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Review

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Therapeutic hypothermia for intracerebral hemorrhage: Systematic review and meta-analysis of the experimental and clinical literature

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Abstract

Background: Intracerebral hemorrhage remains the deadliest form of stroke worldwide, inducing neuronal death through a wide variety of pathways. Therapeutic hypothermia is a robust and well-studied neuroprotectant widely used across a variety of specialties.

Aims: This review summarizes results from preclinical and clinical studies to highlight the overall effectiveness of therapeutic hypothermia to improve long-term intracerebral hemorrhage outcomes while also elucidating optimal protocol regimens to maximize therapeutic effect.

Summary of review: A systematic review was conducted across three databases to identify trials investigating the use of therapeutic hypothermia to treat intracerebral hemorrhage. A random-effects meta-analysis was conducted on preclinical studies, looking at neurobehavioral outcomes, blood brain barrier breakdown, cerebral edema, hematoma volume, and tissue loss. Several mixed-methods meta-regression models were also performed to adjust for variance and variations in hypothermia induction procedures. Twwenty-one preclinical studies and five human studies were identified. The meta-analysis of preclinical studies demonstrated a significant benefit in behavioral scores ($ES = -0.43$, $p = 0.02$), cerebral edema ($ES = 1.32$, $p = 0.0001$), and blood brain barrier ($ES = 2.73$, $p \leq 0.00001$). Therapeutic hypothermia was not found to significantly affect hematoma expansion ($ES = -0.24$, $p = 0.12$) or tissue loss ($ES = 0.06$, $p = 0.68$). Clinical study outcome reporting was heterogeneous; however, there was recurring evidence of therapeutic hypothermia-induced edema reduction.

Conclusions: The combined preclinical evidence demonstrates that therapeutic hypothermia reduced multiple cell death mechanisms initiated by intracerebral hemorrhage; yet, there is no definitive evidence in clinical studies. The cooling strategies employed in both preclinical and clinical studies were highly diverse, and focused refinement of cooling protocols should be developed in future preclinical studies. The current data for therapeutic hypothermia in intracerebral hemorrhage remains questionable despite the highly promising indications in preclinical studies. Definitive randomized controlled studies are still required to answer this therapeutic question.

Keywords

Cerebral hemorrhage, hypothermia, intracerebral hemorrhage, methodology, neuroprotection, rehabilitation, stroke, treatment

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Introduction

Intracerebral hemorrhage (ICH) remains a destructive disease the deadliest form of stroke with over 30% mortality at six months despite years of trials and research.[1–3] Immediate mechanical injury of the bleed is compounded by secondary perihematomal edema (PHE) and inflammation, which occurs immediately following ICH.[4–6] Tissue loss can continue for several months, allowing for the possibility of unique neuroprotectant strategies.[4–8] Minimally invasive surgical (MIS) evacuation of the hematoma remains a promising treatment under evaluation, but to date, no randomized controlled trial has been able to demonstrate a significant benefit.[9,10]

Therapeutic hypothermia (TH) has been shown to reduce tissue injury in preclinical models of transient focal ischemia, and for years was considered a robust neuroprotectant following cardiac arrest.[11–16] While some of the neuroprotective benefit of TH has been limited in the cardiac space, TH may still be an attractive modality to interrupt the neuroinflammation after ICH.[17] In practical terms, hypothermia poses an interesting treatment paradigm, requiring dose-finding studies examining depth and duration of cooling similar to that of drug trials. To better understand the current evidence, we have conducted this systematic review of preclinical and clinical studies with an emphasis on TH cooling protocols, and conducted a meta-analysis on all controlled preclinical studies.

Materials and methods

Search strategy and process

This review was conducted according to the PRISMA-P guidelines for preparation of a systematic review protocol.[18,19] A search was performed through three databases: MEDLINE, SCOPUS, and EMBASE. Search terms for each database can be found in supplementary Table I. Literature results were imported to Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia) for review. After the removal of duplicate studies, two authors (TB and RB) screened studies based on title and abstract. Relevant articles were exported for full-text review, and two authors (TB and ZT/LA) utilized the inclusion and exclusion criteria to include studies for final qualitative synthesis. At least two authors (TB and ZT/LA/JD) independently extracted relevant protocol elements and major findings.

Inclusion and exclusion criteria

Inclusion criteria for clinical studies were: (1) Adult patients diagnosed with spontaneous hemorrhagic stroke; (2) adult patients with both hemorrhagic and ischemic stroke in which patients with spontaneous hemorrhagic stroke could be extracted separately; (3) patients treated with therapeutic hypothermia (lower than 37°C); (4) therapeutic procedure reported.

Exclusion criteria for clinical studies were: (1) no control group; (2) patients with ischemic stroke without hemorrhagic conversion, hypoxic-ischemic encephalopathy, or subarachnoid hemorrhage; (3) studies focusing on neonatal patients.

Inclusion criteria for preclinical studies were: (1) animal ICH model; (2) treated ICH or ICH-related symptoms with therapeutic hypothermia (lower than 37°C); (3) therapeutic procedure reported.

Exclusion criteria for preclinical studies were: (1) No control group; (2) animal model with ischemic stroke or hypoxic-ischemic encephalopathy; (3) animal models have additional condition (e.g. induced or modeled tumors) outside of ICH.

All reviews, meta-analyses, observational studies, and commentaries were excluded.

Methodological quality assessment

Two reviewers (TB, JD) assessed the risk of bias and methodological quality of all studies independently; any disputes were mediated by a third reviewer, CK. The scoring system for quality assessment of preclinical studies was developed using the most recent STAIR recommendations for preclinical trial study design[20] as well as Cui et al. study design in their assessment of deferoxamine in the treatment of ICH in animal models.[21] The presence of the following criteria earned a score of one point each, for a total of 10 possible points: (1) *dose response*; (2) *therapeutic window*; (3) *outcome measures*; (4) *acute outcome measure assessment*; (5) *chronic outcome measure assessment*; (6) *physiological monitoring*; (7) *randomization*; (8) *blinding*; (9) *age of the animal*; and (10) *sex of the animal*.

A modified version of the Physiotherapy Evidence Database (PEDro) scale was used as the tool to assess risk-of-bias in the clinical trials.[22] The PEDro scale consists of 10 items; they are random allocation, concealment of allocation, baseline equivalence, blind subjects, blind therapists, blind assessors, intention-to-treat analysis, adequate follow-up, between-group statistical analysis, and measurement of data variability and point estimates.[23]

Meta-analysis

Standardized mean differences were calculated for four outcomes: blood–brain barrier (BBB) disruption, brain water content, hematoma volume, and tissue loss volume. Due to the reporting of multiple behavioral

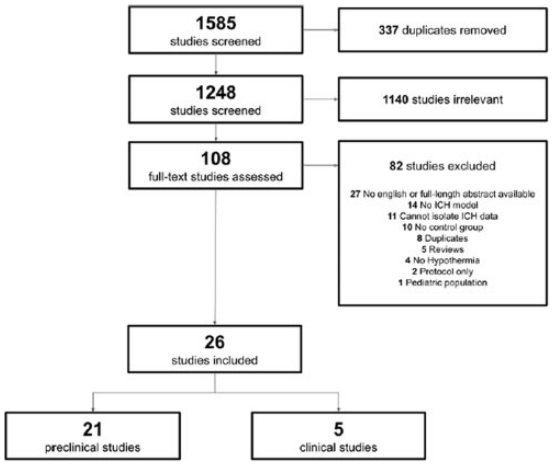
measures, a two-level meta-analysis was performed for this outcome, where standardized mean differences and standard errors were calculated for each study and then combined. Random effects analysis was performed for all outcomes, given the considerable heterogeneity of measurement and reporting. Heterogeneity of each outcome was tested with Cochrane's Q statistic. Publication bias was analyzed through funnel plot asymmetry.[24] A mixed-methods meta-regression was performed for each outcome, adjusting for random between-study variance and fixed within-study variance.[25] A second mixed-methods meta-regression model adjusts for the above as well as additional fixed effects: average study hypothermia application delay and average study hypothermia treatment duration. Meta-analysis was performed with RevMan v5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Meta-regression was performed with SAS® v9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of studies

The initial search yielded 1585 studies; 337 duplicates were removed, and 1248 studies were screened by title and abstract with 1140 deemed irrelevant. A total of 108 were screened by full-text analysis and assessed for eligibility given the inclusion and exclusion criteria. The final emerging 26 studies consisted of 21 preclinical studies and five clinical studies. Figure 1 outlines the flow of study selection. A large portion of studies were excluded from the review, as they grouped subarachnoid hemorrhage (SAH) with ICH, or did not include a matched control group.

Figure 1. PRISMA study flow diagram. The flow of study identification and selection. The original search within the three databases resulted in 1585 records, 337 of which were found to be duplicates. The remaining 1248 studies were screened by title and abstract, finding 1140 studies to be irrelevant, often due to no use of hypothermia as an intervention. This process left 108 records to assess for eligibility through full-text assessment. Full English texts were not included in 27 screened studies, 14 had no ICH patients or models within the study, 11 contained ICH data but did not isolate it from other conditions, 10 studies were single-arm and had no control group, 8 additional duplicates were identified, 5 studies were reviews, 4 studies had no hypothermia as an intervention, 2 only contained protocol descriptions and one study focused on pediatric patients. After screening, 26 studies were assessed in the review, including 21 preclinical studies and 5 clinical studies.

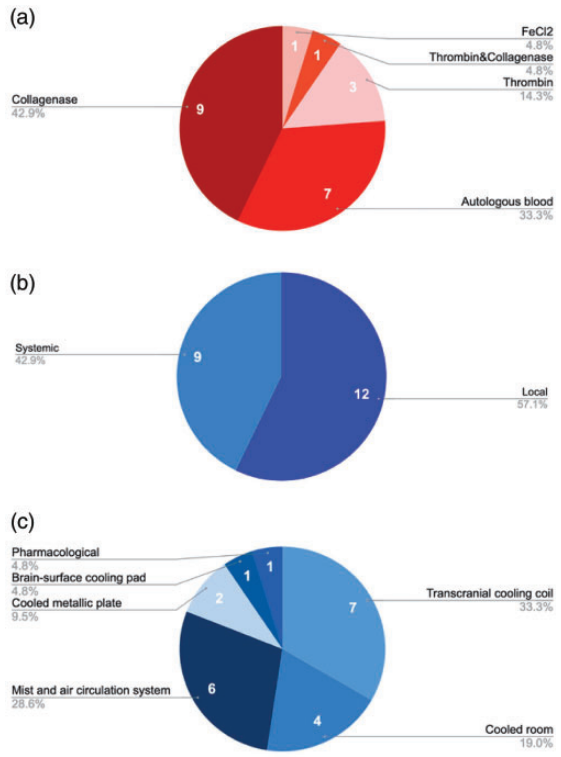


Therapeutic hypothermia in ICH preclinical models

Preclinical experimental designs were heterogeneous across studies, with many studies conducting multiple experiments compared against a singular control group. TH groups were frequently compared to both normothermia and sham-ICH procedures, where ICH was never induced. Collagenase and autologous blood injections were the most common ICH induction, and various studies were identified for systemic and localized cooling strategies. A total of 16 studies used Sprague-Dawley rats, three used Wistar rats, one used C57/BL6 mice, and one used a porcine model. Ten studies used systemic cooling through cold environments, evaporative heat loss, or both; one study used systemic pharmacological cooling; six studies used local implanted cooling coils; three studies used local affixed peltier-cooled metal plate; one study used both systemic cold room cooling and local implanted cooling coils. Systemic cooling target temperatures ranged from 30 to 33°C, while local cooling target temperatures ranged from 11 to 33°C. Figure 2 outlines several key relative frequencies of preclinical studies, while supplementary Tables II and III contain quality scores and descriptive characteristics, respectively, for each included study. Mixed methods regression of effect size by study quality scores did not identify a significant correlation between study quality and improved scores in any outcome: behavioral scores ($\beta = 0.6187$, $p = 0.1115$), BBB disruption ($\beta = -0.1307$, $p = 0.7742$), brain water content ($\beta = -0.4188$, $p = 0.2497$), hematoma volume ($\beta = 0.03786$, $p = 0.8831$), or tissue loss volume ($\beta = -0.1526$, $p = 0.7765$).

A majority of preclinical studies reported behavioral outcomes, using a wide variety of methods. An overall effect favoring hypothermic treatment was found

Figure 2. Relative frequencies of preclinical experimental designs. (a) ICH was primarily induced via direct collagenase or autologous blood infusion, with few studies opting for thrombin or other methods. Volume of injections varied widely across studies. (b) Preclinical studies were split nearly-evenly between systemic cooling and localized cooling techniques. (c) Hypothermia induction methods varied greatly across preclinical studies.



(Figure 3(a): ES = 0.43, p = 0.02), although heterogeneity was high (Figure 3(a): $\chi^2 = 61.67$, df = 14, $p \leq 0.00001$). Visual inspection of the funnel plot (supplementary Figure I(a)) yielded no apparent publication bias.

BBB disruption was reported in seven preclinical studies, all measured by Evan's Blue extravasation. An overall effect favoring hypothermic treatment was found (Figure 3(b): ES = 2.73, $p \leq 0.00001$). Heterogeneity was insignificant in this analysis (Figure 3(b): $\chi^2 = 11.15$, df = 6, p = 0.08). Visual inspection of the funnel plot (supplementary Figure I(b)) yielded no apparent publication bias.

Thirteen studies reported cerebral edema outcomes, measured by brain water content. An overall effect favoring hypothermic treatment was found (Figure 3(c): ES = 1.32, p = 0.0001). Heterogeneity was significant in this analysis (Figure 3(c): $\chi^2 = 77.59$, df = 12, $p \leq 0.00001$). Visual inspection of the funnel plot (supplementary Figure I(c)) yielded no apparent publication bias.

Eight studies used autologous blood to simulate hematomas, eight used collagenase injections, three used thrombin injections, one study used $FeCl_2$ injection, and one study used both thrombin and collagenase injections. Autologous simulated hematomas were excluded from this analysis, as there is no progressive bleeding in this modality. Nine studies had progressive hematoma modalities and reported changes in hematoma volume in a variety of ways, and are included in this analysis. No significant overall effect of cooling was found, although the average effect favored normothermic treatment (Figure 4(a): ES = −0.24, p = 0.12). Heterogeneity was insignificant in this analysis (Figure 4(a), $\chi^2 = 10.15$, df = 8, p = 0.25). Visual inspection of the funnel plot (supplementary Figure I(d)) yielded no apparent publication bias.

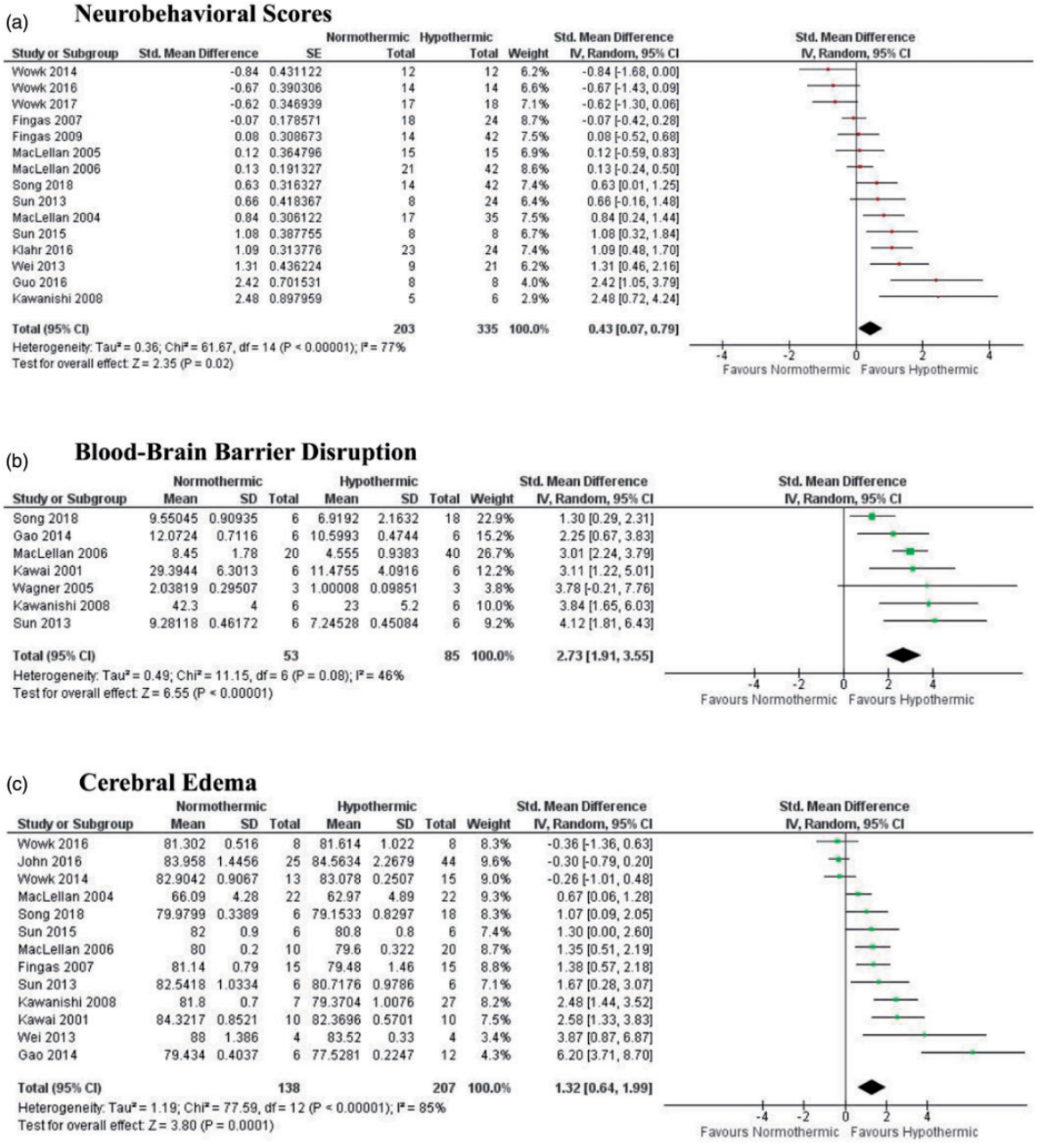
Eight studies reported tissue loss outcomes, measured by lesion volume or total tissue lost, and are included in this analysis. No overall effect was found (Figure 4(b): ES = 0.06, p = 0.68). Heterogeneity was insignificant in this analysis (Figure 4(c): $\chi^2 = 10.09$, df = 7, p = 0.18). Visual inspection of the funnel plot (supplementary Figure I(e)) yielded no apparent publication bias.

Mixed methods meta-regression of each outcome adjusted for between study and within-study variance did not appreciably change effect size or significance (supplementary Table IV). Additional adjustment for hypothermia treatment delay, treatment duration, and local vs. systemic cooling showed no significant associations in any of the outcomes (supplementary Table V).

Therapeutic hypothermia in clinical trials

Clinical studies consisted of two randomized controlled trials (RCTs), a nonrandomized prospective study, and two historically controlled trials. Studies were conducted in China, Malaysia, and Germany. Clinical studies averaged a PEDro score of 4.4, and all but one of the studies achieved a score of 5.[26–29] No study met the predetermined definition of "good quality" for a controlled trial (supplementary Figure II). A majority of studies were non-randomized or used historical cohorts as the control, thereby not allowing for blinding or allocation concealment.[26,27] Details of the individual study designs, TH protocols, and maintenance are outlined in Table 1. Two RCTs were identified, but had short follow-up periods, and did not describe blinding or allocation concealment protocols.[28,29] Abdullah and Husin[30] performed a non-randomized, unblinded prospective study, receiving the lowest score of 2. A meta-analysis was not performed due to the high degree of heterogeneity in outcome reporting between the studies (supplementary Table VI).

Figure 3. Forest plots of preclinical studies showing significant improvement in ICH mechanisms and outcomes following therapeutic hypothermia. (a) Fifteen studies reported behavioral outcomes. Meta analysis of standardized mean differences showed significant improvement in animals that were treated with TH. (b) Seven studies reported blood-brain barrier disruption outcomes measured by Evans Blue dye extravasation. Combined analysis demonstrated significant reduction in BBB disruption in animals treated with TH. (c) Thirteen studies reported cerebral edema measured by brain water content, with outcomes converted to standardized mean differences. A significant reduction in edema formation was seen in animals that underwent TH.



Staykov et al.[26] and Volbers et al.[27] both assessed the use of mild systemic hypothermia as compared to historically matched controls. Staykov et al.[26] found a significant reduction in PHE in response to immediate cooling and no significant change in hematoma growth. Pneumonia and shivering were significantly elevated in the TH group, and there was no significant benefit in functional outcomes. Volbers et al.[27] varied the delay in cooling following the hemorrhage, seeing a significant reduction in edema following cooling under

Figure 4. Forest plots of preclinical studies showing no significant difference in ICH mechanisms and outcomes between cooled and control animals. (a) Nine studies reported hematoma volumes which were converted to standardized mean differences. There was no significant effect involving hypothermia treatment and hematoma volume. (b) Eight studies reported tissue loss (measured by lesion size) outcomes which were converted to standardized mean differences. There was no significant effect involving hypothermia treatment and tissue loss.

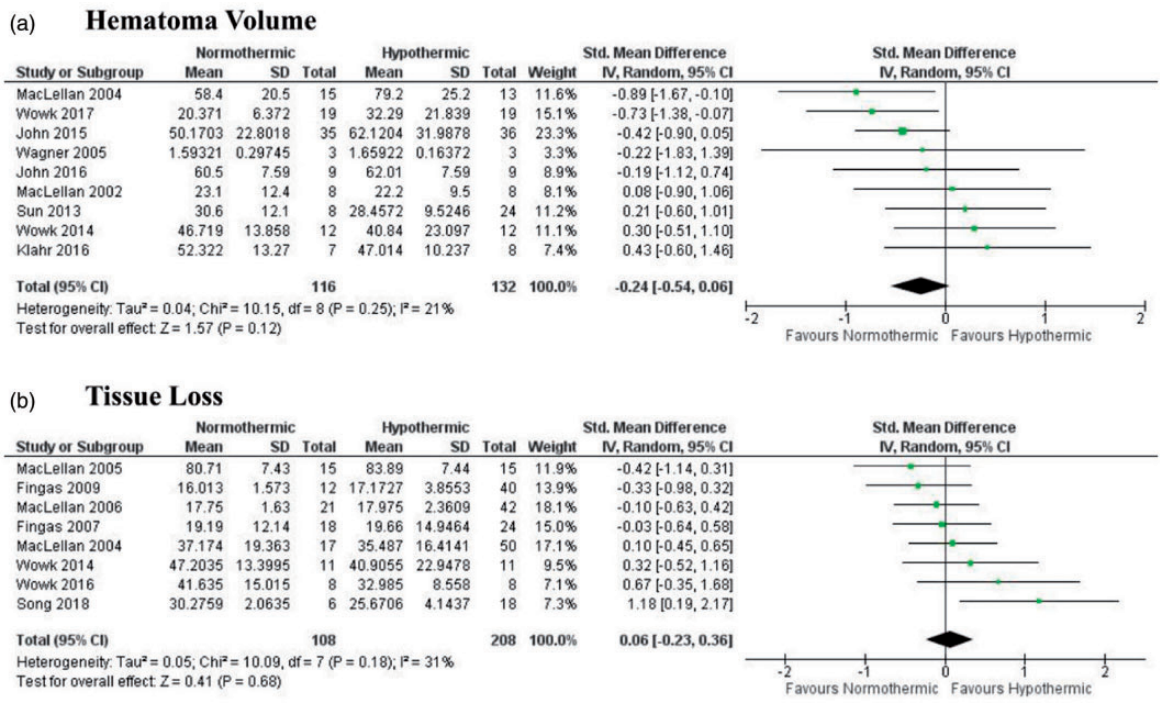


Table 1. Therapeutic hypothermia protocols of included clinical studies.

	Hypothermia type	Hypothermia method	Interval from onset to cooling	Target temperature	Duration of hypothermia	Rewarming rate
Abdullah et al.[30]	Systemic	Cooling central venous catheter	Not reported	34°C	24 h	1°C per h
Staykov et al.[26]	Systemic	Cooling central venous catheter	<24 h	35°C	8–10 days	0.5 LC per 24
Su et al.[28]	Local	Surface head cooling	3.67 h	33–35°C	72 h	<1°C per 4–6 h
Volbers et al.[27]	Systemic	Cooling central venous catheter	1–2 days (n = 30) 4–5 days (n = 3)	35°C	3–8 days (n = 21)	0.5°C per 24 h
Zhao et al.[29]	Systemic	Surface-cooling	not reported	32.5–34.5°C	3–7 days	0.5°C per 12 h

Note: Key TH procedural elements of the clinical studies identified are summarized. Target temperature was similar across all studies, ranging from 32.5 to 34.5°C, as were rewarming rates. There was a wide degree of variability in duration of and delay from TH.

two days, with no significant effect on edema when cooling was induced four days following the bleed. Duration of TH was also varied, with no significant difference seen in terms of extended cooling duration (Table 2).

Su et al.[28] was the only study found to induce localized cooling, inducing TH via a head wrap. Minimal clinical outcomes were reported, but the cooled group was found to have a significant improvement in

Table 2. Key outcomes and characteristics of included clinical studies.

References	Control	N	Age Years (SD)	Gender *%Female*	Baseline hematoma volume (mL)	Follow-up period	Peak PHE volume, *mL (SD)*	Mortality *Dead (%)*	Key results
Abdullah et al.[30]	Standard medical treatment	I: 6 C: 18	I: 49.8 C: 60.7	I: 66.7 C: 66.7	Not reported	One year	Not reported	Not reported	Hematoma volume: Not reported. PHE: Not reported. Functional score (mRS): Follow-up mRS was significantly lower in the intervention group, and represented greater decrease from baseline. Other findings: Not reported.
Staykov et al.[26]	Standard medical treatment (historical matched control)	I: 25 C: 25	I: 63 (9.3) C: 67 (7.5)	I: 44% C: 40%	I: 54,4 (25) C: 57.4 (31.1)	One year	Day 14 I: 87.7 (7.6) C: 53.4 (7.9)	3-month I: 2 (8%) C: 7 (28%) 1-year I: 4 (16%) C: 11 (44%)	Hematoma Volume: There were no significant difference in hematoma volume overthe 14 days between groups. PHE: Edema in the TH group was stable compared to the control, and significantly reduced on days 3–14. Functional score (mRS): There was no significant difference between groups. Other findings: Pneumonia (96%) and shivering occurred at higher rates in the TH group compared to control. Deep vein thrombosis, pulmonary embolism, bradycardia, and thrombocytopenia were also higher in the TH group. Proportion with myocardial infarction was lower in the TH group
Su et al.[28]	Standard medical treatment	I: 19 C: 17	I: 60.21 (12.85) C: 58.59 (15.11)	I: 42% C: 53%	Not reported	21 Days	Not reported	Not reported	Hematoma volume: Not reported. PHE: Not reported. Functional score (NIHSS/GCS): The TH group has a greater improvement in NIHSS and GCS compared to the control. Other findings: Regional cerebral blood flow was significantly elevated in the TH group.

(continued)

Table 2. Continued.

References	Control	N	Age Years (SD)	Gender *%Female*	Baseline hematoma volume (mL)	Follow-up period	Peak PHE volume, *mL (SD)*	Mortality *Dead (%)*	Key results
Volbers et al.[27]	Standard medical treatment (historical matched control)	I: 33 C: 37	I: 63 (11) C: 64.7 (10)	I: 48% C: 41.5%	I: 45.8 (29.2) C: 45.3 (24.3)	90 Days	I: 70.784 (21.567) C: 78.72 (33.12)	90-day I: 4 (15.4%) C: 7 (13.8%)	Hematoma volume: Secondary hematoma expansion was significantly elevated in the TH group compared to control. PHE: Relative edema was substantially lower in patients cooled within one to two days. No significant difference in edema was seen between control and TH initiated 4+ days after onset. There were no significant differences between short or long TH therapy when induced within 1–2 days. Functional score (mRS): Median mRS did not differ between groups. Other findings: There were no difference in complications between groups.
Zhao et al.[29]	Standard medical treatment (historical matched control)	I: 103 C: 103	I: 52.87 (14.40) C: 51.53 (15.39)	Not reported	I: 39.02 (10.74) C: 38.19 (9.32)	Seven days	Not reported	Not reported	Hematoma Volume: Not reported. PHE: Not reported. Functional score (NIHSS): The TH group has significant improvements in NIHSS at the three- and seven-day follow-up periods compared to the control. Other findings: TNF-alpha and NF-kB were significantly reduced in the TH group. There were no difference in complications.
		Total							
		I: 186 C: 200							

Note: Key characteristics of the clinical studies identified are summarized. Hematoma volume, follow-up periods, PHE volume, mortality, and key results were reported.
TH: therapeutic hypothermia; PHE: perihematomal edema mRS: modified Rankin Score; NIHSS: National Institute of Health Stroke Scale; rCBF: regional cerebral blood flow; TNF-alpha: tumor necrosis factor alpha; NF-kB: nuclear factor-kB.

functional outcomes compared to control. Regional cerebral blood flow measured with SPECT imaging was also reported to have increased (Table 2).

Zhao et al.[29] was the only identified study that assessed the combination therapy of ICH evacuation and TH, and was the only study that induced systemic hypothermia via surface cooling. National Institute of Health Stroke Scale (NIHSS) scores were found to be significantly reduced at both the follow up periods; however, follow-up was limited to only seven days and few other clinical characteristics were described. The study was randomized and had the largest sample size of any trial identified, with 206 subjects. The primary aim of the study was to identify the effect of TH on inflammatory markers, demonstrating a significant reduction in tumor necrosis factor alpha (TNF-alpha) and nuclear factor Kappa-light-chain-enhancer of activated beta cells (NF-kb) in the cooled group compared to the control (Table 2).

Discussion

A systematic review of the literature focusing on TH to treat ICH was conducted, identifying 21 preclinical and five clinical studies comparing TH to control. Current preclinical evidence demonstrates significant improvements in behavioral, BBB disruption, and edema outcomes following TH, but conclusive clinical RCTs in humans have not been conducted.

The meta-analysis of the preclinical studies found a clear benefit to ICH-related injury in response to TH, improving neurologic outcome, reducing perihematoma edema, and reducing BBB breakdown. This analysis expands on the prior work of Melmed and Lyden[31] by adding additional studies that have been performed in the interim and including clinical studies. In our analysis, we broke lesion size into its two commonly reported components: hematoma expansion and ICH-related tissue loss. Our findings found tissue loss to not be affected by TH, and while hematoma volume was also found to be non-significant, there was a clear trend towards expansion in association with TH. Hematoma expansion due to TH has been hypothesized to be a result of increased blood pressure soon after hemorrhage,[32] inhibition of coagulopathy,[32] or a propensity towards delayed rebleeding.[33] The effect is likely to be multifaceted and careful preclinical experimentation will be required to determine if beneficial effects of TH on cerebral edema and BBB disruption can be promoted while minimizing potentially harmful effects of TH on hematoma expansion. Without consistent significant findings contraindicating TH for ICH because of hematoma expansion, the relationship is difficult to identify. This is clinically important, as the potential for TH to negatively affect coagulation and hematoma growth is a primary concern of future clinical RCTs. While some preclinical studies suggested a trend of increased bleeding following early cooling in collagenase ICH models, a meta-regression analysis demonstrated that cooling protocol elements did not significantly impact the overall positive effect of cooling. While this may suggest that ICH outcomes are dose independent, there was extensive variation in design across the preclinical studies, particularly in the dosing of TH, which may have limited the ability for the meta-regression to detect trends.

While conclusive, the preclinical evidence could be improved with additional testing. All BBB analysis was performed using Evan's Blue extravasation, which has been criticized previously.[8,34] All but one preclinical study was performed on young or adult rats or mice, with one study using adult pigs. This substantially differs from a majority of ICH patients, who tend to be elderly. It is possible that the use of younger animal models overestimates the true efficacy of TH in a real-world setting. Additional preclinical testing using older or hypertensive animal models would bolster the current level of preclinical evidence. These studies may also shed greater light on the potential risks of cooling-induced rebleeding, as hypertensive rats are known to be at greater risk of bleeding. The major limitation of this meta-analysis was the combining of interventions to conduct the analysis; many of the preclinical studies used the same control group to test intervention groups with varied sample sizes, which would artificially increase sample size should they be assessed independently. While this solidifies the significant findings in edema, BBB, and neurobehavioral scores, it may also explain why hematoma volume was found to be insignificant. Future preclinical work should begin to focus on a central ICH-induction strategy and cooling protocol in order to clearly distinguish optimal procedures.

The lack of definitive outcomes in clinical testing may also be due to the incongruencies between preclinical and clinical cooling protocols. A large portion of preclinical studies used focal cooling methods to induce TH. The negative side-effects of systemic hypothermia are well documented, and focal hypothermia may achieve the benefits of TH while minimizing the pitfalls of systemic cooling. Su et al.[28] was the only study that performed a controlled clinical study assessing the use of focal cooling, finding a significant improvement in functional outcome within the cooled group compared to controls. Several uncontrolled clinical studies have been conducted in recent years utilizing transcranial and intranasal cooling techniques, and the development of specific tools and techniques to induce focal cooling in ICH would be beneficial in combination with a larger controlled study.[35,36] The time between bleed and TH initiation was shorter in all preclinical studies compared

to identified human trials, likely due to the inherent obstacles in rapidly cooling ICH patients. While this may explain the increased benefit to edema reduction in preclinical results, the potential for TH to negatively impact hematoma growth is highest immediately following the bleed, thereby increasing the risk of rapid cooling. Duration of cooling was found to be significantly shorter in preclinical studies compared to human trials. All clinical trials except Abdullah et al.[30] report a cooling duration of three or more days, while only seven preclinical trials have hypothermia durations more than 24 h. Given the immediate initiation and growth of the edema, short-term cooling may do enough to inhibit the evolution of the inflammatory cascade caused by the hemorrhage, as suggested in preclinical results, but PHE is known to progress over several days and increased cooling durations may further improve outcomes if the side effects of long-term TH can be mitigated.

Distinctly lacking from both preclinical and clinical data is the combination of TH with minimally invasive evacuation of the hematoma prior to cooling. Zhao et al.[29] is the only study identified that tested this combination therapy, finding improved neurological scores and reduced inflammatory markers. China has already adopted surgical evacuation of the hematoma following ICH as standard of care, explaining the increased sample size within Zhao et al. A separate meta-analysis was identified that reported an emphatic benefit of TH on ICH when combined with evacuation, but all studies were published in Chinese, and none of the cited articles could be identified or confirmed.[37]

The substantial preclinical data indicates that TH may still be a promising avenue for treating ICH; however, the lack of substantial clinical evidence and recent findings in cardiac arrest[38] dampens optimism. In order for TH to prove effective in improving ICH outcomes, additional optimization of cooling protocols is needed to induce optimal effect while minimizing potential negative effects like worsened bleeding, inhibition of beneficial inflammation, or interference with brain plasticity. A wide array of preclinical experiments has been conducted, and it is important for controlled human studies to attempt to reproduce the success of preclinical findings despite the varied nature of preclinical cooling procedures. Future clinical trials must extrapolate from the cooling protocols identified in animal studies to optimize the key mechanisms seen while accounting for differences in the triage and clinical setting. It is important to note that the preclinical work has been varied in procedure, and no clearly successful protocol has been identified. Nonetheless, finding ways to cool the area of inflammation locally has clear benefits to the weakened ICH patient population, who struggle with the effects of shivering, pneumonia, and other systemic cooling effects. The use of TH may further benefit from a combination treatment alongside clot evacuation. This may prove a symbiotic combination, with evacuation focusing on minimizing the mass effect and iron toxicity of the bleed, and TH minimizing the secondary inflammatory response. It is important for additional RCTs to be conducted to identify optimal cooling protocols for this patient population and informed by the expansive work already conducted in preclinical experiments.

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References

1. Guo T, Ren P, Li X, et al. Neural injuries induced by hydrostatic pressure associated with mass effect after intracerebral hemorrhage. *Sci Rep* 2018; 8: 9195.
2. Wilkinson DA, Pandey AS, Thompson BG, et al. Injury mechanisms in acute intracerebral hemorrhage. *Neuropharmacology* 2018; 134: 240–248.
3. van Asch CJJ, Luitse MJA, Rinkel GJE, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* 2010; 9: 167–176.
4. Zazulia AR, Diringer MN, Derdeyn CP, et al. Progression of mass effect after intracerebral hemorrhage. *Stroke* 1999; 30: 1167–1173.
5. Gebel JM Jr, Jauch EC, Brott TG, et al. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke* 2002; 33: 2631–2635.
6. Venkatasubramanian C, Mlynash M, Finley-Caulfield A, et al. Natural history of perihematomal edema after intracerebral hemorrhage measured by serial magnetic resonance imaging. *Stroke* 2011; 42: 73–80.
7. Nguyen AP, Huynh HD, Sjovold SB, et al. Progressive brain damage and alterations in dendritic arborization after collagenase-induced intracerebral hemorrhage in rats. *Curr Neurovasc Res* 2008; 5: 171–177.
8. MacLellan CL, Silasi G, Poon CC, et al. Intracerebral hemorrhage models in rat: comparing collagenase to blood infusion. *J Cereb Blood Flow Metab* 2008; 28: 516–525.

9. Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet* 2019; 393: 1021–1032.
10. Hanley DF, Thompson RE, Muschelli J, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *Lancet Neurol* 2016; 15: 1228–1237.
11. Zhao H and Steinberg G. Limited therapeutic time windows of mild-to-moderate hypothermia in a focal ischemia model in rat. *Stroke Res Treat* 2011; 2011: 131834.
12. Dumitrascu OM, Lamb J and Lyden PD. Still cooling after all these years: meta-analysis of pre-clinical trials of therapeutic hypothermia for acute ischemic stroke. *J Cereb Blood Flow Metab* 2016; 36: 1157–1164.
13. van der Worp HB, Macleod MR, Kollmar R, et al. Therapeutic hypothermia for acute ischemic stroke: ready to start large randomized trials? *J Cereb Blood Flow Metab* 2010; 30: 1079–1093.
14. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008; 371: 1955–1969.
15. Kollmar R and Schwab S. Hypothermia in focal ischemia: implications of experiments and experience. *J Neurotrauma* 2009; 26: 377–386.
16. Colbourne F, Corbett D, Zhao Z, Yang J and Buchan AM. Prolonged but delayed postischemic hypothermia: a long-term outcome study in the rat middle cerebral artery occlusion model. *J Cereb Blood Flow Metab* 2000; 20: 1702–1708.
17. Mracsko E and Veltkamp R. Neuroinflammation after intracerebral hemorrhage. *Front Cell Neurosci* 2014; 8: 388.
18. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.
19. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA and Chalmers TC. Meta-analyses of randomized controlled trials. *N Engl J Med* 1987; 316: 450–455.
20. Fisher M, Feuerstein G, Howells DW, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. *Stroke* 2009; 40: 2244–2250.
21. Cui H-J, He H-Y, Yang A-L, et al. Efficacy of deferoxamine in animal models of intracerebral hemorrhage: a systematic review and stratified meta-analysis. *PLoS One* 2015; 10: e0127256.
22. Bhogal SK, Teasell RW, Foley NC and Speechley MR. The PEDro scale provides a more comprehensive measure of methodological quality than the Jadad Scale in stroke rehabilitation literature. *J Clin Epidemiol* 2005; 58: 668–673.
23. Gonzalez GZ, Moseley AM, Maher CG, et al. Methodologic quality and statistical reporting of physical therapy randomized controlled trials relevant to musculoskeletal conditions. *Arch Phys Med Rehabil* 2018; 99: 129–136.
24. Higgins J, Green S (eds). *Cochrane handbook for systematic reviews of interventions*. Chichester, England: John Wiley & Sons, 2007.
25. Sheu CF and Suzuki S. Meta-analysis using linear mixed models. *Behav Res Methods Instrum Comput* 2001; 33: 102–107.
26. Staykov D, Wagner I, Volbers B, et al. Mild prolonged hypothermia for large intracerebral hemorrhage. *Neurocritical Care* 2013; 18: 178–183.
27. Volbers B, Herrmann S, Willfarth W, et al. Impact of hypothermia initiation and duration on perihemorrhagic edema evolution after intracerebral hemorrhage. *Stroke* 2016; 47: 2249–2255.
28. Su X, Zheng K, Ma Q, et al. Effect of local mild hypothermia on regional cerebral blood flow in patients with acute intracerebral hemorrhage assessed by 99mTc-ECD SPECT imaging. *J X-Ray Sci Technol* 2015; 23: 101–109.
29. Zhao J, Mao Q, Qian Z, Zhu J, Qu Z, Wang C. Effect of mild hypothermia on expression of inflammatory factors in surrounding tissue after minimally invasive hematoma evacuation in the treatment of hypertensive intracerebral hemorrhage. *Exp Ther Med*. 2018 Jun; 15(6): 4906–4910. doi: 10.3892/etm.2018.6014. Epub 2018 Mar 30. PMID: 29805513; PMCID: PMC5952095.
30. Abdullah JM and Husin A. Intravascular hypothermia for acute hemorrhagic stroke: a pilot study. *Acta Neurochir Suppl* 2011; 111: 421–424.
31. Melmed KR and Lyden PD. Meta-analysis of pre-clinical trials of therapeutic hypothermia for intracerebral hemorrhage. *Ther Hypothermia Temp Manag* 2017; 7: 141–146.
32. MacLellan CL, Girgis J and Colbourne F. Delayed onset of prolonged hypothermia improves outcome after intracerebral hemorrhage in rats. *J Cereb Blood Flow Metab* 2004; 24: 432–440.
33. Wowk S, Fagan KJ, Ma Y, Nichol H and Colbourne F. Examining potential side effects of therapeutic hypothermia in experimental intracerebral hemorrhage. *J Cereb Blood Flow Metab* 2017; 37: 2975–2986.
34. Nadeau CA, Dietrich K, Wilkinson CM, et al. Prolonged blood-brain barrier injury occurs after experimental intracerebral hemorrhage and is not acutely associated with additional bleeding. *Transl Stroke Res* 2019; 10: 287–297.
35. Abou-Chebl A, Sung G, Barbut D and Torbey M. Local brain temperature reduction through intranasal cooling with the RhinoChill device: preliminary safety data in brain-injured patients. *Stroke* 2011; 42: 2164–2169.
36. Poli S, Purrucker J, Priglinger M, et al. Safety evaluation of nasopharyngeal cooling (RhinoChill®) in stroke patients: an observational study. *Neurocrit Care* 2014; 20: 98–105.
37. Han Y, Sheng K, Su M, Yang N and Wan D. Local mild hypothermia therapy as an augmentation strategy for minimally invasive surgery of hypertensive intracerebral hemorrhage: a meta-analysis of randomized clinical trials. *Neuropsychiatric Dis Treat* 2016; 13: 41–49.
38. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med* 2021; 384: 2283–2294.