web-based system releasing assignments only after eligibility confirmation and consent, ensuring auditable, concealed allocation.

2.4. *Blinding*

This is a single-blind trial. Blinding the treating physicians and bedside nursing staff is not feasible, because temperature-management interventions are plainly visible during routine ICU care. To limit resulting bias, outcome assessors, follow-up personnel, and data analysts remain unaware of allocation until the database is locked. The six-month outcome assessor and trial statistician remain blinded throughout, and six-month functional outcome is ascertained via a structured GOSE interview conducted by a trained, blinded assessor to reduce ascertainment bias. Unmasking is permitted only when a serious safety concern makes disclosure of treatment allocation necessary, and any such breach is documented as a protocol deviation and reviewed at scheduled safety monitoring visits.

2.5. *Standard care in both groups*

All patients receive protocol-based sTBI management, airway protection, mechanical ventilation, invasive hemodynamic monitoring where indicated, sedation/analgesia, osmotherapy, vasopressors, seizure prophylaxis/treatment, neurosurgical intervention, nutrition, glucose control, and other supportive measures at clinical discretion. All major co-interventions (osmotherapy, decompressive craniectomy, CSF drainage, anticonvulsants, vasopressor requirement, renal replacement therapy, other rescue measures) are prospectively documented.

2.6. *Interventions*

2.7. *Barbiturate Coma Therapy (BCT)*

All randomized patients will undergo sodium thiopental using a standardized institutional protocol, applied within the standard tiered management of severe traumatic brain injury (36-38). Loading: 2.5 mg/kg intravenous (IV) every 15 minutes for up to 4 doses (maximum cumulative 10 mg/kg), titrated to hemodynamic tolerance at the intensivist's discretion. Maintenance: 5 mg/kg/h for 3 hours, then 2 mg/kg/h, adjusted per standard practice; where continuous EEG is available, dosing may target burst suppression with 6–10 second interburst intervals. Planned duration is 72–96 hours, extendable if refractory and hemodynamically tolerated. Predefined dose-reduction triggers (mean arterial pressure <65 mmHg despite optimized vasopressors, or significant arrhythmia) prompt reduction by 1 mg/kg/h every 30 minutes to the lowest adequate dose; noradrenaline is first-line for perfusion support, with further dose reduction or early discontinuation if instability persists. Discontinuation involves tapering by 1 mg/kg/h every 4–6 hours with monitoring for rebound intracranial hypertension. Cumulative dose, escalation pattern, infusion duration, reasons for early discontinuation, and taper details are recorded prospectively for all patients.

2.8. *Mild therapeutic hypothermia group*

Core temperature is lowered to 34–35°C as soon as possible after randomization and sodium thiopental initiation, and maintained for 72–96 hours using a non-invasive, servo-controlled surface cooling system (e.g., Arctic Sun or equivalent) applied to torso and thighs, with consistent device/settings across patients; intravascular catheters are not used as the primary method. Overshoot below 33.5°C triggers an alarm and bedside adjustment; temperature <33.0°C for >30 minutes is recorded as a protocol deviation (39). Shivering is assessed via the validated 4-point Bedside Shivering Assessment Scale (BSAS), with stepwise escalation from non-pharmacological counter-warming to optimized sedation/analgesia and pharmacological adjuncts, while avoiding unnecessary deep sedation or paralysis (40, 41). Fever burden (time–temperature area above 37°C) and percentage time-in-target-range are calculated for both arms.

2.9. *Active controlled normothermia group*

Core temperature is actively maintained at 36–37°C throughout, via antipyretics, environmental adjustment, and active cooling as needed, with continuous monitoring identical to the intervention arm. This active comparator ensures the trial captures the effect of hypothermia itself rather than the mere presence of temperature control. The intervention procedures, temperature targets, monitoring methods, thiopental regimen, safety limits, rewarming procedures, anti-shivering management, and ICP/CPP management strategies for both randomized groups are summarized in Table 1.

2.10. *Data collection*

Baseline data include age, sex, injury mechanism, injury-to-admission intervals, GCS and components, pupillary reactivity, pre-enrolment hypoxia/hypotension, extracranial injury burden, and neurosurgical history, plus CT assessed via a structured form (lesion type/distribution, Marshall and Rotterdam scores, traumatic subarachnoid hemorrhage, mass lesion characteristics, midline shift, basal cistern status), repeated at follow-up. Serial ICU variables (temperature metrics, hemodynamics, vasopressor requirement, ICP/cerebral perfusion pressure where monitored, ventilator settings, arterial blood gases, fluid balance, urine output, cumulative sodium thiopental dose, osmotherapy, neuromuscular blockade, decompressive craniectomy, other co-interventions) and laboratory variables (hematology, coagulation, glucose, renal/hepatic panels, electrolytes, inflammatory markers, troponin I, amylase/lipase, thyroid axis, 25-hydroxyvitamin D, B12, cultures, superoxide dismutase, creatine phosphokinase, urinalysis) are recorded pre-intervention and daily. Severity/follow-up scales include APACHE, SOFA, GOSE, Cerebral Performance Category, and MoCA where feasible; baseline nutritional risk uses BMI, albumin, and NUTRIC/mNUTRIC scores.

2.11. *Outcomes*

Six-month functional status via GOSE as primary outcome, assessed by a trained, blinded research nurse/coordinator uninvolved in intervention delivery, using a certified structured interview (in-person or telephone), with caregiver/next-of-kin proxy if the patient cannot communicate. Patients dying before six months receive GOSE=1, included in all primary analyses; unmasking occurs only for documented serious safety concerns.

GOSE is analyzed as a seven-level ordinal outcome (scores 1-8, with 2 pooled into 1) using proportional odds ordinal logistic regression with treatment as predictor; the Brant test checks the proportional odds assumption, with Mann-Whitney rank-sum testing as the prespecified alternative. A key secondary analysis dichotomizes GOSE into unfavorable (1-4) versus favorable (5-8) outcomes via logistic regression, reporting common odds ratios (ordinal) and risk differences/ratios (dichotomized) with 95% CIs. If >10% of six-month GOSE data are missing, multiple imputation under missing-at-random serves as a sensitivity analysis. Given the pilot nature of the trial, results are interpreted descriptively without definitive efficacy claims.

Secondary outcomes include Cerebral Performance Category (ICU/hospital discharge, 1 and 6 months), all-cause mortality (ICU/hospital discharge, 6 months), duration of mechanical ventilation and vasopressor support, ICU/hospital length of stay, and six-month MoCA where feasible. Prespecified adverse events (infection, arrhythmia, hemodynamic instability, coagulopathy/bleeding, electrolyte disturbance, acute kidney injury, seizures, device-related skin injury) are reported as secondary outcomes.

2.7.1 Exploratory outcomes comprise serial trajectories of oxidative stress, thyroid, inflammatory, renal, coagulation, cardiac, and other biochemical/physiological markers during cooling and rewarming. Definitions, assessment methods, and prespecified time points for the primary, secondary, and exploratory outcomes are summarized in Table 2.

2.12. *AI-assisted prognostic substudy*

This exploratory substudy uses the trial dataset to generate hypotheses about associations between candidate predictors and two outcomes: six-month unfavorable functional status and in-hospital mortality without expectation of an externally validated, clinically deployable model. "AI-assisted" follows the 2024 TRIPOD+AI framework, applicable regardless of whether methods are regression- or machine-learning-based, and the substudy follows its full 27-item checklist(31) .

Two exploratory outcomes will be examined: six-month unfavorable functional status and in-hospital mortality. Given the limited sample size, six-month unfavorable functional outcome will serve as the principal modelling endpoint, whereas the mortality analysis will be treated as secondary and descriptive. This distinction is important because outcome-specific event frequencies directly affect the feasibility of model development, and the number of in-hospital deaths is expected to be lower than the number of unfavorable six-month outcomes.

Sample size was assessed using the Riley et al. framework for binary prediction models rather than informal events-per-variable rules: assuming an event proportion of ~0.70, anticipated adjusted Cox–Snell R^2 of 0.15, and target shrinkage of 0.90, approximately 165 participants are required for three predictor parameters (219 for four). With a planned sample of 42 and 28–32 expected unfavorable outcomes, the substudy is underpowered for formal model development and must be regarded as exploratory; any derived model represents a preliminary signal rather than a stable tool (42).

To preserve the data-to-parameter ratio, the candidate predictor set is restricted a priori to three clinically justified variables available pre-randomization: bilateral pupillary non-reactivity, post-resuscitation GCS motor score, and Rotterdam CT score. A fourth candidate, mean ICP during the first 24 hours, may be explored only in sensitivity analysis if unfavorable outcomes exceed 35 with adequate completeness, clearly labelled exploratory given increased overfitting risk. No additional predictors, stepwise procedures, or post hoc expansion will be used, though LASSO's embedded shrinkage permits data-driven coefficient selection within the prespecified set, which will be transparently reported (43).

For the principal endpoint, LASSO-penalized logistic regression is the primary approach, with λ selected via leave-one-out cross-validation (binomial deviance). LASSO is preferred over unpenalized regression to reduce coefficient inflation, though substantial sampling variability is expected at this sample size; cross-validated λ instability will be acknowledged. No random forest, boosting, neural network, or other ensemble method will be applied given insufficient sample size. Mortality modelling remains strictly descriptive/univariable if deaths are too few for multivariable analysis.

Continuous predictors are entered as linear terms; restricted cubic splines are avoided given insufficient sample size for stable nonlinear estimation. All three baseline predictors are expected complete; if missingness exceeds 5%, complete-case analysis remains primary, with single stochastic imputation as sensitivity analysis.

Internal validation uses bootstrap resampling (2,000 iterations) with full model-building repeated per resample (including λ re-selection) to derive optimism-corrected discrimination (C-statistic) and calibration (slope, intercept); split-sample validation is avoided as inefficient at this sample size. Performance is reported via optimism-corrected C-statistic, calibration slope/intercept, a LOESS-smoothed calibration plot (interpreted cautiously given n≈42), and Brier score, with predictor effects reported as penalized log-odds coefficients and any interval estimates treated as descriptive.

The substudy will follow the 2024 TRIPOD+AI statement with the completed checklist submitted as supplementary material, explicitly describing predictor selection, missing-data handling, model-building, validation, calibration/discrimination, and the absence of claims to clinical readiness or generalizability. Predefined limitations include: sample size well below recommended minimums; inability of internal validation to replace external validation; admission-only predictors missing dynamic ICU evolution; potential instability in λ selection and calibration displays; greater underpowering for mortality than functional outcome; and unsuitability of any resulting model for clinical decision-making outside research.

2.13. *Safety monitoring*

An independent Data Safety Monitoring Board (DSMB), comprising two experienced intensivists or neurocritical care physicians and one independent biostatistician uninvolved in patient recruitment, clinical management, or outcome assess-

ment, is convened before enrolment begins. The DSMB operates according to a written charter approved by the institutional ethics committee, defining membership, responsibilities, meeting schedule, and decision-making procedures (44). Unblinded safety data are provided at predefined time points: an initial review after the first 10 enrolled patients, allowing early assessment of safety signals, and a second scheduled interim review after 20 patients complete 30-day follow-up. The DSMB may additionally convene at any time if the coordinating center becomes aware of a cluster of serious adverse events that might plausibly relate to the intervention.

Prespecified stopping rules trigger DSMB-recommended suspension or termination if: (1) ≥3 severe treatment-attributable arrhythmias occur among the first 20 hypothermia patients enrolled; (2) interim analysis shows statistically significant excess 30-day mortality in the hypothermia group (one-sided Fisher's exact test, $p<0.05$); or (3) the DSMB judges continued risk unacceptable. Individual stopping criteria for hypothermia include: mean arterial pressure <55 mmHg for >15 minutes despite noradrenaline ≥0.5 μg/kg/min and adequate volume resuscitation; hemodynamically compromising arrhythmia; INR >3.5 with active bleeding; core temperature <33°C for >30 minutes; or intensivist judgment of unacceptable risk. Adverse events consistent with known thiopental/hypothermia effects (hypotension, electrolyte disturbance, arrhythmia, coagulopathy, infection, acute kidney injury, rebound intracranial hypertension) are classified as expected, and all other events as unexpected. Serious adverse events are reported to the ethics committee within 7 days and to the trial registry within 15 days.

2.14. *Statistical analysis*

All efficacy analyses follow intention-to-treat; a parallel per-protocol analysis restricts to participants maintaining assigned temperature regimen for ≥48 hours without crossover. The primary effect of hypothermia versus normothermia on six-month GOSE is expressed as a common odds ratio from a proportional odds model, with intercurrent events handled under a treatment-policy strategy. The primary model contains treatment alone, with sensitivity analysis adding randomization strata; proportional odds is checked descriptively (Brant test, cumulative odds plots) without altering the primary analysis, alongside a Mann–Whitney U/Hodges–Lehmann sensitivity analysis (45-48).

Binary outcomes use Firth's penalized logistic regression with profile-likelihood CIs, supported descriptively by Fisher's exact test; continuous outcomes use Mann-Whitney U tests; time-to-event outcomes use Kaplan-Meier curves and log-rank tests, interpreted descriptively; and repeated measures use linear mixed-effects models (fixed effects for time, group, interaction; random participant intercept), with a prespecified fallback simplification if convergence fails (45, 49). Missing six-month GOSE data are handled via multiple imputation by chained equations (missing-at-random), regardless of missing fraction, with complete-case analysis as sensitivity. No multiplicity adjustment is applied across secondary/exploratory outcomes, which are read descriptively. No interim efficacy analysis is planned; the DSMB conducts a single prespecified safety review using safety data only. The trial statistician and steering committee finalize the statistical analysis plan (SAP) before database lock. Analyses use R (≥4.3) with rms, lme4, and logistf.

2.15. *Sample size*

The original sample size of 42 (21/group) was calculated for hospital mortality, not the stated primary outcome of six-month GOSE, using a two-sided alpha of 0.05 and 80% power based on prior barbiturate coma studies. With only 42 participants, the trial cannot detect a clinically meaningful ordinal GOSE difference (several hundred participants would be needed for a common odds ratio of 1.5-2.0 at 80% power), so it is explicitly framed as pilot/exploratory, aimed at feasibility, safety, and early signal detection. Six-month GOSE remains the primary outcome for descriptive reporting with exact 95% CIs, informing future multicenter trial design, while hospital mortality and ICP burden serve as co-primary safety/physiological endpoints; all analyses, including the AI substudy, are exploratory and hypothesis-generating.

2.16. *Ethics and registration*

The study has ethics approval from Tabriz University of Medical Sciences and follows the Declaration of Helsinki and applicable national regulations. It is registered as IRCT20090923002496N14. Data confidentiality is maintained; only authorized personnel access identifiable data, and analyses use de-identified datasets where possible.

2.17. *Limitations*

Several limitations warrant emphasis. First, the single-center pilot design and small sample size limit statistical power, rendering estimates of treatment effect on six-month GOSE and mortality imprecise and inherently exploratory. Second, because the trial was not conceived as a confirmatory efficacy study, all clinical, physiological, biomarker, and AI-assisted prognostic analyses are hypothesis-generating; the observed distributions and confidence intervals are best used to inform the design of a future, adequately powered multicenter trial rather than to drive immediate changes in clinical practice. Third, blinding of bedside clinicians and treating physicians is not feasible because the intervention is visible and integral to daily care, creating a risk of performance bias even though outcome assessment and data analysis remain blinded. Fourth, sTBI is biologically heterogeneous; even among patients receiving sodium thiopental within tiered management, differences in lesion type, injury mechanism, timing of intervention, prior hypotensive or hypoxic insults, and neurosurgical history may all influence the response to hypothermia in ways this trial is not powered to examine. Fifth, the true therapeutic "dose" of hypothermia is defined not only by the assigned target temperature but also by achieved depth, duration, fever burden, and rewarming quality; variation in these factors may produce meaningful exposure heterogeneity within the hypothermia group and could attenuate an observable between-group difference even if a true subgroup benefit exists. Finally, the study does not incorporate multimodal neuromonitoring such as continuous pressure-reactivity index, brain tissue oxygen tension, or cerebral microdialysis. Invasive intracranial pressure monitors are not part of the routine equipment available at our center, so we could not rely on continuous ICP values to determine whether intracranial hypertension was truly refractory or whether a patient was responding to Barbiturate Coma Therapy; these judgments were instead made by the treating team on clinical and radiological grounds, combining findings from repeated neurological examination, serial CT imaging, and the patient's broader physiological course. This approach, based on clinical signs and imaging rather than direct pressure

readings, is inherently less precise, may introduce variability between cases, and limits comparability with trials that mandated invasive multimodal neuromonitoring. Because the 2024 ESICM/NACCS consensus recommends individualized, physiology-guided temperature targets where feasible, the absence of such data limits our ability to determine whether any treatment effect is mediated by differences in cerebral autoregulation or tissue oxygenation.

3. Declarations

3.1. *Acknowledgments*

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3.2. *Conflict of interests*

The authors declare that they have no competing interests.

3.3. *Funding and supports*

None.

3.4. *Authors' contributions*

All authors fulfilled the four ICMJE authorship criteria, including substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work.

3.5. *Ethical statement*

This study received approval from the Research Ethics Committee of Tabriz University of Medical Sciences and was subsequently registered at www.irct.ir (IRCT20090923002496N14). The research protocol was developed in accordance with the Declaration of Helsinki and its later amendments governing ethical principles for medical research. All relevant institutional review boards and regulatory authorities reviewed and approved the protocol prior to registration. The research team will provide detailed explanations of the study procedures and any protocol modifications to participants, their legal representatives, or guardians. At study initiation, a modified version of the World Health Organization informed consent template will be used to obtain written informed consent, facilitated by HS. Ethical consent forms will be completed for all participants before enrollment.

3.6. *Informed consent*

There will be no personal identifying information published.

3.7. *Availability of supporting data*

All primary and secondary outcome data will be presented upon completion of the trial. Participant-level data will be accessible from the corresponding author upon reasonable request.

3.8. *Using artificial intelligence chatbots statement*

The author declares that ChatGPT was used solely for grammar correction and paraphrasing. All content, data, and analytical arguments presented in this work were developed by the author, who retains full responsibility for the accuracy and integrity of the text.

3.9. *Other declarations*

Conceptualization: HS Data curation: A.Mot, MML Formal analysis: RME Investigation: HS, MML, FS, SZ, A.Mot, HH, AV, RJ, MS, LN Methodology: HS, A.Mot, RME, A.Mah Project administration: HS Resources: AV, SP, MS, LN Software: SP Supervision: HS Validation: MS, HS, A.Mot Visualization: MS, HS, SZ, MML Writing–original draft: A.Mot, HS Writing–review & editing: A.Mot, HS, MS N/A

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Table 1: Intervention procedures in both groups

Procedure	Mild hypothermia group	Active controlled normothermia group
Temperature target	Core temperature 34–35°C	Core temperature 36–37°C
Cooling strategy/device	Non-invasive servo-controlled surface cooling system (for example, Arctic Sun or equivalent) applied to the torso and thighs; same device and settings used for all patients; intravascular cooling catheters not used as the primary method	Antipyretics, environmental adjustment, and active external cooling when needed to prevent or treat hyperthermia
Temperature monitoring	Continuous core temperature monitoring using a standardized method	Continuous core temperature monitoring using the same method as the hypothermia group
Intervention duration	72–96 hours of target temperature management	Normothermia maintained throughout the intervention period, concurrent with thiopental therapy
Overshoot and safety limits	Alarm triggered if core temperature falls below 33.5°C; core temperature below 33.0°C for more than 30 minutes recorded as a protocol deviation	If fever occurs, temperature is actively reduced back to the 36–37°C target
Rewarming	Controlled rewarming after the maintenance phase; comfort and level of sedation monitored closely during cooling and rewarming	Not applicable; normothermia is maintained, with prevention and treatment of fever throughout
Anti-shivering management	Stepwise protocol guided by the Bedside Shivering Assessment Scale, escalating from non-pharmacological measures to optimized sedation and analgesia and then pharmacological adjuncts where required, while avoiding unnecessary deep sedation or neuromuscular blockade	Anti-shivering measures used as clinically indicated for comfort
Thiopental regimen	Standardized institutional protocol: loading dose 2.5 mg/kg every 15 minutes up to four doses (maximum total dose 10 mg/kg), then 5 mg/kg/h for 3 hours followed by 2 mg/kg/h maintenance; dose titrated to burst suppression with an interburst interval of about 6–10 seconds when continuous EEG is available; intended duration 72–96 hours	Same standardized thiopental protocol applied to all randomized patients
ICP and CPP management	Intracranial pressure and cerebral perfusion pressure managed according to contemporary neurocritical care judgment rather than fixed numeric thresholds	Same approach, with ICP and CPP managed according to clinical judgment
Dose-reduction triggers	Thiopental dose reduced by 1 mg/kg/h every 30 minutes if mean arterial pressure remains below 65 mmHg despite optimized vasopressor therapy or if a clinically significant arrhythmia occurs; noradrenaline used as first-line vasopressor; thiopental tapered by 1 mg/kg/h every 4–6 hours while monitoring for rebound intracranial hypertension	Same dose-reduction and tapering protocol
Process measures	Time to reach target temperature, percentage of time in target range, and overall temperature–time profile; fever burden quantified as the area under the temperature–time curve above 37°C	Fever burden and temperature–time profile measured and reported for both groups

Table 2: Study outcomes, definitions, and assessment time points

Outcome	Definition	Assessment time points
Primary		
Six-month GOSE	Glasgow Outcome Scale–Extended (1–8), analyzed as a 7-level ordinal outcome with score 2 pooled into score 1; structured interview (in-person or telephone) by trained, blinded assessor; caregiver or next-of-kin interview if the patient cannot communicate; death before 6 months counted as GOSE 1	6 months post-injury
Secondary		
CPC	Cerebral Performance Category (1–5)	ICU discharge, hospital discharge, 1 month, 6 months
All-cause mortality	Death from any cause	ICU discharge, hospital discharge, 6 months
Duration of mechanical ventilation	Days from intubation to extubation or decannulation	Continuous from ICU admission
Duration of vasopressor support	Days requiring any vasopressor infusion	Continuous from ICU admission
ICU length of stay	Days from ICU admission to ICU discharge or death	Continuous
Hospital length of stay	Days from hospital admission to hospital discharge or death	Continuous
MoCA	Montreal Cognitive Assessment (0–30) administered by a blinded assessor where feasible	6 months
Prespecified adverse events	Infection, arrhythmia, hemodynamic instability, coagulopathy or bleeding, electrolyte disturbance, acute kidney injury, seizures, and device-related skin injury	Continuous during ICU stay
Exploratory		
Biomarker and physiological trajectories	Serial oxidative-stress markers; thyroid-related variables (TSH, free T4, T3); inflammatory markers; renal indices; coagulation parameters; cardiac biomarkers; and other selected variables	During cooling and rewarming phases
AI-assisted prognostic substudy	Candidate predictor associations with six-month unfavorable functional status and in-hospital mortality; reported according to the TRIPOD+AI guidance (27-item checklist); exploratory substudy with n = 42	At analysis completion

ICU: intensive care unit; TSH: thyroid-stimulating hormone; TRIPOD+AI: Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis + artificial intelligence.