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REVIEW ARTICLE

Safety and Efficacy of Therapeutic Hypothermia in Traumatic Spinal Cord Injury Management: A Systematic Review and Meta Analysis

Farzan Fahim[1,2#*], Mahdi Mehmandoost[2,3#], Pouya Karami Dehkordi[4], Ali Khorram[5], Shahriar Heshmaty[6], Fatemeh Zolfaghari[7], Mobina Ghamarpour[8], Sayeh Oveisi[2,9], Amir Saied Seddighi[2,10], Alireza Zali[2,10]

1. Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Functional Neurosurgery Research Center, Research Institute of Functional Neurosurgery, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Student Research Committee, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
5. Student Research Committee, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
6. Medical student at Isfahan University of Medical Science, Isfahan, Iran
7. Medical Student at Shahid Beheshti University of Medical Sciences, Tehran, Iran
8. Medical Student at Kurdistan University of Medical Science, Student Research Committee, Sanandaj, Iran
9. Microbiology Student, Tehran Azad University of Medical Science, Tehran, Iran
10. Shohada Tajrish Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran

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Abstract: **Introduction:** Therapeutic hypothermia as a neuroprotective strategy can reduce secondary injury after acute traumatic spinal cord injury(SCI). We conducted a systematic review and meta analysis to evaluate the impact of systemic or local hypothermia on neurological outcomes, mortality, and Intensive Care Unit (ICU) stay of SCI patients.
Methods: A systematic search in PubMed, Scopus, Web of Science, Embase, and The Cochrane Central Register of Controlled Trials (CENTRAL) with no limitation of time and language was performed. Following PRISMA 2020 guidelines, two independent reviewers screened records across four databases up to 20 September 2025. Eligibility was determined using PICOS criteria: adults with acute traumaticSCI (P), receiving any hypothermic protocol(I), compared with standard normothermic management(C), with reported functional, sensory, or survival outcomes(O), and original human clinical designs(S). Data extraction and risk-of-bias evaluation were performed independently using the JoannaBriggsInstitute (JBI) checklist. Pooled relative risks(RR) or mean differences(MD) were calculated with random effects models using RevMan4.5.1 **Results:** From305initial records, sixhuman studies (156 patients) met inclusion criteria. There were threesystemic hypothermia trials and onelocal extradural protocol, plus twosupportive cohorts providing timing and assessment data, but only three studies met the minimum criteria for meta-analysis processes. Overall methodological quality of included studies was low to moderate and none of the studies were randomized. Intervention methods included surface, and endovascular techniques maintaining body temperature at 32-34Celsius for24-72hours, initiated between 1.6-70hours post injury. Pooled analyses showed decreased mortality with RR=0.57(95%CI:0.05-5.88; p = 0.6883), improvement in Association Impairment Scale (AIS) with RR=2.96(95%CI:0.01-939.31; p = 0.3098); and decrease in the ICU length of stay withMD=-1.27(95%CI:-2.46to-0.07; p = 0.9658) days in SCI patients receiving hypothermia. Complications included pneumonia, hypotension, and bradycardia. No hypothermia related deaths were reported. Early initiation (<6hours) was consistently linked with superior functional improvement. **Conclusion:** The findings of sixhuman studiesreveal that therapeutic hypothermia may be a feasible, safe, and effective intervention in acute traumatic SCI. While current evidence cannot yet demonstrate mortality benefit, the observed results were directed toward neurological improvement, especially when therapy is initiated early and systemically, supporting ongoing investigation.

Keywords: Spinal cord trauma; Spinal cord injuries; Hypothermia, induced; Recovery of function; Meta analysis; Critical care

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[*] **Corresponding Author:** Farzan Fahim; Functional Neurosurgery Research Center, Research Institute of Functional Neurosurgery, Shohada Tajrish Com-

1. Introduction

Traumatic spinal cord injury (SCI) remains a devastating neurological condition associated with substantial mortality, long term disability, and socioeconomic burden worldwide. Recent estimates indicate approximately 0.9 million new cases annually, with more than 20 million individuals living with chronic SCI and significant years lived with disability (1).

The pathophysiology of acute SCI extends beyond the initial mechanical insult and involves a complex secondary injury cascade occurring over hours to weeks. This secondary phase is characterized by ischemia and hypoxia, glutamate mediated excitotoxicity, calcium overload, oxidative stress, mitochondrial dysfunction, and a robust inflammatory response driven by microglial activation and pro inflammatory cytokines such as TNF and IL 1β (2-5).

Therapeutic hypothermia has emerged as a potential neuroprotective strategy targeting multiple components of the secondary injury cascade, experimental and translational studies demonstrate that hypothermia reduces metabolic demand, attenuates inflammation, limits excitotoxicity, and suppresses apoptotic pathways, thereby preserving neural tissue (3, 5, 6). Clinically, both systemic and local hypothermia have been explored as adjuncts to standard acute SCI management, with pilot studies and prospective case series suggesting feasibility and short term safety (7, 8).

However, evidence regarding the efficacy of hypothermia in improving neurological outcomes remains inconsistent. While some clinical studies report motor or sensory improvement following hypothermia, others demonstrate minimal or no benefit, likely reflecting heterogeneity in patient populations, injury levels, cooling methods, timing, and outcome measures (6, 8, 9). Previous systematic reviews have often pooled heterogeneous interventions or mixed experimental and clinical data, limiting conclusions specific to hypothermia (10) . Therefore, a focused systematic review and meta analysis examining the safety and efficacy of therapeutic hypothermia exclusively in acute traumatic SCI is warranted to synthesize current clinical evidence, clarify its therapeutic value, and inform future trial design and clinical decision making.

2. Methods

2.1. Study design and setting

This systematic review and meta-analysis was conducted in alignment with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, version, 2020, and was registered in PROSPERO database (PROSPERO ID: CRD420251173039).

We covered various databases, namely PubMed, Scopus, Web of Science, Cochrane and Embase, from inception to September 2025. Limitation of time and language were not applied. If studies were found in languages other than English in our search strategy, we planned to translate them into English before starting screening. The search strategy was based on MeSH entry terms and keywords related to our title and PICOS. The core search strategy words were spinal cord injury, hypothermia, function recovery, motor and sensory recovery, and anti-inflammation. The complete search strategy syntax was illustrated in supplementary table 1.

2.2. Study selection

After defining the PICO framework and retrieving records from all databases, studies were imported into Rayyan, an online platform for systematic review screening, where title and abstract screening was performed.

The screening process was conducted in two phases. In the first phase, two reviewers, P.K.D and S.A., independently performed title and abstract screening. Each reviewer independently filled the exclusion sheets. The exclusion sheet consisted of title, first author, year of study and the reason for exclusion.

Related and original studies, except for case reports, were included to be assessed for their eligibility in the second phase. The third reviewer (MM) solved the conflicts between the two reviewers.

In the second phase, the full-text of each included study was assessed, two independent reviewers, P.K.D and A.KH, assessed each study by considering the PICO, which was defining the participants with SCI injury who were under a hypothermia treatment method for finding out the outcomes of the surgeries and rehabilitation. The reviewers separately filled out two Excell 2016 sheets. The inclusion sheet consisted of title, first author, year of study, PICO, and study design.

Animal studies weren't excluded in the initial screening and they were also assessed in the second screening process. Same as the initial screening, the third author (MM) resolved the conflicts between the two reviewers, which could be any disagreement in defining the type of hypothermia or the type of spinal cord injury. A total of six human studies that fully met the predefined PICO framework and eligibility criteria were included in the final analysis.

2.3. Inclusion and exclusion criteria

We defined our inclusion criteria based on PICOS framework: Participants (P): Participants after any spinal cord injury, which was in an acute phase; Intervention (I): Hypothermia and cooling procedure; Comparison(C): Patients with SCI who didn't receive hypothermia as therapeutic intervention; Outcome (O): Improving SCI patients, motor function,

prehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: Farzn.fahim@gmail.com, ORCID: 0000-0003-0591-674X, Tel: +989120943182
[#] **Co-First Authors (these two authors contributed equally)**

sensory function, improving quality of life and, rehabilitation; and Study (S): All human studies such as cohort, case series, clinical trials were included.

Non-original studies were excluded. Case reports and conferences proceedings, which did not have a full-text were excluded. Studies which didn't investigate hypothermia as an intervention or their injury site wasn't in the spinal cord or the injury wasn't in an acute phase, were excluded. The animal studies were also excluded.

2.4. Data extraction

A structured data extraction sheet was used, which included the following columns: title, authors and year of publication, DOI, funding sources and conflict of interest, country, study design, center type, time period of data collection, inclusion criteria, exclusion criteria, follow-up duration, ethical approval, age, male sex, mechanism of injury, NLI (Neurological level of injury), time from injury to intervention initiation, time from injury to enrollment, Association Impairment Scale (AIS)/ Spinal Cord Independence Measure (SCIM)/ Functional Independence Measure (FIM) /Walking Index for Spinal Cord Injury (WISCI)/ modified Rankin Scale (mRS)/Other, AIS (A,B,C,D,E), AIS Motor Score (0-5), American Spine Injury Association Impairment Scale (ASIA) Sensory Score, type of hypothermia, timing of initiation post-injury, cooling initiation setting (emergency room (ER), intensive care unit (ICU), Intraoperative), target temperature, duration of hypothermia (total cooling period), time to reach target temperature (hours), rewarming protocol (rate/hour), active warning post-rewarming (yes, no, method), temperature monitoring method (esophageal, bladder, intravascular), use of sedation or neuromuscular blockage during cooling (yes/no), concurrent treatment, type of surgery, steroid type (dosage, duration of use), change in ASIS motor score, mortality rate, change in ASIS sensory score, change in SCIM score, change in FIM score, change in quality of life score, length of ICU stay, safety and adverse outcomes, timing of outcomes assessments, concomitant injury, static adjustment and adverse events.

2.5. Risk of bias (ROB) assessment

We assessed the methodology of studies using Joanna Briggs Institute's (JBI) critical appraisal checklist, based on the study design. Two independent reviewers (MB and AK) who did not participate in inclusion of the studies, performed the ROB assessment. We included four cohort studies and the JBI checklist for cohort studies includes five key areas:

1) Selection bias, the way which the study was selected.

2) Performance Bias, the blindness of participants in the study

3) Attrition Bias, balancing dropouts between intervention and control group

4) Detection Bias, suitable measurement of outcome's study

5) Appropriate statistical analysis, addressing the follow up in study as the sufficiency and ability to outcome occurrence.

We included one case control study and we evaluated the studies based on their variables,

1) Appropriate matching between the case and control study

2) Similar criteria between the case and control study

3) Reliable and measurable exposure

4) Identifying exposures in case and controls

5) Strategies for dealing with cofounding factors

6) Appropriate statistical analysis

2.6. Statistical analysis

2.6.1 The mortality outcome analysis

Mortality was analyzed using data from three studies: Batchelor etal.(2023), Hansebout etal.(2014), and Levi etal.(2010). Given the presence of zero events in one or both arms (Batchelor, Hansebout), a continuity correction of 0.5 was applied to all cells (incr = 0.5 in R's metabin function), in line with Cochrane Handbook (version6.4). Risk Ratio (RR) was used as the primary effect size, because of being rare of mortality and clinical interpretability; Risk Difference (RD) was also calculated for absolute effect size estimation. A random-effects model (DerSimonian–Laird τ^2 estimator) was used for the meta-analysis, with Hartung–Knapp adjustment for confidence intervals (method.random.ci = "HK"). Common-effect (inverse variance fixed-effect) estimates were also reported. Between-study heterogeneity was quantified using the I^2 statistic, τ^2, and Cochran's Q-test. Analyses were conducted in R (v4.5.1) using the meta and metafor package. Forest plots were generated.

2.6.2 The AIS outcome analysis

The outcome "AIS Grade Improvement" was defined as neurological recovery after acute SCI, assessed according to the International Standards for Neurological Classification of SCI (ISNCSCI). In Batchelor etal. study (2023) (10), improvement was defined as ≥2 AIS grades at 6-month follow-up, whereas in Levi etal. study (2010) (11) improvement was defined as ≥1 AIS grade at 12-month follow-up. Binary data (improved vs. not improved) were extracted from these included studies.

Meta-analysis was performed in R (version4.5.1) using the meta and metafor packages and the Mantel–Haenszel method for pooling risk ratios (RR) with both common-effect and random-effects models. Between-study variance (τ^2) was estimated using the DerSimonian–Laird method. Hartung–Knapp adjustment was applied to random-effects confidence intervals (CIs) to improve accuracy in meta-analyses with very few included studies. Continuity correction (0.5) was specified in the script to handle potential zero-event cells, although not required for the present dataset.

2.6.3 The length of staying in ICU as an outcome analysis

The length of ICU stay was analyzed as a continuous variable, comparing systemic hypothermia intervention groups with normothermic control groups in acute SCI. Data were extracted from two non-randomized controlled studies: Levi etal. (2010) and Batchelor etal. (2023). Meta-analysis was conducted in R (version4.5.1) using the meta and metafor packages. Mean differences (MD) between groups

were calculated, with negative values indicating shorter ICU stays in hypothermia-treated patients. Both common-effect (fixed-effect) and random-effects models were calculated. Between-study variance (τ^2) was estimated via DerSimonian–Laird; heterogeneity was quantified with I^2 statistics.

3. Results

3.1. Study characteristics

From305initial records, sixhuman studies (156 patients) met inclusion criteria (10-15). Figure 1 shows the flowchart of study inclusion. The studies were conducted between 2009 to 2023. Two studies were performed in Australia, two in the United States, one in Canada, and one in the United Kingdom. The study designs included cohort, case–control, and phase I clinical trials. Sample sizes ranged from 5 to 118 patients. The patients' ages across studies spanned from 15 to 70 years, and the male proportion varied between 66% and 94%. All studies were conducted in human models. The focus of these investigations was to evaluate the effects of hypothermia approaches (systemic, local, endovascular, and surface cooling) on spinal trauma. The main extracted data from the included studies are summarized in Table 1.

Mechanisms of injury included motor vehicle and motorcycle accidents, falls, sports injuries, and blunt trauma. Most studies focused on cervical spinal cord injury, while one study evaluated thoracic injuries (15). Four studies investigated systemic hypothermia (10, 11, 13, 14), one assessed local extradural hypothermia (13), and one focused on early neurological assessment using the SPEED tool without specifying hypothermia type (12). Injury severity was primarily evaluated using the AIS classification, supported by ASIA motor and sensory scores, with follow up durations ranging from 12 hours to one year.

Three studies reported neurological improvement, including AIS grade conversion and increases in ASIA motor and sensory scores, particularly in patients receiving early systemic cooling (10, 13, 14). Common adverse events across studies included respiratory complications and wound infections, with no consistent reports of severe hypothermia related morbidity. Heterogeneity in cooling methods, timing, and outcome assessment limited definitive conclusions regarding efficacy.

3.2. Meta-analysis

3.2.1 Effect of hypothermia on mortality of SCI patients

The data of three studies (total 102 participants, 51 hypothermia, 51 control) were pooled. In Batchelor et al. study (10), the RRof hypothermia on mortality was1.00 (95%CI:0.02–47.63) with no deaths in either arm. Moreover, in the Hansebout et al. investigation (15), the RRwas0.20 (95%CI:0.01–3.91) with two deaths in control arm and none in hypothermia arm. Also, in the Levi et al. study (11), the RRwas1.00 (95%CI:0.07–14.45) with one death in each arm.

The pooled RRof hypothermia on mortality based on random-effects and common-effect models were0.57 (95%CI:0.05–5.88; p=0.4058) and 0.57 (95%CI:0.10–3.32; p=0.5285), respectively. The random-effects RDwas–0.03 (95%CI:–0.14 to0.08; p=0.45). The heterogeneity was I^2=0.0%, τ^2=0, Q-test p=0.695. The study weights on random-effects model were 20.9% for Batchelor, 35.3% for Hansebout, and 43.8% for Levi. The forest plot demonstrates the wide confidence intervals and lack of heterogeneity (Figure2).

3.2.2 Effect of hypothermia on AIS outcome of SCI patients

Two studies (Batchelor etal., 2023; Levi etal., 2010) (10, 11) including 62 participants (31 hypothermia, 31 control) were included in the analysis (Figure 2).

In Batchelor etal. study (10), systemic prehospital hypothermia with early decompression resulted in 10/17 patients improving vs. 2/17 controls (RR=5.00, 95%CI:1.28–19.50). In Levi etal. study (11), intravascular hypothermia initiated within 12hours yielded improvement in 6/14 patients vs. 3/14 controls (RR=2.00, 95%CI:0.62–6.45).

The pooled RR on hypothermia on AIS outcome based on random-effects (with Hartung–Knapp adjustment produced) and common-effect models were 2.96 (95%CI:0.01–939.31, p=0.310) and3.20 (95%CI:1.33–7.70, p < 0.01), respectively (I^2=3%, τ^2=0.0132, p for heterogeneity=0.31).

3.2.3 Effect of hypothermia on ICU length of stay of SCI patients

Two studies (10, 11) involved the data of ICU length of stay, which we could analyse, with a total of 21 patients undergoing hypothermia intervention and 21 controls (Figure 2).

Levi etal. (2010) (11) reported a mean difference of –1.40days (95%CI: –8.86 to 6.08), favoring hypothermia but non-significant. Batchelor etal. (2023) (10) found a mean difference of –1.20days (95%CI: –6.44 to 4.04), also non-significant.

The pooled MD of the effect of hypothermia on ICU length of stay based on the random-effects model was –1.27days (95%CI –5.56 to 3.03; p = 0.9658) (I^2=0%, τ^2=0, pfor heterogeneity =0.97).

3.3. Risk of bias assessment

An assessment of the risk of bias was conducted for all six studies using the JBI critical appraisal checklist. All studies had a low risk of bias, except for those by Batchelor et al. (10), Levi et al. (11), and Hansebout et al. (15), which were assessed as having a moderate risk of bias due to limitations such as unclear reporting of follow-up, inadequate control for confounders, or selection bias (table 2).

3.4. Adverseeffects of hypothermia in patients with traumatic SCI

Overall, therapeutic cooling was feasible and relatively safe, but the incidence of complications, particularly respiratory and infectious events, was considerable. In the early phase trial by Levietal.(2009) (14), intravascular cooling was used within 9hours after injury in 14 patients with complete cervi-

cal lesions. Goal temperature (33°C) was reached and maintained for 48hours by an endovascular catheter. Despite common respiratory complications, atelectasis in about 85%, and pneumonia in 57%, no deaths or device related serious events were reported. More than 14% of patients gained at least oneAISgrade improvement, which suggests a possible neurological benefit.

The Hanseboutetal.(2014) (15) case control study included 40 participants (20treated,20controls) with cervical injuries. Systemic surface cooling to 32–34°C was started during the first 8 hours after injury and maintained for 72hours. Mild shivering and transient pneumonia were the only notable adverse events. No deaths were reported, and functional recovery at 3months showed relative and possible efficacy of the hypothermia, but statistical power was limited.

Batcheloretal.(2023) (10) performed the most technically advanced pilot, integrating prehospital cold saline infusion and controlled intravascular or surface cooling for 24hours at 33–34°C. Cooling began on average 1.6hours after injury, earlier than in any previous report. Among 17 patients, including seven with complete injuries, 60% achieved at least one grade AIS improvement compared with 12% in historical controls(p=0.03). The treatment was generally well tolerated: hypotension occurred in 80%, bradycardia in all participants, pneumonia in 60%, and a single case of inferior vena cava thrombosis was noted. No mortality occurred. These data indicate that early and systemic hypothermia combined with early surgical decompression is technically feasible in acute care settings.

Gallagheretal.(2020) (13) evaluated a local extradural cooling catheter in 5 patients with thoracic injuries (T3–T6). Cooling began seventyhours post injury, achieved 33°C for 12hours, and rewarming proceeded at 0.5°Cperhour. Two participants improved by at least oneAISgrade, while three developed wound site infections. The conclusion from this study, with consideration of statistical limitation, may be the relative efficacy of hypothermia and increasing risk of surgical site infection.

When all studies are considered together, respiratory complications (pneumonia, atelectasis) and transient hemodynamic instability (hypotension) were the most frequent adverse outcomes. No evidence suggested increased mortality or neurologic worsening attributable to cooling itself. Early initiation, within sixhours of injury, appears to yield more favorable functional recovery than delayed (after two to threedays). Taken together, these findings support the clinical feasibility of therapeutic hypothermia as an adjunct to decompression after acute (specially in cervical) SCI, but the small sample sizes and heterogeneity highlight the urgent need for larger randomized trials.

4. Discussion

This systematic review and meta analysis evaluated the effectiveness and safety of hypothermia as a therapeutic option in acute traumatic SCI.Six human studies published between 2009and2023 were included after careful evaluation based on the PICOS criteria (10-15). These studies demonstrated that systemic hypothermia (the goal temperature :32–34°C) is technically feasible and relatively safe under careful hemodynamic monitoring. The final result is toward improvement of neurological outcomes in acute (especially cervical) cord injuries. Quantitative analysis showed that mortality was not significantly reduced by hypothermia (pooledRR:0.57;95%CI0.05–5.88;I^2=0%). Nevertheless, all point estimates favored the intervention.Functional outcomes were improved: the pooled AIS grade improvementRR=2.96(95%CI0.01–939.31), which suggests a higher chance of neurological recovery in intervened patients despite wide confidence intervals.Mean ICU stay was slightly shorter in the hypothermia group (MD=–1.27days;95%CI–2.46to–0.07) with negligible heterogeneity(I^2=0%,τ^2=0) which indicates possible efficiency of hypothermia without significant harm.

The biological mechanisms of neuroprotection effect of hypothermia are well understood. In the SCI situation, secondary injury cascades including ischemia, glutamate excitotoxicity, oxidative stress, inflammation, and apoptosis, make additional tissue damage(2, 5). Decreasing body temperature to 33°C suppresses metabolic demand, stabilizes cellular membranes, and decreases cytokine release and apoptosis.The clinical data synthesized confirm that starting time of hypothermia as intervention is critical:trials initiating systemic hypothermia in the first 6 hours after trauma (7, 10, 11)reported greater neurological improvement, whereas delayed or localized cooling (>48h) (15)showed limited benefit.

From these six studies(10-15), adverse events were consistent with systemic cooling physiology: hypotension(70–80%), bradycardia(upto100%), pneumonia(60%), and electrolyte disturbances(<10%).Gallagher's protocol recorded the highest wound infection rate (60%).Importantly, there were no deaths reported due to hypothermia. In all studies, active temperature monitoring was applied (with esophageal or bladder probes), sedation and/or neuromuscular blockage to prevent shivering, and slow rewarming (0.1–0.25°Ch^{1}).These measures confirm that, under ICU care, therapeutic hypothermia is clinically safe.

JBI appraisal identified low overall but moderate methodological risk driven by non randomized design, limited control comparability, and incomplete confounding adjustment(10, 11, 14).Gallagher's low bias rating stemmed from transparent patient inclusion; however, small cohorts and heterogeneity in cooling technique reduce precision.As such, evidence certainty is low to moderate, providing hypothesis generation rather than definitive support.

Estimations from included studies and results of meta-analysis were underpowered for statistical significance. But improvements in AISgrade and shortened ICU stay indicate that therapeutic hypothermia is a promising additional therapy to surgical decompression and standardized hemo-

dynamic therapy(7, 10, 11, 14, 16, 17).Based on aggregated evidence, clinical pearls concluded:

1. Initiate hypothermia during thre first 6h after trauma.
2. Target 33°C for 24–48h, with continuous invasive monitoring.
3. Employ sedation or neuromuscular blockade to suppress shivering and additional decreasing metabolic demands.
4. Rewarm slowly (0.25°Ch¹) with monitoring and try to discover possible inflammatory reactions and if occurred, finish trial.
5. Parallel to hypothermic period, monitor hemodynamic stability and prevent hypotension, maintain mean arterial pressure (MAP) much more than 85 mmHg.

With these parameters hypothermia may maximize safety and may improve functional recovery. Advancement now requires multicenter randomized controlled trials powered to detect functional differences.Priorities include:

• Standardization of target temperature (33°C,24–48h) and rewarming protocol.
• Immediate initiation: ideally 3h after injury period, even in the prehospitalsetting (10).
• Incorporation of biomarkers (such as IL 6,S100B,GFAP) and advanced spinal imaging for mechanistic correlation (such as fMRI or DTI) along with or after hypothermia as an additional intervention(2, 5).
• Detailed adverse event registries and management protocols, to ensure reproducibility.
• Economic evaluation of resource utilization given the high lifetime cost of SCI(18, 19).

Such trials would clarify both efficacy and patient selection to reach maximum benefit.

5. Limitations

In interpretation of our meta analytic outputs one must consider:(a)limited number of eligible human studies(n=6,118patients)(10-15);(b)heterogeneity in temperature initiation (1.6–70h) and duration (12–72h);(c)male predominance(66–94%);and(d)follow up rarely exceeding12months.Absence of randomization, varying definitions of "neurological improvement," and small event counts contributed to broad confidence intervals and publication bias potential.

6. Conclusions

Synthesizing sixhuman studiesrevealed that therapeutic hypothermia may be feasible, safe, and biologically effective as an acute intervention in traumatic SCI.While current evidence cannot yet demonstrate mortality benefit, the observed results were directed toward neurological improvement, especially when therapy is initiated early and systemically, and support ongoing investigation.Until large randomized data are available, hypothermia could be regarded as an experimental yet promising neuroprotective additional therapeutic option complementing early decompression.

7. Declarations

7.1. Acknowledgments

Not applicable.

7.2. Authors' contributions

Conceptualization: MM, FF; Data curation: PK, AK; Investigation: PK, AK; Methodology: MM Project administration: PK, AK; Supervision: SH, FZ; Visualization: MG; Writing – original draft: PK, AK, SH, FZ. Writing – review and editing: SO, AS, AZ, FF, MM. All authors reviewed and confirmed the final draft of this manuscript for submission. All authors read and approved the final version.

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7.4. Consent to publish

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7.5. Availability of data

Not applicable.

7.6. Conflict of interest

There is no conflict of interest.

7.7. Using artificial intelligence chatbots

None.

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Table 1: Characteristics of included studies on therapeutic hypothermia in acute traumatic spinal cord injury (SCI)

Study	Sample (N)	Injury level	Hypothermia type & setting	Target temperature / duration	Main outcomes	Adverse events
Batchelor et al. 2023 (10)	17 total (7 complete, 10 incomplete) vs historical controls (17)	Cervical C3–T1 (AIS A–D)	Systemic IV cold saline + surface/intravascular cooling	33–34°C / 24 h (mean 22.5 h)	Feasible and safe; neurological monitoring with AIS/ASIA; supportive trend toward neurological recovery	Hypotension (80%), bradycardia (100%), pneumonia (60%), one IVC thrombus
Levi et al. 2010 (11)	14 treated / 14 matched controls	Cervical C4–C6 (AIS A complete)	Systemic intravascular cooling (CoolGard catheter, ICU)	33°C / 48 h	AIS improvement in 42.8% versus 21.4% in controls	Atelectasis (85%), pneumonia (57%), pleural effusion (57%), arrhythmia (21%)
Battistuzzo et al. (12)	58	Cervical C3–C8 (all AIS grades)	No hypothermia (control reference)	NA	Neurological assessment feasible; some neurological improvement at approximately 6 months	Not specified
Gallagher et al. 2016 (13)	5 (no control)	Thoracic T3–T6 (AIS A–C)	Local extradural cooling catheter (Neuro ICU)	33°C / 12–72 h	Mean ASIA motor score increased by 8.8 points; 40% AIS grade improvement	Wound infection (60%); one catheter failure without neurological deterioration
Levi et al. 2009 (14)	14	Cervical (AIS A)	Systemic intravascular cooling catheter	33°C / 48 h	Feasible and safe; maintained stable target temperature; established foundation for subsequent clinical trials	Respiratory complications, arrhythmias, sepsis
Hansebout et al. 2014 (15)	20 hypothermia + 20 matched controls	Cervical C4–C7 (complete and incomplete)	Systemic surface cooling using ice packs and cooling blankets	32–34°C / 48–72 h	Significant neurological improvement compared with controls; no mortality in hypothermia group	Occasional mild pneumonia or shivering; otherwise well tolerated

Table 1: **(continued)** Characteristics of included studies on therapeutic hypothermia in acute traumatic spinal cord injury (SCI)

Study (Country)	Study design	Time to cooling	Rewarming protocol	Concomitant treatment	Primary outcomes	Main findings
Batchelor et al., 2023 (Australia)	Prospective pilot, multicenter (prehospital + ICU)	Mean 1.6 h	0.15°C/h until 36°C, then normothermia for 72 h	Early decompression (<8 h for complete injury), spinal fixation, sedation for shivering	AIS grade improvement, mortality, ICU length of stay	60% improved by at least one AIS grade versus 12% of historical controls (p = 0.03); zero mortality in the hypothermia group.
Levi et al., 2010 (USA)	Phase I clinical trial (retrospective analysis of prospective protocols), single center	Mean 9.2 ± 2.2 h	Controlled slow rewarming (0.1°C/h) over 24–32 h to normothermia	Surgical decompression, fixation, MAP >90 mmHg, LMWH prophylaxis	Feasibility, safety, AIS improvement	Feasible and safe; 42.8% improved by at least one AIS grade; no DVT, pulmonary embolism, or cardiac arrest observed.
Battistuzzo et al., 2016 (Australia)	Retrospective cohort (2010–2014), multicenter	Assessment within 1 h after injury	Not reported	Standard surgical management	Validation of neurological scoring tools	Provided a non-cooled reference cohort for comparison with hypothermia studies.
Gallagher et al., 2020 (UK & Germany)	Prospective pilot (ISCoPE substudy), multicenter	70 h	Gradual rewarming at 0.5°C/h	Posterior fixation, antibiotics, anticoagulants	ASIA motor and sensory scores, safety	40% of patients improved by at least one AIS grade; local cooling was feasible but associated with a relatively high infection risk.
Levi et al., 2009 (USA)	Phase I feasibility study, single center	Mean 9.17 ± 2.24 h	Slow rewarming at 0.1°C/h over 24–32 h	Cervical traction and surgical decompression	Feasibility, safety, baseline data for future RCTs	Feasible and safe; maintained stable target temperature with manageable complications.
Hansebout et al., 2014 (Canada)	Case-controlled observational study, single center	Within 8 h	Slow rewarming over approximately 12 h	Surgical stabilization in selected patients and supportive ICU care	Neurological recovery and mortality	Systemic hypothermia initiated within 8 h was feasible and appeared safe; associated with improved long-term neurological recovery and zero mortality compared with matched controls.

AIS: American Spinal Injury Association Impairment Scale; ASIA: American Spinal Injury Association; ICU: intensive care unit; IV: intravenous; IVC: inferior vena cava; LMWH: low molecular weight heparin; LOS: length of stay; MAP: mean arterial pressure; PE: pulmonary embolism; DVT: deep vein thrombosis; NA: not available; RCT: randomized clinical trial.

Table 2: The studies' risk of bias assessment using JBI 2020 checklists

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Overall
Batchelor 2023	×	✓	✓	✓	✓		✓	✓		×	✓	Moderate
Battistuzzo 2016	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	Low
Gallagher 2020	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Low
Hansebout 2014	✓	✓	✓	✓	✓	✓	✓			✓	–	Low
Levi 2009	✓	✓	✓	✓	✓	✓	✓		✓	✓	–	Low
Levi 2010		✓	✓	✓	✓		✓	✓				Moderate

JBI: JoannaBriggsInstitute. The JBI items are as follows: Q1: Was it clear in the study what the 'cause' was and what the 'effect' was? Q2: Were the participants included in any comparisons similar? Q3: Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q4: Was there a control group? Q5: Were there multiple measurements of the outcome both pre and post the intervention/exposure? Q6: Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed? Q7: Were the outcomes of participants included in any comparisons measured in the same way? Q8: Were outcomes measured in a reliable way? Q9: Was there appropriate statistical analysis used? Q10: Was the trial design appropriate? Q11: Were the participants, treatments and setting included in the study described in detail?

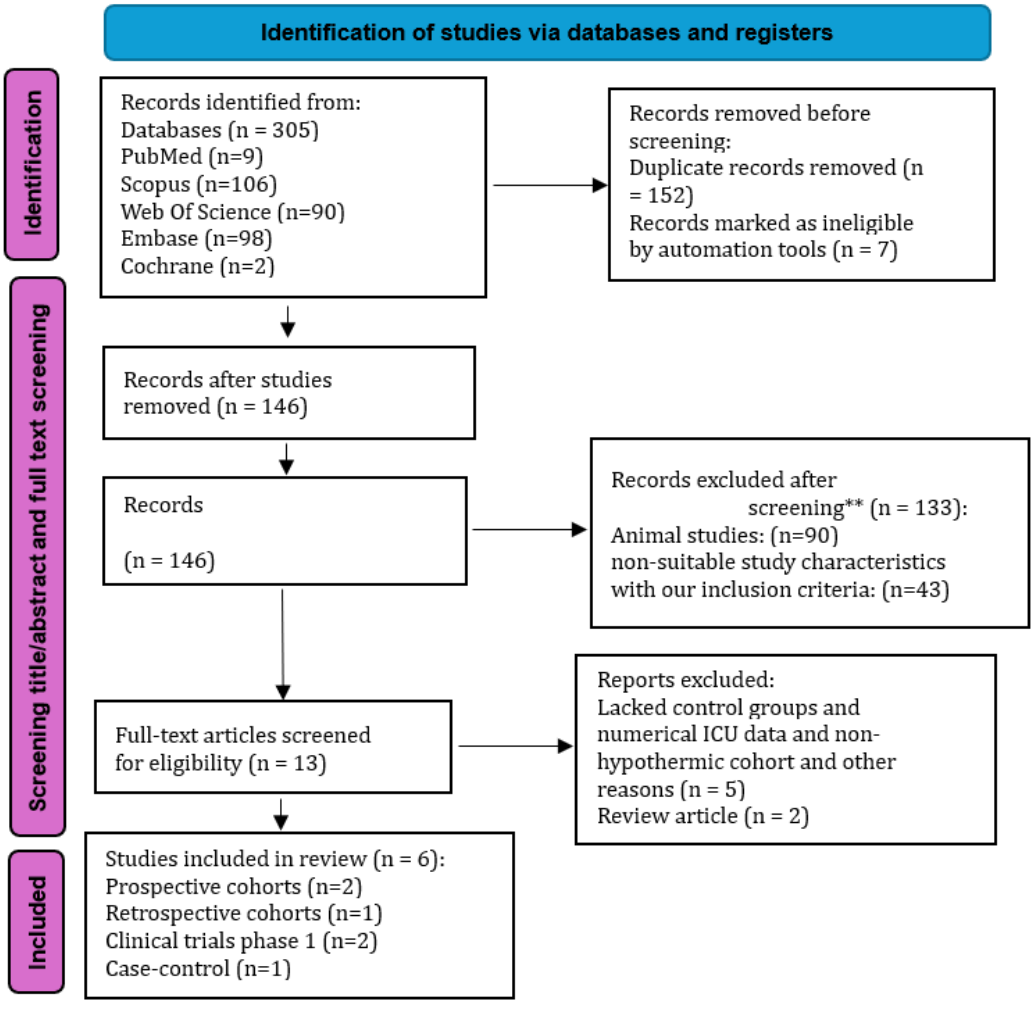

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart. ICU: intensive care unit.

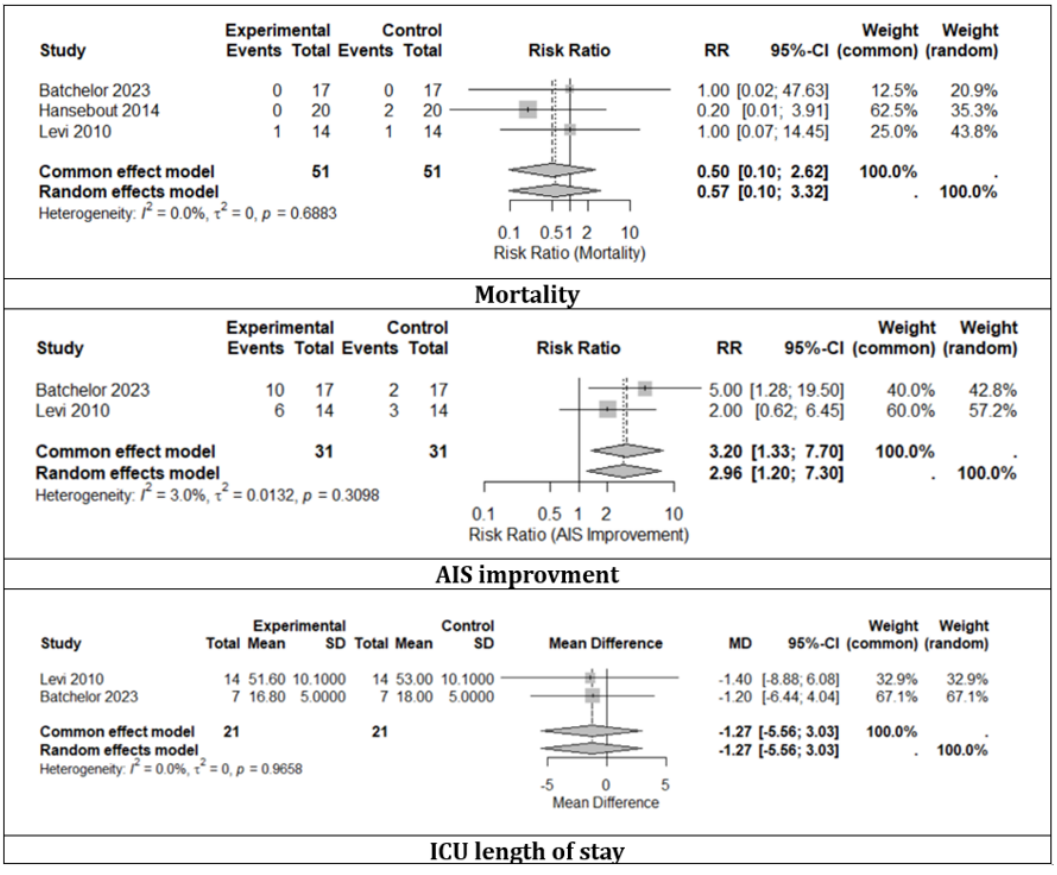

Figure 2: The effects of hypothermia on mortality, AIS (abbreviated injury scale) outcome, and ICU (intensive care unit) length of stay among SCI (spinal cord injury) patients. CI: confidence interval; RR: relative risk; SD: standard deviation; MD: mean difference.

Supplementary table 1: Search strategy in different databases

Scopus (n=106)
TITLE-ABS-KEY ("Spinal Cord Injury" OR "SCI" OR "acute spinal cord trauma" OR "spinal cord trauma") AND (TITLE-ABS-KEY ("Hypothermia, Induced" OR "therapeutic hypothermia" OR "systemic hypothermia" OR "local hypothermia" OR "cooling therapy" OR "targeted temperature management" OR "regional hypothermia")) OR INDEXTERMS ("hypothermia") AND (TITLE-ABS-KEY ("Recovery of Function" OR "neurological recovery" OR "motor recovery" OR "sensory recovery" OR "neuroprotection" OR "secondary injury" OR "inflammation" OR "decreasing second insult" OR "anti-inflammatory") OR INDEXTERMS ("recovery" OR "neuroprotection")) AND (TITLE-ABS-KEY ("acute" OR "early phase" OR "post-injury" OR "subacute"))
PubMed (n=9)
(("Spinal Cord Injury"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR "SCI"[Title/Abstract] OR "acute spinal cord trauma"[Title/Abstract] OR "spinal cord trauma"[Title/Abstract]) AND ("Hypothermia, Induced"[Mesh] OR "therapeutic hypothermia"[Title/Abstract] OR "systemic hypothermia"[Title/Abstract] OR "local hypothermia"[Title/Abstract] OR "cooling therapy"[Title/Abstract] OR "targeted temperature management"[Title/Abstract] OR "regional hypothermia"[Title/Abstract] OR "hypothermia"[Mesh]) AND ("Recovery of Function"[Mesh] OR "neurological recovery"[Title/Abstract] OR "motor recovery"[Title/Abstract] OR "sensory recovery"[Title/Abstract] OR "neuroprotection"[Title/Abstract] OR "secondary injury"[Title/Abstract] OR "inflammation"[Title/Abstract] OR "decreasing second insult"[Title/Abstract] OR "anti-inflammatory"[Title/Abstract] OR "recovery"[Mesh] OR "neuroprotection"[Mesh]) AND ("acute"[Title/Abstract] OR "early phase"[Title/Abstract] OR "post-injury"[Title/Abstract] OR "subacute"[Title/Abstract]))
WOS (n=90)
TS=(("Spinal Cord Injury" OR "Spinal Cord Injuries" OR "SCI" OR "acute spinal cord trauma" OR "spinal cord trauma") AND ("Hypothermia, Induced" OR "therapeutic hypothermia" OR "systemic hypothermia" OR "local hypothermia" OR "cooling therapy" OR "targeted temperature management" OR "regional hypothermia" OR "hypothermia") AND ("Recovery of Function" OR "neurological recovery" OR "motor recovery" OR "sensory recovery" OR "neuroprotection" OR "secondary injury" OR "inflammation" OR "decreasing second insult" OR "anti-inflammatory" OR "recovery") AND ("acute" OR "early phase" OR "post-injury" OR "subacute"))
Embase (n=98):
('spinal cord injury'/exp OR 'spinal cord injury':ti,ab OR 'spinal cord injuries':ti,ab OR 'sci':ti,ab OR 'acute spinal cord trauma':ti,ab OR 'spinal cord trauma':ti,ab) AND ('induced hypothermia'/exp OR 'therapeutic hypothermia':ti,ab OR 'systemic hypothermia':ti,ab OR 'local hypothermia':ti,ab OR 'cooling therapy':ti,ab OR 'targeted temperature management':ti,ab OR 'regional hypothermia':ti,ab OR 'hypothermia'/exp) AND ('recovery of function'/exp OR 'neurological recovery':ti,ab OR 'motor recovery':ti,ab OR 'sensory recovery':ti,ab OR 'neuroprotection':ti,ab OR 'secondary injury':ti,ab OR 'inflammation':ti,ab OR 'decreasing second insult':ti,ab OR 'anti-inflammatory':ti,ab OR 'recovery'/exp OR 'neuroprotection'/exp) AND ('acute':ti,ab OR 'early phase':ti,ab OR 'post-injury':ti,ab OR 'subacute':ti,ab)
Cochrane (n=2):
(("Spinal Cord Injury" OR "Spinal Cord Injuries" OR "SCI" OR "acute spinal cord trauma" OR "spinal cord trauma") AND ("Hypothermia, Induced" OR "therapeutic hypothermia" OR "systemic hypothermia" OR "local hypothermia" OR "cooling therapy" OR "targeted temperature management" OR "regional hypothermia" OR "hypothermia") AND ("Recovery of Function" OR "neurological recovery" OR "motor recovery" OR "sensory recovery" OR "neuroprotection" OR "secondary injury" OR "inflammation" OR "decreasing second insult" OR "anti inflammatory" OR "recovery") AND ("acute" OR "early phase" OR "post-injury" OR "subacute"))