Protocol: Systematic Review for the Treatment of Traumatic Brain Injury Using Therapeutic Hypothermia

Authors

Samantha Crossley, Clair Clark, Imogen Murray, Jenny Reid, Judith Hayton, Rachel McLatchie, Peter Andrews, Margaret MacDougall

Contact Person

Professor Peter Andrews
Professor in Anesthetics & Intensive Care at the University of Edinburgh and Consultant in Anesthesia and Intensive Care at the Western General Hospital, Edinburgh.
Ward 20, Critical Care
Western General Hospital
Lothian University Hospitals Division
Edinburgh
EH4 2XU
0131 5371131
p.andrews@ed.ac.uk

Background

Therapeutic hypothermia has emerged as a potentially life saving treatment for the care of the critically ill. Research in the 1980’s using animal models demonstrated the benefits of cooling to 32-34 degrees Celsius [1], and it has since been proposed that there are a number of potential applications for therapeutic hypothermia [2]. In February 2011, NHS National Institute for Health and Clinical Excellence (NICE) guidelines were published to support the use of therapeutic hypothermia for hypoxic perinatal brain injury [3]. Similarly NICE guidelines for the use of therapeutic hypothermia in cardiac arrest have also recently been published [4]. In the United States, the American Heart Association recommends hypothermia as a standard of care for survivors of cardiac arrest [5] as there is significant evidence to support its improvements in outcome [6]. Whilst a number or studies have identified an improvement in outcome with the application of therapeutic hypothermia following stroke, the question as to whether therapeutic hypothermia is indicated in traumatic brain injury remains unanswered.

Traumatic brain injury (TBI) is a leading cause of disability and death, particularly in the young [7]. The application of hypothermia has been shown to decrease cerebral metabolic rate and is thought to alter the release of post trauma excitatory neurotransmitters [8], reducing and preventing disruptions during and following cerebral insults [9]. Laboratory studies, clinical trials and systematic reviews have largely suggested sufficient potential to warrant the use of therapeutic hypothermia following TBI. However, research into therapeutic hypothermia following TBI has been characterised by a large number of small trials of poor methodological validity, producing mixed results. The duration of therapeutic hypothermia utilised in TBI trials
also varies depending on trial protocol, and optimum duration remains unclear. Further to this, studies have also raised concerns surrounding potentially increased risks of pneumonia resulting from the induction of therapeutic hypothermia [10].

A number of reviews (including eight meta-analyses and a series of Cochrane reviews) have been published into the use of therapeutic hypothermia following TBI. However, no single review has encompassed a comprehensive summary of all published trials. In particular, the most recent Cochrane review fails to include a number of relevant trials, most notably Jiang 2006 [11] Polderman 2001 [12] and Polderman 2002 [13]. Consequently, it is the aim of this systematic review to identify all randomized controlled trials that investigate the relationship between traumatic brain injury and the application of therapeutic hypothermia. The terms below will be used throughout our analysis. As such we wish to define them in order that our objectives are clear:

We define traumatic brain injury as being any acute closed head injury sustained following head trauma. We define therapeutic hypothermia as any intervention carried out with the intention of reducing core body temperature to below the physiological norm (36.0 degrees Celsius). We define poor outcome as death, vegetative state and severe disability at final follow up as defined by the Glasgow Outcome Score (Glasgow Outcome Scores 1,2 and 3 respectively, or an equivalent scoring system such as the Ranchos Los Amigos scale. We define improved outcome as a positive effect of greater than 5% in the outcome of the treatment group compared with the control group.

Objectives

Our primary outcome is to assess the effects of the application of therapeutic hypothermia when administered to adult patients who have been admitted to hospital following traumatic brain injury.

Our secondary outcomes are to investigate the following hypotheses:
   a. Duration of cooling lasting greater than 48 hours confers improved outcome compared with cooling of less than this duration.
   b. Re-warming patients at a speed of greater than 1 degree Celsius every four hours increases the risk of poor outcome.
   c. Patients who have undergone only modest cooling (35-36 degrees Celsius) experience greater poor outcomes compared with patients cooled to below 35 degrees Celsius.
   d. Increased length of time between the onset of injury and induction of cooling increases the risk of poor outcome.
Methods

Criteria for selecting studies for this review

- Types of studies
  Randomised control trials (RCT) of treatment with therapeutic hypothermia versus control (trials permitting rewarming of control group are excluded).

- Types of participants
  Adult patients (18 years and older) with closed traumatic head injury (any severity) admitted to hospital.

- Types of interventions
  Any therapeutic intervention, including, but not limited to: fluid and air based surface cooling devices, anti-pyretic agents, infusion of cold fluids and intravascular cooling catheters, used with the intention of lowering core body temperature below normothermia.

- Types of outcome measures
  Primary – Unfavourable outcomes at the end of the follow up period to include death: persistent vegetative state or severe disability as defined by the Glasgow Outcome Scale or equivalent scoring scale (Ranchos Los Amigos Scale).
  Secondary - New onset pneumonia during the application of therapeutic hypothermia.

Search methods for identification of studies

Searches will not be restricted by date, language or publication status (other than those restrictions imposed by the databases themselves). Where necessary papers will be translated. We will search the following electronic databases

- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE
- EMBASE
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index – Science (CPCI-S)
- PubMed
- Zetoc

All electronic database searches will be conducted using versions of the following MEDLINE search strategy adapted where necessary for each database.
1. exp Craniocerebral Trauma/
2. exp Brain Edema/
3. exp Glasgow Coma Scale/
4. exp Glasgow Outcome Scale/
5. exp Unconsciousness/
6. exp Cerebrovascular Trauma/
7. exp Intracranial Hypertension/
8. ((head or cran$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$ or concuss$ or pressure$)).ab,ti.
9. ((head or cran$ or cerebr$ or capitis or tentori$ or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or hernia$ or oedema$ or edema$ or swell$)).ab,ti.
10. (Glasgow adj3 (coma or outcome) adj3 (scale$ or score$)).ab,ti.
11. Rancho Los Amigos Scale.mp.
12. "diffuse axonal injur$".ab,ti.
13. ((unconscious$ or coma$ or concuss$ or 'persistent vegetative state') adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ab,ti.
14. or/1-13
15. exp Hypothermia, Induced/
16. exp Cryotherapy/
17. exp Hypothermia/
18. (hypotherm$ or normotherm$ or cool$ or cold$ or temperature$ or cryo$).ab,ti.
19. ((refri?geration$ or cryo$) adj3 anaesthes$).ab,ti.
20. ((cool$ or cold$) adj3 (therap$ or device$ or equipment$)).ab,ti.
21. (temperature adj3 (reduc$ or low$)).ab,ti.
22. (intravenous adj3 (cold$ or cool$ or ice$ or refrigerat$) adj3 (fluid$ or catheter$)).ab,ti.
23. ((cool$ or cold$) adj3 (blanket$ or cap$ or pad$ or neck collar$ or helmet$ or hood$)).ab,ti.
24. or/15-23
25. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial$).tw,hw.
26. clinical trial.pt.
27. randomized controlled trial.pt.
28. or/25-27
29. exp models, animal/
30. exp Animals/
31. exp Animal Experimentation/
32. exp Animals, Laboratory/
33. or/29-32
34. Humans/
35. 33 not 34
36. 28 not 35
37. 36 and 14 and 24

Other sources: Reference lists of all relevant trials and review articles will be hand searched and where necessary authors contacted to find information relevant to studies or conference proceedings.
Data Collection and Analysis

- Identification and selection of studies
The primary output of the above searches will be divided amongst four authors who will discard studies that are not related to the use of therapeutic hypothermia as a medical intervention or to the general management of traumatic brain injury, recording reasons for their removal from this analysis. Six authors will then retrieve abstracts and full text of the remaining papers. Each study will be assessed independently by two authors for inclusion criteria. Abstracts that match exclusion criteria will be disregarded. Where authors are uncertain and discrepancies remain about studies, a majority decision between the six authors and a clinical specialist (Professor Peter Andrews) will determine if the study meets inclusion criteria. The titles, abstracts and content of non-English language papers will be translated.

Inclusion criteria:
- Trials must be randomised control trials.
- Trials must have a control group that is treated to normothermia, which is defined as standard body temperature.
- Patients must be adults. We define this as being the legal age for consent.
- Patients enrolled must have closed head injuries.

Exclusion criteria:
- Trials in which patients have not been randomised to each treatment arm and/or where there is no control group.
- The trial has been performed entirely in neonates or children, whom we define as being below the legal age for consent.
- Trials containing patients with open head injuries such as gunshot wounds will be excluded.

- Data extraction
On meeting inclusion criteria, data will be extracted by two authors for each study using a standard data extraction form.

Information to be extracted includes:

General Information
a. Trial name (where there is no trial name the name of the published paper will be recorded)
b. Method of intervention
c. Lowest body temperature attained
d. Duration of intervention
e. Maximum time between initial injury and cooling started
f. Lowest limit of GCS on admission
g. Any neurological deterioration after cooling started
h. Total sample size
i. Rate of rewarming of the treatment arm
j. Total number of patients randomised to each treatment arm, control and intervention
k. Specific information on the number and percentage of patients in each group with the following outcomes:
   i. Death
   ii. Long term disability or vegetative state
   iii. Pneumonia and other serious infections occurring during treatment.

l. Odds ratio, mean difference or relative risk measurements and confidence intervals for outcome measures between the two groups.

Confounding factors
i) Have the control group been managed to normothermia: Yes/No/Not stated
ii) Were the control group actively rewarmed on admission if hypothermic: Yes/No/Not stated
iii) Has the treatment arm received barbiturates in addition to therapeutic hypothermia: Yes/No/Not stated
iv) Have patients been enrolled on an ‘intention to treat’ basis: Yes/No/Not stated
v) Are there significant differences between the treatment and control sample populations: Yes/No/Not stated
vi) Has the 'standard treatment' that the control group received been clearly outlined: Yes/No/Not stated

Assessment of methodological quality
a. Allocation Concealment
Document randomisation technique used plus:
A. Adequate - randomisation method described that would not allow investigator or participant to know or influence intervention group before eligible participant entered in the study.
B. Unclear - Randomisation stated but no information on method used is available.
C. Inadequate - Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence the intervention group.

b. Blinding
Blinding of investigators: Yes/No/Not stated
Blinding of participants: Yes/No/Not stated
Blinding of outcome assessor: Yes/No/Not stated
Blinding of data analysis: Yes/No/Not stated
The above are not considered blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

c. Intention-to-treat Analysis
Yes - specifically reported by the authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
Yes - not stated, but confirmed on study assessment.
No - not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study, or were not included because of protocol violation).
No - stated but not confirmed upon study assessment.
Not stated.

d. Completeness of follow-up
Per cent of patients excluded or lost to follow-up.

e. Publication of protocol
Has the final publication included details about the protocol they have followed or a link through which to access the protocol: Yes/No

Assessment of statistical quality

In the event that it is possible to perform a meta-analysis on the data extracted, we also feel it is important to extract the following information:

- Have confidence intervals been recorded for effect sizes, such as odds ratios or mean differences: Yes/No.
- Where confidence intervals have been recorded what was the level of confidence and the values of the confidence intervals?
- What is the p-value of the analysis and to what level of significance has been stated?
- Have the authors highlighted the size of effect that they deem clinically significant: Yes/No.
- Where authors have stated a size of effect they deem significant, what is its value?
- Where authors have stated a size of effect, at what stage in the trial has it been stated? During study design or retrospectively?
- Are odds ratios, relative risk ratios or mean difference values the product of a univariate or multivariate analysis?
- Was a sample size calculation performed: Yes/No/Not stated
- Did the authors adhere to the suggestion of sample size from this test: Yes/No/Not stated

Only randomised controlled trials which meet the study quality criteria, having obtained missing data from the investigators if necessary, will be included in the formal analysis, taking into account that blinding of investigators and participants to head cooling may not be feasible.

Data analysis

For temperature data the difference in means will be calculated with 95% confidence intervals. If there are sufficient good quality trials for a meta-analysis a weighted mean difference will be calculated. In this case a clinically significant size of effect of 5% has been decided upon.
Statistical heterogeneity will be calculated using the chi-squared test and $I^2$ index. Depending on the outcome of this test and whether there is true heterogeneity between the results of studies, pooled relative risk and 95% confidence intervals for all-cause mortality and improved neurological outcome will be calculated using either a random-effects model or fixed effect model. Subsequent models may be applied should the data be suitable for meta-analysis.

It is likely to be appropriate to conduct sensitivity analyses of some aspects of therapeutic hypothermia, in relation to all-cause mortality for example, but it is difficult to pre-specify these precisely. Factors which may be relevant include target temperature, cooling rate, duration and rate of rewarming.

**Acknowledgements**

The authors would like to thank Marshall Dozier, Senior Liaison Librarian for the College of Medicine and Veterinary Medicine, the Cochrane Renal Group and authors of the previous Cochrane reviews on therapeutic hypothermia for TBI.

**Contributions for authors**

Professor Peter Andrews is the clinical specialist involved in this work. Dr Maragret MacDougal is the medical statistician. Samantha Crossley, Clair Clark, Rachel McLatchie, Judith Hayton, Jenny Reid and Imogen Murray are all third year medical students at the University of Edinburgh. All information is correct at the time of publication of this protocol.

**Declarations of interests**

Our motivation for undertaking this systematic review is to assess the outcomes and quality of clinical trials in order to analyse the effect of therapeutic hypothermia for the treatment of TBI. It is possible that at present there is insufficient good quality evidence to determine whether this treatment is of benefit. Consequently we are seeking to clarify this and identify areas where future trials may be able to improve in terms of quality and outcome measures.
References


Appendix I: Data Collection

**General Information**

a. Trial name (where there is no trial name the name of the published paper will be recorded)
b. Method of intervention
c. Lowest body temperature attained
d. Duration of intervention
e. Maximum time between initial injury and cooling started
f. Lowest limit of GCS on admission
g. Any neurological deterioration after cooling started
h. Total sample size
i. Rate of rewarming of the treatment arm
j. Total number of patients randomised to each treatment arm, control and intervention

k. Specific information on the number and percentage of patients in each group with the following outcomes:
   i. Death
   ii. Long term disability or vegetative state
   iii. Pneumonia and other serious infections occurring during treatment.
l. Odds ratio, mean difference or relative risk measurements and confidence intervals for outcome measures between the two groups.

**Confounding factors**

i) Have the control group been managed to normothermia: Yes/No/Not stated
ii) Were the control group actively rewarmed on admission if hypothermic: Yes/No/Not stated

iii) Has the treatment arm received barbiturates in addition to therapeutic hypothermia: Yes/No/Not stated

iv) Have patients been enrolled on an ‘intention to treat’ basis: Yes/No/Not stated
v) Are there significant differences between the treatment and control sample populations: Yes/No/Not stated

vi) Has the 'standard treatment' that the control group received been clearly outlined: Yes/No/Not stated

**Assessment of methodological quality**

b. Allocation Concealment

Document randomisation technique used plus:

A. Adequate - randomisation method described that would not allow investigator or participant to know or influence intervention group before eligible participant entered in the study.

B. Unclear - Randomisation stated but no information on method used is available.

C. Inadequate - Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence the intervention group.
b. Blinding
Blinding of investigators: Yes/No/Not stated
Blinding of participants: Yes/No/Not stated
Blinding of outcome assessor: Yes/No/Not stated
Blinding of data analysis: Yes/No/Not stated
The above are not considered blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

c. Intention-to-treat Analysis
Yes - specifically reported by the authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
Yes - not stated, but confirmed on study assessment.
No - not reported and lack of intention-to-treat analysis confirmed on study assessment.
(Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study, or were not included because of protocol violation).
No - not stated but not confirmed upon study assessment.
Not stated.

d. Completeness of follow-up
Per cent of patients excluded or lost to follow-up.

f. Publication of protocol
Has the final publication included details about the protocol they have followed or a link through which to access the protocol: Yes/No

Assessment of statistical quality
In the event that it is possible to perform a meta-analysis on the data extracted, we also feel it is important to extract the following information:

- Have confidence intervals been recorded for effect sizes, such as odds ratios or mean differences: Yes/No.
- Where confidence intervals have been recorded what was the level of confidence and the values of the confidence intervals?
- What is the p-value of the analysis and to what level of significance has been stated?
- Have the authors highlighted the size of effect that they deem clinically significant: Yes/No.
- Where authors have stated a size of effect they deem significant, what is its value?
- Where authors have stated a size of effect, at what stage in the trial has it been stated? During study design or retrospectively?
- Are odds ratios, relative risk ratios or mean difference values the product of a univariate or multivariate analysis?
- Was a sample size calculation performed: Yes/No/Not stated
- Did the authors adhere to the suggestion of sample size from this test: Yes/No/Not stated
Appendix II: Search terms and MESH headings.

- CENTRAL (The Cochrane Library);
- MEDLINE
- PubMed
- EMBASE
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index-Science (CPCI-S);
- Controlled Trials metaRegister of trials (mRCT) http://www.controlled-trials.com/mRCT/;
- Zetoc

Searches Performed 5th Jan 2012

**Cochrane Central Register of ControlLed Trials (Central)**

#1 MeSH descriptor **Craniocerebral Trauma** explode all trees

#2 MeSH descriptor **Brain Edema** explode all trees

#3 MeSH descriptor **Glasgow Coma Scale** explode all trees

#4 MeSH descriptor **Unconsciousness** explode all trees

#5 MeSH descriptor **Glasgow Outcome Scale** explode all trees

#6 MeSH descriptor **Cerebrovascular Trauma** explode all trees

#7 MeSH descriptor **Intracranial Hypertension** explode all trees

#8 (head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or concuss* or pressure*) in Clinical Trials

#9 (head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran* or tentori*) near3 (haematomat* or hematoma* or haemorrhag* or hemorrhag* or bleed* or hernia* or oedema* or edema* or swell*) in Clinical Trials

#10 (Glasgow near3 (coma or outcome) near3 (scale or score)) in Clinical Trials

#11 "Rancho Los Amigos Scale" in Clinical Trials

#12 (diffuse near3 axonal near3 injur*) in Clinical Trials

#13 (unconscious* or coma* or concuss* or 'persistent vegetative state') near3 (injur* or trauma* or damag* or wound* or fracture*) in Clinical Trials

#14 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)

#15 MeSH descriptor **Hypothermia, Induced** explode all trees

#16 MeSH descriptor **Cryotherapy** explode all trees

#17 MeSH descriptor **Hypothermia** explode all trees

#18 (hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*) in Clinical Trials

#19 (refrigeration* or cryo*) near3 anaesthes* in Clinical Trials

#20 (cool* or cold*) near3 (therap* or device* or equipment*) in Clinical Trials

#21 (temperature near3 (reduc* or low*)) in Clinical Trials

#22 intravenous near3 (cold* or cool*) near3 (fluid* or catheter*) in Clinical Trials

#23 (cool* or cold*) near3 (blanket* or neck collar* or helmet* or hood*) in Clinical Trials

#24 (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

#25 (#14 AND #24)

#26 Search protocol produced 432 results.
MEDLINE
1. exp Craniocerebral Trauma/
2. exp Brain Edema/
3. exp Glasgow Coma Scale/
4. exp Glasgow Outcome Scale/
5. exp Unconsciousness/
6. exp Cerebrovascular Trauma/
7. exp Intracranial Hypertension/
8. (head or cranial or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or concuss* or pressure*).ab,ti.
9. (head or cranial or cerebr* or capitis or tentori* or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or hernia* or oedema* or edema* or swell*).ab,ti.
10. (Glasgow adj3 (coma or outcome) adj3 (scale* or score*).ab,ti.
11. Rancho Los Amigos Scale.mp.
12. "diffuse axonal injur*".ab,ti.
13. ((unconscious* or coma* or concuss* or 'persistent vegetative state') adj3 (injur* or trauma* or damag* or wound* or fracture*).ab,ti.
14. or/1-13
15. exp Hypothermia, Induced/
16. exp Cryotherapy/
17. exp Hypothermia/
18. (hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*).ab,ti.
19. ((refrigeration* or cryo*) adj3 anaesthes*).ab,ti.
20. ((cool* or cold*) adj3 (therap* or device* or equipment*)).ab,ti.
21. (temperature adj3 (reduc* or low*)).ab,ti.
22. (intravenous adj3 (cold* or cool*) adj3 (fluid* or catheter*).ab,ti.
23. ((cool* or cold*) adj3 (blanket* or neck collar* or helmet* or hood*).ab,ti.
24. or/15-23
25. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial*).tw,hw.
26. clinical trial.pt.
27. randomized controlled trial.pt.
28. or/25-27
29. exp models, animal/
30. exp Animals/
31. exp Animal Experimentation/
32. exp Animals, Laboratory/
33. or/29-32
34. Humans/
35. 33 not 34
36. 28 not 35
37. 36 and 14 and 24

PubMed
2. (head OR cranial OR cerebral OR capitis OR brain OR forebrain* OR skull* OR hemispher* OR intra-cran* OR inter-cran*) AND (injur* OR trauma OR damag* OR wound* OR fracture* OR contusion* OR concuss* OR pressure*)
3. (head OR cranial OR cerebral OR capitis OR brain OR forebrain* OR skull* OR hemispher* OR intra-cran* OR inter-cran* OR tentori*) AND (haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed* OR hernia* OR oedema* OR edema* OR swell*)
4. glasgow AND (scale OR score) AND (outcome OR coma)
5. Ranchos Los Amigos
6. diffuse axonal injur*
7. (unconscious OR coma* OR concuss* OR persistent vegetative state) AND (injur* OR trauma OR damag* OR wound* OR fracture*)
8. COMBINE
10. hypotherm* OR normotherm* OR cool* OR cold* OR temperature* OR cryother* OR cryogen* OR cryotreat*
11. ((refrigeration* OR cryo*) AND anaesthes*) OR ((cool* OR cold*) AND (therap* OR device* OR equipment*))) OR ((temperature AND (reduc* OR low*)) OR ((intravenous AND (cold* OR cool*) AND (fluid* OR catheter*))) OR ((cool* OR cold*) AND (blanket* OR neck collar* OR helmet* OR hood*)))

Search protocol produced 477 results
12. COMBINE
13. (randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [MeSH Terms]) NOT ((models, animal [MeSH Terms] OR Animals [MeSH Terms] OR Animal Experimentation [MeSH Terms] OR Disease Models, Animal [MeSH Terms] OR Animals, Laboratory [MeSH Terms]) NOT (Humans [MeSH Terms]))

14. COMBINE

(can also be written and input as protocol below)

((Craniocerebral Trauma [MeSH Terms] OR Brain Edema [MeSH Terms] OR Glasgow Coma Scale [MeSH Terms] OR Glasgow Outcome Scale [MeSH Terms] OR Unconsciousness [MeSH Terms] OR Cerebrovascular Trauma [MeSH Terms] OR Intracranial Hypertension [MeSH Terms]) OR ((head OR cranial OR cerebral OR capitis OR brain OR forebrain* OR skull* OR hemispher* OR intra-cran* OR inter-cran*) AND (injur* OR trauma OR damag* OR wound* OR fracture* OR contusion* OR concuss* OR pressure*))) OR (head OR cranial OR cerebral OR capitis OR brain OR forebrain* OR skull* OR hemispher* OR intra-cran* OR inter-cran* OR tenori*) AND (haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed* OR hernia* OR oedema* OR edema* OR swell*)) OR (glasgow AND (scale OR score) AND (outcome OR coma)) OR (Rancho Los Amigos) OR (diffuse axonal injur*) OR ((unconscious OR coma* OR concuss* OR persistent vegetative state) AND (injur* OR trauma OR damag* OR wound* OR fracture*)) AND ((Hypothermia, Induced [MeSH Terms] OR Cryotherapy [MeSH Terms] OR Hypothermia [MeSH Terms]) OR (hypotherm* OR normotherm* OR cool* OR cold* OR temperature* OR cryother* OR cryogen* OR cryotreat*)) OR (((refrigeration* OR cryo*) AND anaesthes*) OR ((cool* OR cold*) AND (therap* OR device* OR equipment*))) OR (temperature AND (reduc* OR low*)) OR ((intransive AND (cold* OR cool*) AND (fluid* OR cather*)) OR ((cool* OR cold*) AND (blanket* OR neck collar* OR helmet* OR hood*)) AND (randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR at random OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [MeSH Terms]) NOT ((models, animal [MeSH Terms] OR Animals [MeSH Terms] OR Animal Experimentation [MeSH Terms] OR Disease Models, Animal [MeSH Terms] OR Animals, Laboratory [MeSH Terms]) NOT (Humans [MeSH Terms])))

Search protocol produced 806 results
Search protocol produced 1210 results

**ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index-Science (CPCI-S)**

# 1
Topic=(head OR crani* OR capitis OR brain* OR forebrain* OR skull* OR hemisphere* OR intracran* OR intercran) AND Topic=(injur* OR trauma* OR lesion* OR damag* OR wound* OR haematoma* OR oedema* OR edema* OR fracture* OR contusion* OR concus* OR commotion* OR pressur*) AND Topic=(hypotherm* OR normotherm* OR cool* OR cold* OR temperature* OR cryother* OR cryogen* OR cryotreat)
Databases=SCI-EXPANDED, CPCI-S Timespan=1960-2011
Lemmatization=On

# 2
Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR controlled trial OR clinical trial) NOT Topic=(animal model* OR Animals OR Animal Experiment* OR Laboratory animal* OR animal disease model*)
Databases=SCI-EXPANDED, CPCI-S Timespan=1960-2011
Lemmatization=On

# 3
#2 AND #1
Databases=SCI-EXPANDED, CPCI-S Timespan=1960-2011
Lemmatization=On

Search protocol produced 955 results

Zetoc
Hypotherm* head injur* trial*
Hypotherm* head injur* random*
Hypotherm* head injur* control*
Hypotherm* brain injur* trial*
Hypotherm* brain injur* random*
Hypotherm* brain injur* control*
Hypotherm* head trauma* trial*
Hypotherm* head trauma* random*
Hypotherm* head trauma* control*
Hypotherm* brain trauma* trial*
Hypotherm* brain trauma* random*
Hypotherm* brain trauma* control*

Search protocol produced 547 results