

Methodological quality of systematic reviews addressing therapeutic hypothermia and/or cooling therapy for traumatic brain injury

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Abstract

Therapeutic hypothermia and/or cooling therapy are suggested to have benefits in patients with acute traumatic brain injury, and several systematic reviews (SRs) have been performed to synthesize the evidence from randomized clinical trials (RCTs). The objective of this critical appraisal study was to assess the methodological quality of SRs that evaluated the use of therapeutic hypothermia and/or cooling therapy in patients with acute traumatic brain injury. A broad and sensitive search of the literature was performed in March 2019. Four major electronic databases (MEDLINE, EMBASE, LILACS and Cochrane Library) were considered. The study selection, data extraction and the appraisal of the methodological quality was carried out by two independent reviewers. The methodological quality of the included SRs was assessed using the AMSTAR-2 (A Measurement Tool to Assess systematic Reviews) tool. The search strategy retrieved 149 articles, and 16 SRs were included after the selection process. They were published between 2003 and 2018, and the number of included clinical trials varied from 0 to 37. The overall confidence in the results from included SRs was graded as critically low in 53.3%, low in 13.3%, moderate in 20%, high in 13.3%. In Conclusion, most of the included SRs had poor methodological quality and only two systematic reviews were judged as having high overall confidence in the results in accordance to AMSTAR-2. Decision makers should consider the overall quality of the synthesis when using or recommending hypothermia and/or cooling therapy for practice.

Palavras-chave: Induced hypothermia; Traumatic Brain Injuries; Review.

INTRODUCTION

Well conducted systematic reviews are described as the most reliable source of evidence to guide health clinical practice^{1,2,3}. It involves a rigorous methodology that identifies, summarizes and critically analyzes the data from all relevant studies on a specific topic. Systematic reviews are used by health professionals, researchers, patients and health policy makers to answer an explicit clinical question, which helps in clinical decision making and formulating healthcare guidelines; apart from avoiding the duplication of

information already explored^{1,4,5}.

Over the last two decades, the number of published systematic reviews on a variety of health specialties has increased rapidly. However, not every systematic review represents a high level of evidence and it is imperative that users can differentiate between high-quality and low-quality reviews. There is a lack of uniformity in methodological aspects of a large number of published systematic reviews, raising the concern about the credibility of the information

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delivered^{3,6}. Additionally, many published systematic reviews overlap on the same topics^{6,7}.

The measurement tool to assess systematic reviews 2 (AMSTAR 2) is an updated version of a tool developed to critically appraise systematic reviews of healthcare interventions. The AMSTAR 2 is composed of 16 domains (10 of the original AMSTAR) which are judged with simple response categories: completely adequate (“yes”); partially adequate (“partially yes”); inadequate (“no”); or not applicable⁸. The domains include questions about: the components of PICO in the research question; the review protocol; the selection of the study design; adequate literature search strategies; study selection and data extraction performed in duplicate; the list of excluded studies with reasons for exclusion; the description of the characteristics of the included studies; the risk of bias assessment of the included studies; the source of funding for the included studies; the methods for statistical combining of results (meta-analysis); the potential impact of risk of bias assessment when interpreting and discussing the results; the explanation for any heterogeneity observed in the results; the adequate investigation of publication bias and reports of any conflict of interest from the review authors⁸.

As in other health areas, a substantial number of systematic reviews have been currently published on the use of hypothermia therapy for the treatment of traumatic brain injury, and it is important to identify and critically analyze these reviews, to provide more reliable evidence. Traumatic brain injury (TBI) is a serious health and socioeconomic problem, that accounts for approximately 1.7 million new cases in the United States per year^{9,10}. It is the primary cause of death and disability among young adults, frequently associated with road traffic accidents¹¹. Therapeutic hypothermia (cooling to 32 to 34°C) is a recognized method to improve the events developed following a TBI, like intracranial hypertension, since the effects of hypothermia seems to control intracranial pressure by reducing brain edema, leading to an improvement of functional outcomes^{9,10}. However, the benefits and harms of the use of this intervention remains controversial in the literature.

Therefore, the objective of this study was to assess the methodological quality of systematic reviews that evaluated the use of therapeutic hypothermia and/or cooling therapy in patients with acute traumatic brain injury.

METHODS

Study setting and design

A review of SRs with critical appraisal occurred at the Centro Universitário São Camilo (CUSC), Brazil.

Criteria for including reviews

Type of studies

Any published SRs that included randomized clinical trials were included. We did not include published protocols of SRs nor protocol registries published in the PROSPERO database.

Types of participants

Participants (adults and children) with acute TBI that were considered by the SR authors. SRs that included a variety of neurological conditions were not included, even if they considered a subgroup of participant with acute TBI.

Types of interventions

Only SRs that compared hypothermia as a therapeutic approach with any inactive or active intervention or with no intervention were included.

Searching for systematic reviews

A broad and sensible search strategy on March 19, 2019 was performed in the following databases:

- Cochrane Database of Systematic Reviews - CDSR (via Wiley).
- Embase (Excerpta Medica dataBASE) (via Elsevier).
- MEDLINE (Medical Literature Analysis and Retrieval System Online) (via Pubmed).
- LILACS (Latino-American and Caribbean Literature in Health Science) (via Biblioteca Virtual em Saúde - BVS).

No limits were imposed regarding date or language of publication. The search strategies were developed using the descriptor terms for the interventions (“Hypothermia” OR “Hypothermia, Induced”) and for the conditions (“Brain injuries, traumatic” OR “Brain concussion”). Synonyms were added to increase sensitivity. The search strategies for each database are fully displayed in **Supplementary file 1**. Additional manual searches were performed in the reference list of included studies and other relevant sources.

Selection process

The selection process was performed by two independent reviewers (RLP and COCL) and a third reviewer solved any conflict (ALCM). The selection was performed in a two-stage process aided by the Rayyan Platform (<https://rayyan.qcri.org/>)¹². The first phase consisted of reading the titles and abstracts of all studies retrieved by the search strategy. The studies referenced were marked as “excluded in the first phase” or “potentially included”. The second phase consisted in reading the full text of those marked “potentially included” to check if they indeed fulfilled the inclusion criteria, and then decide to “include” or “exclude in the second phase”. Reasons for excluding in the second phase were presented in this report.

Methodological quality assessment of the included systematic reviews

The methodological quality assessment of the included systematic reviews was performed by checking their compliance with the domains from the AMSTAR-2 tool (A Measurement Tool to Assess systematic Reviews)⁸. The quality assessment was not performed on the included SRs that were published only in a conference proceeding. The AMSTAR-2 tool includes the following 16 domains that are related to:

- 1) research questions and inclusion criteria for the review includes the components of PICO (Patients, Interventions, Comparators, Outcomes);
- 2) *a priori* design;
- 3) justifications for the selection of the study design;
- 4) search strategies;
- 5) duplicate study selection;
- 6) duplicate data extraction;
- 7) reference to the excluded studies;
- 8) characteristics of included studies;
- 9) technique for assessing the risk of bias from the included studies;
- 10) report of the source of funding for the included studies;
- 11) methods for combining results;
- 12) evaluation of the impact of risk of bias in meta-analysis results;
- 13) consideration of the risk of bias in the interpretation and discussion of the results;
- 14) discussion and explanation of heterogeneity;
- 15) investigation of publication bias;

16) report of the conflict of interest from the review authors.

The domains 1,4,7,9,11,13 and 15 are considered critical by the AMSTAR-2 tool. The judgment of each domain was performed by two independent authors (RLP and COCL), who judged each item as being: completely adequate (“yes”); partially adequate (“partially yes”); inadequate (“no”); or not applicable. Any disagreement was resolved by consulting a third author (ALCM).

After all judgments, we used the AMSTAR-2 framework to grade the overall confidence in the results using the checklist from the AMSTAR-2 website (http://amstar.ca/Amstar_Checklist.php). Following the AMSTAR-2 recommendations, the overall confidence in the results was graded into four categories: critically low; low; moderate and high.

Data presentation and analysis

A narrative synthesis of the results was performed, and the data was presented using percentages.

RESULTS

Results of the search

The diagram of the selection process is presented in Figure 1. The search retrieved 149 records. After the reading of titles and abstracts, 17 references were marked as “potentially included” and read in full. After the second phase, 1 reference¹³ was excluded because it was not a SR and 16 SRs were included¹⁴⁻³⁰.

Characteristics of the included systematic reviews

The 16 included SRs were published between 2003 and 2018. The population consisted of adults in 7 SRs, children in 3 SRs and 6 SRs that did not specify the age of the population. The countries of the reviews were Canada (3 reviews), China (4 reviews), United States of America (4 reviews) and United Kingdom (5 reviews). The number of included RCTs ranged from 0 to 37. One included SR²² was published only as a conference proceeding and therefore was not assessed.

Methodological assessment

The results of the judgments from AMSTAR-2



items are presented in the Table 1. The judgment for each SR is presented in Table 2. The overall confidence in the results of the included SRs was

graded as critically low in 53.3% (8/15), low in 13.3% (2/15), moderate in 20% (3/15) and high in 13.3% (2/15).

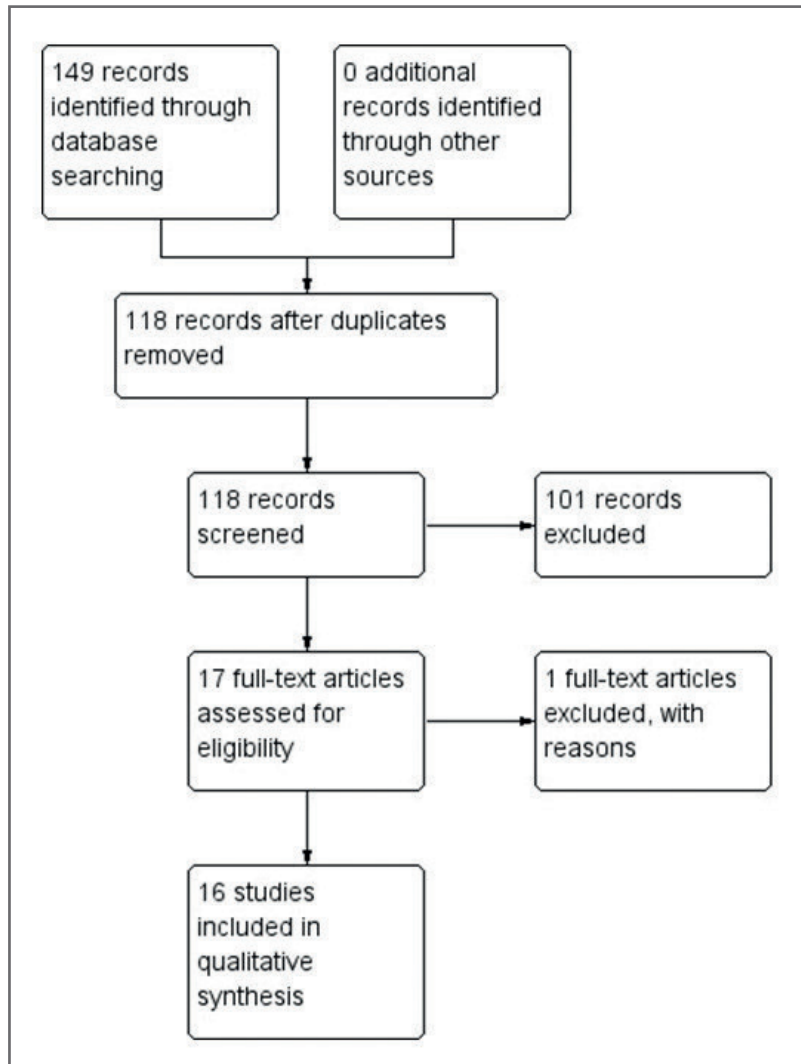


Figure 1 – Study selection process diagram. São Paulo, 2019

Table 1 – Overall judgments for AMSTAR-2 items. Results from 15 systematic reviews

AMSTAR-2 Item	“Yes” judgments	“Partially yes” judgments	“No” judgments	“Not applicable” judgments
Research questions and inclusion criteria	6 (40%)	0	9(60%)	0
A priori design	4 (26.67%)	1 (6.67%)	10 (66.67%)	0
Justifications for the selection of the study design	2 (13.33%)	0	13 (86.67%)	0
Search strategies	5 (33.33%)	2 (13.33%)	8 (53.33%)	0
Duplicate study selection	10 (66.67%)	0	5 (33.33%)	0
Duplicate data extraction	10 (66.67%)	0	5 (33.33%)	0
Reference to the excluded studies	6 (40%)	0	9 (60%)	0
Characteristics of included studies	2 (13.33%)	11 (73.33%)	1 (6.67%)	1 (6.67%)
Technique for assessing the risk of bias from the included studies	3 (20%)	4 (26.67%)	7 (46.67%)	1 (6.67%)
Report of the source of funding for the included studies	1 (6.67%)	0	13 (86.67%)	1 (6.67%)
Methods for combing results	9 (60%)	0	3 (20%)	3 (20%)
Evaluation of the impact of risk of bias in meta-analysis results	7 (46.67%)	0	5 (33.33%)	3 (20%)
Consideration of the risk of bias in the interpretation and discussion of the results	7 (46.67%)	0	7 (46.67%)	1 (6.67%)
Discussion and explanation of heterogeneity	6 (40%)	0	8 (53.33%)	1 (6.67%)
Investigation of publication bias	8 (53.33%)	0	5 (33.33%)	2 (13.33%)
Report of the conflict of interest from the review authors	11 (73.33%)	0	4 (26.67%)	0



Table 2 – Judgments for each included SR.

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Systematic review identification (Author Year)	AMSTAR-2 item																Overall confidence
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Crossley 2014	yes	yes	no	yes	yes	yes	yes	py	yes	no	yes	yes	yes	yes	yes	yes	Moderate
Dunkley 2017	no	no	no	no	yes	yes	no	py	no	no	na	na	no	no	na	no	Critically low
Fox 2010	no	py	no	yes	yes	yes	yes	yes	py	no	yes	yes	yes	yes	yes	yes	Moderate
Georgiou 2013	no	no	no	no	no	no	no	py	no	no	yes	yes	yes	yes	yes	yes	Critically low
Henderson 2003	yes	no	no	no	yes	no	yes	no	no	no	no	no	no	no	no	no	Critically low
Leng 2018	no	no	no	no	no	no	no	py	no	no	no	no	no	no	no	no	Critically low
Lewis 2017	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	High
Ma 2013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
McIntyre 2003	yes	no	no	yes	no	yes	yes	py	py	no	yes	yes	yes	yes	yes	yes	Moderate
Peterson 2008	no	no	no	no	yes	yes	no	py	py	no	yes	yes	yes	yes	no	no	Low
Sadaka 2012	no	no	no	no	no	no	no	py	no	no	na	na	no	no	no	yes	Critically low
Saxena 2014	yes	yes	yes	yes	yes	yes	yes	na	na	na	na	na	na	na	na	yes	High
Tasker 2017	no	no	no	no	no	no	no	py	no	no	yes	no	no	no	yes	yes	Critically low
Watson 2018	no	yes	no	no	yes	yes	no	py	no	no	yes	yes	yes	no	no	yes	Critically low
Zang 2017	no	no	no	py	yes	yes	no	py	yes	no	yes	no	no	no	yes	yes	Low
Zhang 2015	yes	no	no	py	yes	yes	no	py	py	no	no	no	no	no	yes	yes	Critically low

PY: probably yes; NA: not applicable

Supplementary file 1– Search strategies

Database	Search Strategy
Medline via Pubmed	<p>#1 "Hypothermia"[Mesh] OR Hypothermia OR Hypothermias OR (Hypothermia, Accidental) OR (Accidental Hypothermia) OR (Accidental Hypothermias) OR (Hypothermias, Accidental)</p> <p>#2 "Hypothermia, Induced"[Mesh] OR (Hypothermia, Induced) OR (Therapeutic Hypothermia) OR (Hypothermia, Therapeutic) OR (Targeted Temperature Management) OR (Targeted Temperature Managements) OR (Induced Hypothermia) OR (Moderate Hypothermia, Induced) OR (Induced Moderate Hypothermia) OR (Induced Moderate Hypothermias) OR (Moderate Hypothermias, Induced) OR (Mild Hypothermia, Induced) OR (Induced Mild Hypothermia) OR (Induced Mild Hypothermias) OR (Mild Hypothermias, Induced)</p> <p>#3 #1 OR #2</p> <p>#4 "Brain Injuries, Traumatic"[Mesh] OR (Brain Injuries, Traumatic) OR (Brain Injury, Traumatic) OR (Traumatic Brain Injuries) OR (Trauma, Brain) OR (Brain Trauma) OR (Brain Traumas) OR (Traumas, Brain) OR (TBI (Traumatic Brain Injury)) OR (Encephalopathy, Traumatic) OR (Encephalopathies, Traumatic) OR (Traumatic Encephalopathies) OR (Injury, Brain, Traumatic) OR (Traumatic Encephalopathy) OR (TBIs (Traumatic Brain Injuries)) OR (TBI (Traumatic Brain Injuries)) OR (Traumatic Brain Injury)</p> <p>#5 "Brain Concussion"[Mesh] OR (Brain Concussion) OR (Brain Concussions) OR (Concussion, Brain) OR (Comotio Cerebri) OR (Cerebral Concussion) OR (Cerebral Concussions) OR (Concussion, Cerebral) OR (Concussion, Intermediate) OR (Intermediate Concussion) OR (Intermediate Concussions) OR (Concussion, Severe) OR (Severe Concussion) OR (Severe Concussions) OR (Concussion, Mild) OR (Mild Concussion) OR (Mild Concussions) OR (Mild Traumatic Brain Injury)</p> <p>#6 #4 OR #5</p> <p>#7 #3 AND #6</p> <p>#8 ((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti]) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]</p> <p>#9 #7 AND #8</p>
Cochrane Library via Wiley	<p>#1 MeSH descriptor: [Hypothermia] explode all trees</p> <p>#2 Hypothermia OR Hypothermias OR (Hypothermia, Accidental) OR (Accidental Hypothermia) OR (Accidental Hypothermias) OR (Hypothermias, Accidental) OR (Hypothermia, Induced) OR (Therapeutic Hypothermia) OR (Hypothermia, Therapeutic) OR (Targeted Temperature Management) OR (Targeted Temperature Managements) OR (Induced Hypothermia) OR (Moderate Hypothermia, Induced) OR (Induced Moderate Hypothermia) OR (Induced Moderate Hypothermias) OR (Moderate Hypothermias, Induced) OR (Mild Hypothermia, Induced) OR (Induced Mild Hypothermia) OR (Induced Mild Hypothermias) OR (Mild Hypothermias, Induced)</p> <p>#3 #1 OR #2</p> <p>#4 MeSH descriptor: [Brain Injuries, Traumatic] explode all trees</p> <p>#5 MeSH descriptor: [Brain Concussion] explode all trees</p> <p>#6 (Brain Injuries, Traumatic) OR (Brain Injury, Traumatic) OR (Traumatic Brain Injuries) OR (Trauma, Brain) OR (Brain Trauma) OR (Brain Traumas) OR (Traumas, Brain) OR (TBI (Traumatic Brain Injury)) OR (Encephalopathy, Traumatic) OR (Encephalopathies, Traumatic) OR (Traumatic Encephalopathies) OR (Injury, Brain, Traumatic) OR (Traumatic Encephalopathy) OR (TBIs (Traumatic Brain Injuries)) OR (TBI (Traumatic Brain Injuries)) OR (Traumatic Brain Injury) OR (Brain Concussion) OR (Brain Concussions) OR (Concussion, Brain) OR (Comotio Cerebri) OR (Cerebral Concussion) OR (Cerebral Concussions) OR (Concussion, Cerebral) OR (Concussion, Intermediate) OR (Intermediate Concussion) OR (Intermediate Concussions) OR (Concussion, Severe) OR (Severe Concussion) OR (Severe Concussions) OR (Concussion, Mild) OR (Mild Concussion) OR (Mild Concussions) OR (Mild Traumatic Brain Injury)</p> <p>#7 #4 OR #5 OR #6</p> <p>#8 #3 AND #7</p> <p>In: Cochrane Reviews</p>





Database	Search Strategy
LILACS via BVS	<p>#1 MH:Hipotermia OR MH:Hypothermia OR Hipotermia OR Hypothermia OR (Hypothermia, Accidental) OR (Accidental Hypothermia) OR (Accidental Hypothermias) OR Hypothermias OR (Hypothermias, Accidental) OR MH:C23.888.119.565\$</p> <p>#2 MH:"Hipotermia Induzida" OR MH:"Hypothermia, Induced" OR MH:"Hipotermia Inducida" OR (Hipotermia Induzida) OR (Hypothermia, Induced) OR (Hipotermia Inducida) OR (Manutenção da Temperatura Alvo) OR (Induced Hypothermia) OR (Mild Hypothermia, Induced) OR (Moderate Hypothermia, Induced) OR (Targeted Temperature Management) OR (Therapeutic Hypothermia) OR (Hypothermia, Therapeutic) OR (Induced Mild Hypothermia) OR (Induced Mild Hypothermias) OR (Induced Moderate Hypothermia) OR (Induced Moderate Hypothermias) OR (Mild Hypothermias, Induced) OR (Moderate Hypothermias, Induced) OR (Targeted Temperature Managements) OR (Mantenimiento de la Temperatura Diana) OR MH:E02.258.750\$</p> <p>#3 #1 OR #2</p> <p>#4 MH:"Lesiones Traumáticas del Encéfalo" OR MH:"Brain Injuries, Traumatic" OR MH:"Lesões Encefálicas Traumáticas" OR (Lesiones Traumáticas del Encéfalo) OR (Brain Injuries, Traumatic) OR (Lesões Encefálicas Traumáticas) OR (Encefalopatia Traumática) OR (Lesión Cerebral Traumática) OR (Lesión Encefálica Traumática) OR (Lesiones Cerebrales Traumáticas) OR (Lesiones del Encéfalo Traumáticas) OR (Lesiones Encefálicas Traumáticas) OR (TBI (Lesiones Cerebrales Traumáticas)) OR (TBI (Lesión Cerebral Traumática)) OR (TCE (Traumatismo Craneoencefálico)) OR (Trauma del Cerebro) OR (Traumatismo Cerebral) OR (Traumatismo Craneoencefálico) OR (Traumatismo Encefálico) OR (Lesión del Encéfalo Traumática) OR (Traumatismos Cerebrales) OR (Traumatismos Encefálicos) OR (Encephalopathy, Traumatic) OR (Injury, Brain, Traumatic) OR (TBI (Traumatic Brain Injury)) OR (TBIs (Traumatic Brain Injuries)) OR (Traumatic Encephalopathy) OR (Brain Injury, Traumatic) OR (Brain Trauma) OR (Brain Traumas) OR (Encephalopathies, Traumatic) OR (TBI (Traumatic Brain Injuries)) OR (Traumas, Brain) OR (Traumatic Brain Injuries) OR (Traumatic Encephalopathies) OR (Trauma, Brain) OR (Traumatic Brain Injury) OR (Lesões Traumáticas Encefálicas) OR (Encefalopatia Traumática) OR (Lesão Traumática do Encéfalo) OR (LCT (Lesão Cerebral Traumática)) OR (LCTs (Lesões Cerebrais Traumáticas)) OR (Trauma de Encéfalo) OR (Traumatismo Cerebral) OR (Traumatismo do Encéfalo) OR (Lesão Encefálica Traumática) OR (Traumatismos Cerebrais) OR (Traumatismos Encefálicos) OR MH:C10.228.140.199.444\$ OR MH:C10.900.300.087.235\$ OR MH:C26.915.300.200.194\$</p> <p>#5 MH:"Conmoción Encefálica" OR MH:"Brain Concussion" OR MH:"Concussão Encefálica" OR (Conmoción Encefálica) OR (Brain Concussion) OR (Concussão Encefálica) OR (Concusión Cerebral) OR (Conmoción Cerebral) OR (Concusión Encefálica) OR (Comotio Cerebri) OR (Concussion, Intermediate) OR (Concussion, Mild) OR (Concussion, Severe) OR (Mild Traumatic Brain Injury) OR (Brain Concussions) OR (Cerebral Concussions) OR (Concussion, Brain) OR (Concussion, Cerebral) OR (Intermediate Concussion) OR (Intermediate Concussions) OR (Mild Concussion) OR (Mild Concussions) OR (Severe Concussion) OR (Severe Concussions) OR (Cerebral Concussion) OR (Comocão Cerebral) OR (Concussão Cerebral) OR (Comocão Encefálica) OR MH:C10.228.140.199.444.250\$ OR MH:C10.900.300.087.235.250\$ OR MH:C10.900.300.350.300\$ OR MH:C26.915.300.200.194.250\$ OR MH:C26.915.300.450.500\$ OR MH:C26.974.382.200\$</p> <p>#6 #4 OR #5</p> <p>#7 #3 AND #6</p>
Embase	<p>#1 'hypothermia'/exp OR 'hypothermia' OR 'pathological hypothermia'/exp OR 'pathological hypothermia'</p> <p>#2 'induced hypothermia'/exp OR 'induced hypothermia' OR 'artificial hibernation'/exp OR 'artificial hibernation' OR 'artificial hypothermia'/exp OR 'artificial hypothermia' OR 'body cooling'/exp OR 'body cooling' OR 'chilling'/exp OR 'chilling' OR 'extracorporeal hypothermia'/exp OR 'extracorporeal hypothermia' OR 'hibernation, artificial'/exp OR 'hibernation, artificial' OR 'hypothermia, artificial'/exp OR 'hypothermia, artificial' OR 'hypothermia, induced'/exp OR 'hypothermia, induced' OR 'refrigeration anaesthesia'/exp OR 'refrigeration anaesthesia' OR 'refrigeration anesthesia'/exp OR 'refrigeration anesthesia' OR 'therapeutic hypothermia'/exp OR 'therapeutic hypothermia'</p> <p>#3 #1 OR #2</p> <p>#4 'traumatic brain injury'/exp OR 'traumatic brain injury' OR 'brain injuries, traumatic'/exp OR 'brain injuries, traumatic' OR 'brain lesion, traumatic'/exp OR 'brain lesion, traumatic' OR 'brain system trauma'/exp OR 'brain system trauma' OR 'brain trauma'/exp OR 'brain trauma' OR 'cerebral trauma'/exp OR 'cerebral trauma' OR 'cerebrovascular trauma'/exp OR 'cerebrovascular trauma' OR 'encephalopathy, traumatic'/exp OR 'encephalopathy, traumatic' OR 'mild traumatic brain injury'/exp OR 'mild traumatic brain injury' OR 'organic cerebral trauma'/exp OR 'organic cerebral trauma' OR 'posttraumatic encephalopathy'/exp OR 'posttraumatic encephalopathy' OR 'traumatic brain injuries'/exp OR 'traumatic brain injuries' OR 'traumatic brain lesion'/exp OR 'traumatic brain lesion' OR 'traumatic cerebral lesion'/exp OR 'traumatic cerebral lesion' OR 'traumatic encephalopathy'/exp OR 'traumatic encephalopathy'</p> <p>#5 'brain concussion'/exp OR 'brain concussion' OR 'brain commotion'/exp OR 'brain commotion' OR 'cerebral concussion'/exp OR 'cerebral concussion' OR 'commotio'/exp OR 'commotio' OR 'commotio cerebri'/exp OR 'commotio cerebri' OR 'commotion'/exp OR 'commotion'</p> <p>#6 #4 OR #5</p> <p>#7 #3 AND #6</p> <p>#8 'systematic review (topic)'/exp OR 'systematic review':ti,ab OR 'systematic reviews':ti,ab OR 'systematic review'/exp OR 'review, systematic':ti,ab OR 'meta analysis'/exp OR 'analysis, meta':ti,ab OR 'meta-analysis':ti,ab OR 'metaanalysis':ti,ab OR 'meta analysis (topic)'/exp OR 'meta-analysis as topic':ti,ab OR 'metaanalyses':ti,ab OR 'world literature':ti,ab OR 'medicine in literature':ti,ab</p> <p>#9 #7 AND #8</p> <p>#10 #9 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)</p>

DISCUSSION

This critical appraisal study included 16 SRs that evaluated the use of therapeutic hypothermia and/or cooling therapy in patients with acute traumatic brain injury. The SRs were published within a small range of time (15 years) and included 0 to 37 RCTs. Two of the included SRs^{21,26} were judged as having an overall high confidence in the results, with none of the AMSTAR-2 items judged as inadequate.

The methodological quality assessment was very limited in more than half of the included SRs, as 53.3% had critically low overall confidence in the results and 13.3% had low overall confidence in the results. Additionally, critical items were judged inadequate, frequently. Item 1, related to the objective and the research question developed was judged adequate in only 40% of the SRs. Moreover, the transparency and adequacy of search strategies (item 4) was judged to be adequate only in 33.33% of the SRs. Other issues were related to the assessment of risk of bias from included RCTs (item 9), judged to be adequate in 20% of the included SRs.

Other important aspects of the carrying out of the SRs were judged inadequate frequently. The reporting of conflicts of interest and funding of included studies were judged inadequate in 86.67% of the included SRs (item 10); and in 26.67% there was insufficient reports of conflict of interest from the review authors (item 16).

This study has some limitations. Some judgments of AMSTAR-2 may be related to the poor reporting quality of the SRs and not with the poor methodological quality. In some cases, missing information could lead to more "inadequate judgments." We also were unable to retrieve the full text of one of the included SRs, that was published only as a conference

proceeding; but we believe that this would not change our conclusion.

These findings, despite disappointing, raise concerns regarding the quality and redundancy of the synthesis being published. These results should encourage the discussion of prioritizing research questions and increase the effort to reduce waste in research. To the best of our knowledge, this is the first critical appraisal study that assessed the methodological quality of SRs of therapeutic hypothermia and/or cooling therapy in patients with acute traumatic brain injury.

Similar results as ours were found with other clinical questions, with the overall confidence in the results being judged as critically low in 95.1%⁶ and 94%⁷ of the included SRs. Therefore, we believe that our results can be extrapolated in other clinical scenarios.

Concerning clinical practice implications, decision-makers should use the two high quality SRs for recommending practices^{21,26}. One of these reviews²¹ showed that included RCTs were poorly reported and heterogeneous, and there was not enough evidence to support the routine use of hypothermia in the treatment of people with TBI. The other review²⁶ did not find any RCTs on cooling therapies after TBI.

Clinicians should be aware that most of the SRs of this topic are low or of critically low quality, and the decision to use these interventions should be based on the SRs with more methodological rigor.

As for research implications, future studies should focus on developing primary evidence to close the gaps in evidence and not to resynthesize the available evidence. The two high-quality SRs should be updated when new primary evidence is available.

CONCLUSION

This study included 16 systematic reviews that assessed the use of therapeutic hypothermia and/or cooling therapy in patients with acute traumatic brain injury. Most of the included systematic reviews had poor methodological quality and only two

systematic reviews were judged as having high overall confidence in the results according to AMSTAR-2. Decision-makers should consider the overall quality of the synthesis when using or recommending hypothermia and/or cooling therapy for practice.



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