The Lund Concept for Severe Traumatic Brain Injury

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[Intervention Review]

The Lund concept for severe traumatic brain injury

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ABSTRACT

Background

Severe traumatic brain injury is a significant cause of morbidity and mortality. Treatment strategies in management of such injuries are directed to the prevention of secondary brain ischaemia, as a consequence of disturbed post-traumatic cerebral blood flow. They are usually concerned with avoiding high intracranial pressure (ICP) or adequate cerebral perfusion pressure (CPP). An alternative to this conventional treatment is the Lund concept, which emphasises a reduction in microvascular pressures.

Objectives

To assess the role of the Lund concept versus other treatment modalities such as ICP-targeted therapy, CPP-targeted therapy or other possible treatment strategies in the management of severe traumatic brain injury.

Search methods

We searched the Cochrane Injuries Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL; Issue 10, 2013), MEDLINE (OvidSP), EMBASE (OvidSP), CINAHL Plus (EBSCO Host), ISI Web of Science (SCI-EXPANDED and CPCI-S) and trials registries. We searched the reference lists of relevant studies and published reviews found with our search. The most recent search was 5 November 2013.

Selection criteria

Randomised controlled trials (RCTs, level 1 evidence) exploring the efficacy of the Lund concept in the treatment of traumatic brain injury.

Data collection and analysis

Two review authors independently selected papers and made decisions about the eligibility of potentially relevant studies.

Main results

We found no studies that met the inclusion criteria for this review.

Authors' conclusions

There is no evidence that the Lund concept is a preferable treatment option in the management of severe traumatic brain injury.

PLAIN LANGUAGE SUMMARY

The Lund concept in the treatment of brain injuries

Background

Brain injuries are a significant cause of death and permanent disability. It is recognised that the magnitude of the injury is not defined at the moment of the injury, but rather develops in the hours and days that follow. Treatment in the hours following brain injury is aimed at the maintenance of adequate brain blood flow and the prevention of brain swelling. The Lund concept differs from conventional treatment strategies in emphasising the pressures inside small blood vessels in the brain.

Study characteristics

We searched the medical literature in order to find randomised controlled trials (RCTs) (studies where people are randomly assigned to a treatment or non-treatment group) that compared the Lund concept versus other treatments. We included people with severe traumatic brain injury, irrespective of their gender, age or race. The latest search was 5 November 2013.

Key results

We found no studies comparing the Lund concept versus other treatments. There is no evidence from RCTs that the Lund concept is a preferable treatment for brain injury and further research is needed.

BACKGROUND

Description of the condition

Severe traumatic brain injury is a significant cause of morbidity and mortality. The general incidence of traumatic brain injury in developed countries is estimated to be 200 per 100,000 population at risk per year (Bruns 2003). Historically, the Glasgow Coma Scale has been most widely used for the classification of traumatic brain injury severity (Teasdale 1974). People with an admission Glasgow Coma Score of between three and eight are considered to have severe traumatic brain injury, and about 10% to 15% of all people with head injuries are classified as such (Bruns 2003).

Since the 1990s, it has been recognised that much of the neuronal damage following severe head injury does not occur instantaneously, but rather evolves over several hours and days after the impact (Chesnut 1993). A distinction is made between primary injury, which occurs as a direct result of the trauma, and secondary injury that develops over hours to days after the initial traumatic insult. Secondary injury is of particular importance because the process of its development is open to therapeutic interventions. Therefore, critical care management to prevent or reduce secondary brain injury is extremely important.

Cerebral ischaemia is the most important consequence of secondary brain injury. The central pathophysiological problem in its development is disturbance in post-traumatic cerebral blood flow caused by increased intracranial pressure (ICP) and the formation of brain oedema.

The traditional approach in the prevention of secondary brain injury is ICP-targeted therapy, characterised by the use of head elevation, sedation, active treatment of systemic hypertension, neuromuscular blockade, cerebrospinal fluid (CSF) drainage usually by external ventriculostomy, osmotherapy and induction of a barbiturate coma to reduce and control ICP (Miller 1993).

A similar approach, cerebral perfusion pressure (CPP)-targeted therapy, emphasises the role of CPP, a difference between mean arterial pressure (MAP) and ICP. It differs from the ICP-targeted therapy in terms of the flat head position, avoidance of sedation, hyperventilation and barbiturate coma, but similarly advocates the use of osmotherapy, CSF drainage and neuromuscular blockade (Rosner 1995) (Table 1).

Description of the intervention

In contrast to the previously described 'traditional' therapeutic approaches, the Lund concept emphasises a reduction in microvascular pressures to minimise cerebral oedema formation. Cerebral oedema occurs due to leakage of large molecules such as albumins from blood vessels through the damaged blood brain barrier. Water flows into the brain after the albumins by osmosis. This vasogenic oedema causes compression of and damage to brain tissue. The goals of the Lund concept approach are to preserve a normal colloid osmotic pressure (by infusion of the albumin and correction of anaemia), to reduce capillary hydrostatic pressure (by medical control of the blood pressure) and to reduce cerebral blood volume by vasoconstriction (Eker 1998). This is achieved by a flat head position, sedation, strict control of systemic hypertension (usually with metoprolol and clonidine) and avoidance of the neuromuscular blockade, hyperventilation, osmotherapy and barbiturate coma, i.e. all treatments that would favour the increased transcapillary filtration of the plasma (Grande 1997) (Table 1).

Table 1. Management approaches in people with traumatic brain injury (Eker 1998; Grande 1997; Miller 1993; Rosner 1995).

	Management approach		
Treatment	**ICP-targeted therapy**	**CPP-targeted therapy**	**Lund concept**
Head position	Elevation 15-30°	Flat	Flat
Sedation	Morphine plus lorazepam	None	Low-dose thiopental
Treatment of systemic hypertension	Treat systolic blood pressure > 160 mm Hg using labetalol	No	Metoprolol plus clonidine
Nutritional support	Yes, avoid hyperglycaemia	No	Yes, avoid hyperglycaemia
Neuromuscular blockade	Yes	Yes	No
CSF drainage	Yes	Yes	No
Osmotherapy	Yes	Yes	No
Barbiturate coma	Yes	No	No

How the intervention might work

Maintenance of a normal colloid osmotic pressure retains intracapillary water content, and thereby reduces transudation and interstitial oedema formation. Keeping the MAP within a low normal range, and consequently maintaining the low capillary hydrostatic pressure, facilitates this effect. To enforce this concept, it is vital not to perform any procedure that counteracts the principles stated above. An efficient reduction in brain oedema formation improves cerebral blood flow and reduces the frequency, duration and magnitude of ischaemic episodes, as well as secondary brain injury sequelae. Consequently, this may lead to a more favourable management outcome (i.e. reduced mortality and long-term disability in such people).

Why it is important to do this review

Despite the growing body of evidence in the research of traumatic brain injury, not all aspects of secondary brain injury are completely understood. Accordingly, the concepts supporting injury treatment differ, with ICP- and CPP-based therapies currently being the preferred treatment choices. However, the Lund concept offers an interesting theoretical background, which is confirmed in practice by some studies (Eker 1998). Uncontrolled trials have yielded results comparable to established management protocols (Dunn 2002). There is evidently a need to evaluate the Lund concept protocol systematically in controlled trials and to compare it to the more established protocols. If proved to be more efficient or at least equal to the other treatments, the Lund concept could be more frequently applied in the management of people suffering severe traumatic brain injury. Therefore, the aim of this review is to determine the possible advantages as well as the limitations of the Lund concept in comparison to existing strategies.

OBJECTIVES

To assess the role of the Lund concept versus other treatment modalities such as ICP-targeted therapy, CPP-targeted therapy or other possible treatment strategies in the management of severe traumatic brain injury.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs, Level 1 evidence) exploring the efficacy of the Lund concept in the treatment of severe traumatic brain injury. We included studies irrespective of publication status, language or date.

Types of participants

People with severe traumatic brain injury, irrespective of their gender, age or race.

Types of interventions

We included studies where at least one of the arms in the trial was treated by an intervention described as the Lund concept or modified Lund concept.

We considered the following comparisons:

- Lund concept versus ICP-targeted therapy;
- Lund concept versus CPP-targeted therapy;
- Lund concept versus any other possible treatment or combination of treatments.

Types of outcome measures

Primary outcomes

- Mortality.

Secondary outcomes

- Treatment outcome, as expressed by the Glasgow Outcome Scale (GOS) or Extended Glasgow Outcome Scale (GOSE).
- Treatment complications.

Search methods for identification of studies

We did not restrict the search for trials by language, date or publication status.

Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator searched the following:

- Cochrane Injuries Group Specialised Register (November 2013);
- Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 10, 2013);
- Ovid MEDLINE(R) (1946 to November week 1 2013);
- EMBASE Classic and EMBASE (1947 to 2013 week 44);
- CINAHL Plus (EBSCO Host) (1939 to November 2013);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to November 2013);
- ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to November 2013).

All search strategies are listed in full in Appendix 1.

Searching other resources

We searched the reference lists of relevant studies and published reviews found with our search. We contacted experts in the field in order to identify any published or unpublished work not found with our electronic search. We used the Google search engine to find online information relevant to this systematic review and we searched the following online trials registers on 11 November 2012:

- World Health Organization Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/);
- Clinicaltrials.gov (www.clinicaltrials.gov);
- Current controlled trials (www.controlled-trials.com);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Data collection and analysis

The Trials Search Co-ordinator of the Cochrane Injuries Group conducted the searches, collated the results and removed any duplicates before transferring the records to the review authors for screening.

Selection of studies

The two review authors independently selected papers and made decisions about study eligibility, based on a review of the title,

abstract or MeSH terms. We resolved any disagreements by discussion and consensus. We consulted a statistician in case of doubt about study inclusion or data extraction. We contacted the authors of the original papers to obtain additional data or to clarify issues in order to perform the systematic review. We also translated studies published in languages other than English.

Data extraction and management

We contacted study authors for clarification and further data if trial reports were unclear, and we arranged translations of papers where necessary. We extracted the relevant data from the selected studies and recorded it in customised forms. The two review authors performed the extraction, after determining the study eligibility. We contacted authors of the original article, when necessary.

We extracted the following data:

- study design, setting and duration;
- participants;
- sample size;
- inclusion and exclusion criteria;
- details of the experimental intervention (protocol);
- details of the control intervention;
- outcome (the effect of treatment, described by GOS or GOSE);
- presence of ethical approval;
- funding sources;
- conclusions as reported by the authors.

Assessment of risk of bias in included studies

We found no studies that met our inclusion criteria. Should studies be included in the future, the two review authors will independently assess the risk of bias of the included trials with the following domain taken into consideration, as guided by the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in the Review Manager 5 software (RevMan 2012), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry as 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

If studies are included in future versions of the review, we will analyse data using Review Manager 5 (RevMan 2012). We will analyse dichotomous data using risk ratio (with 95% confidence intervals) and continuous outcomes by calculating mean and standard deviations (with 95% confidence intervals). We will either pool scores as continuous variables using means or standardised means.

If the selection process identifies up to three studies, we will perform an additional analysis. We will contact the authors of the relevant studies to obtain data files. According to the method described by Hukkelhoven et al (Hukkelhoven 2005), we will calculate the likelihood of death and unfavourable outcome for each person. For all groups of people compared, we will calculate and compare observed versus expected ratios for death and unfavourable outcomes.

Unit of analysis issues

The unit of analysis will be the individual person.

Dealing with missing data

Missing summary data will not be a reason to exclude a study from the review. If necessary, we will contact the authors of the original papers for more information on missing data.

Assessment of heterogeneity

We will test all included studies for clinical homogeneity. For studies considered as clinically homogeneous, we will test the statistical heterogeneity using the Chi^2 test and I^2 statistic. We will assume statistical significance of the Chi^2 test at a P value < 0.10. We will consider an I^2 value greater than 50% to be substantial.

Assessment of reporting biases

Aside from within-study biases tested as described in the Assessment of risk of bias in included studies section, we will assess between-study biases by comparing outcomes as stated in protocols to those reported or, where protocols are not available, by comparing outcomes listed in the methods section to those reported in the results section.

Data synthesis

We could not perform data synthesis, as we included no studies in the review. We will use Review Manager to perform meta-analysis if we identify at least three studies with comparable outcomes in the future (RevMan 2012). We will use a fixed-effect model for dichotomous data.

Subgroup analysis and investigation of heterogeneity

If feasible, we will analyse participants with isolated severe traumatic brain injury separately to poly-trauma participants.

Sensitivity analysis

If necessary, we will use allocation concealment (done versus not done/unclear) in sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of excluded studies.

Results of the search

We identified 408 references from our literature search (6 November 2012 and 5 November 2013). Other sources searched (11 November 2012) provided no additional records. When we removed duplicates, 374 references remained for further analysis. Based on the title, abstract and key words, we selected 25 references as potentially relevant for the review, and obtained them in full text

(Figure 1). We found no ongoing trials. There are no studies awaiting assessment.

Figure 1. Study flow diagram.

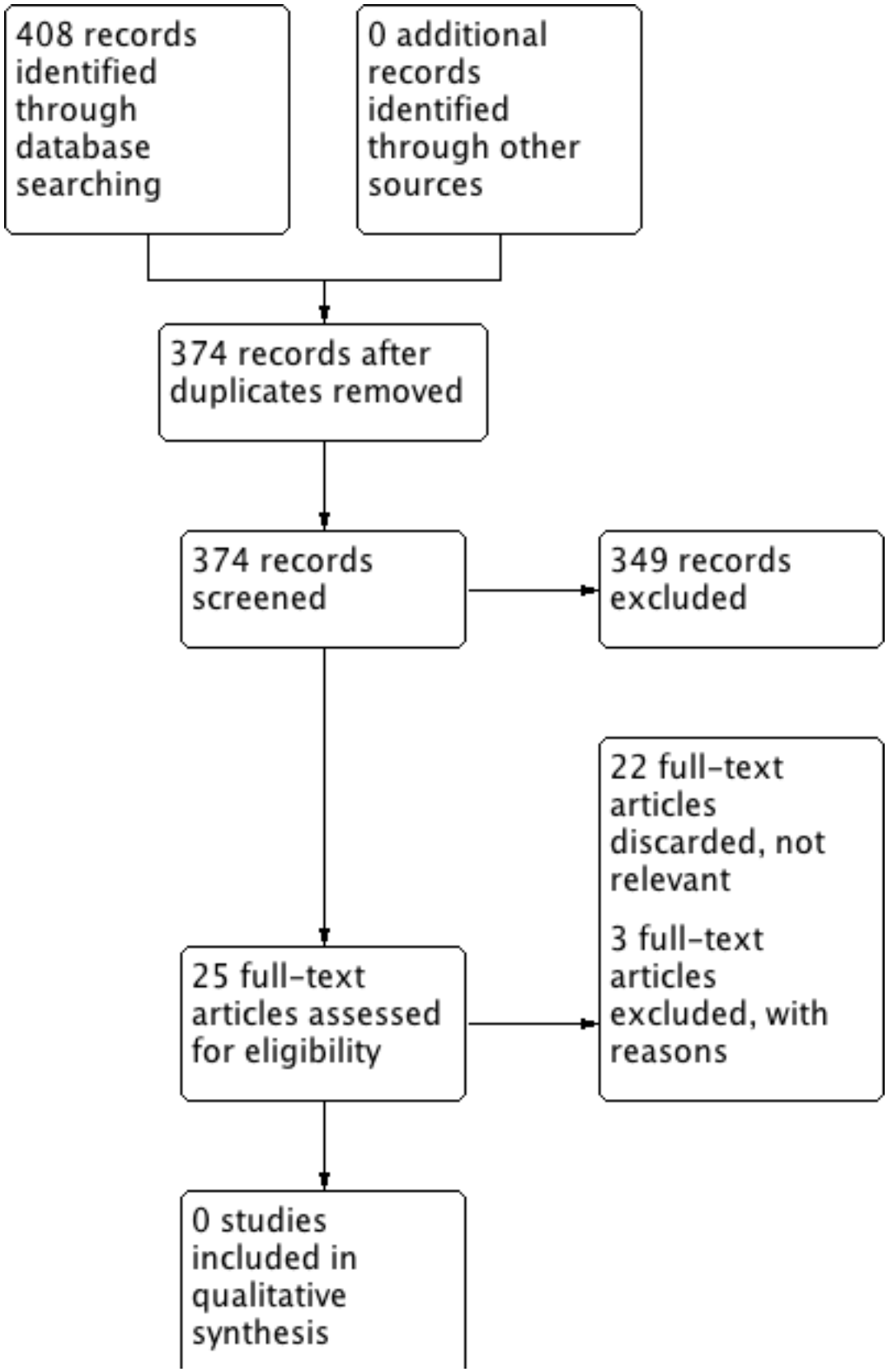
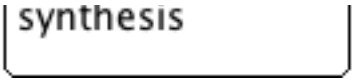


Figure 1. (Continued)



Included studies

After we considered the full-text articles, we found that none of the studies met the inclusion criteria. There were no disagreements on the inclusion of the studies between the review authors.

Excluded studies

We excluded one study because of the lack of randomisation (Liu 2010). It compared people with severe traumatic brain injury treated with either the Lund concept or ICP-targeted therapy, but the participants were not randomised. Another study was a prospective, randomised controlled study comparing relative effectiveness of two treatment strategies: CPP-targeted therapy and modified Lund concept based on ICP-targeted therapy (Dizdarevic 2012). However, it included both people suffering traumatic brain injury and people with secondary brain ischaemia following aneurysmal subarachnoid haemorrhage. Furthermore, the treatment described as Lund concept could not unequivocally be described as such.

Risk of bias in included studies

No studies met the inclusion criteria.

Effects of interventions

No studies met the inclusion criteria.

DISCUSSION

Summary of main results

We did not identify any studies that met the inclusion criteria, mainly because of the lack of randomisation. Therefore, we currently have to conclude that there is insufficient evidence to support the use of the Lund concept in the treatment of severe traumatic brain injury.

Quality of the evidence

The main issue with studies considered for this review was the lack of randomisation (Liu 2010), or precise definition of what was considered to be the Lund concept in comparison to other treatment strategies (Liu 2010). Most studies on the Lund concept were reviews that explain underlying physiological principles. Some of the studies used comparison to the historical controls.

Potential biases in the review process

The only possible bias in the review process could be related to the accidental missing of relevant studies. As we performed an extensive and up-to-date search of the literature in November 2013, which covered important international databases, we consider that this is unlikely.

Agreements and disagreements with other studies or reviews

We found no other reviews for comparison.

AUTHORS' CONCLUSIONS

Implications for practice

There was no evidence from randomised controlled trials on the effects of the Lund concept in the management of severe traumatic brain injury. This treatment should not be used outside of a randomised controlled trial because its effects are not known.

Implications for research

Randomised controlled trials could be designed to compare the Lund concept to other treatment strategies in the management of severe traumatic brain injury.

ACKNOWLEDGEMENTS

We would like to thank to Emma Sydenham, Managing Editor, and Deirdre Beecher, Trials Search Co-ordinator and Information Specialist, for their advice, support, editing and contribution to the literature search.

REFERENCES

References to studies excluded from this review

Dizdarevic 2012 *{published data only}*

Dizdarevic K, Hamdan A, Omerhodzic I, Kominlija-Smajic E. Modified Lund concept versus cerebral perfusion pressure-targeted therapy: a randomised controlled study in patients with secondary brain ischaemia. *Clinical Neurology and Neurosurgery* 2012;**114**:142-8.

Liu 2010 *{published data only (unpublished sought but not used)}*

Liu CW, Zheng YK, Lu J, Yu WH, Wang B, Hu W, et al. Application of Lund concept in treating brain edema after severe head injury. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue (Chinese Critical Care Medicine)* 2010;**22**(10):610-3.

Additional references

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RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Rosner 1995

Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. *Journal of Neurosurgery* 1995;**83**:949-62.

Teasdale 1974

Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;**304**(7872):81-4.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by year of study]

Study	Reason for exclusion
Liu 2010	ALLOCATION Not randomised
Dizdarevic 2012	ALLOCATION Randomised PARTICIPANTS People with secondary brain ischaemia after severe traumatic brain injury, but also people with spontaneous subarachnoid haemorrhage INTERVENTION

Study	Reason for exclusion
	Participants received either cerebral perfusion pressure-targeted therapy or intracranial pressure-targeted therapy based on the Lund concept. This approach, as described by the authors, could not be unequivocally described as the Lund concept OUTCOMES Treatment outcome data reported

APPENDICES

Appendix 1. Search strategy

Cochrane Injuries Group Specialised Register
(isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP) AND lund

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: [Brain Ischemia] explode all trees
#4 MeSH descriptor: [Intracranial Pressure] explode all trees
#5 MeSH descriptor: [Cerebrovascular Circulation] explode all trees
#6 MeSH descriptor: [Intracranial Hypertension] explode all trees
#7 MeSH descriptor: [Brain Injuries] explode all trees
#8 MeSH descriptor: [Decompression, Surgical] explode all trees
#9 MeSH descriptor: [Monitoring, Physiologic] explode all trees
#10 ((Intracranial or Cerebr* or brain) near/3 Hypertens*):ti,ab,kw (Word variations have been searched)
#11 (brain near/3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP)):ti,ab,kw (Word variations have been searched)
#12 (cerebral near/3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP)):ti,ab,kw (Word variations have been searched)
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 lund*:ti,ab,kw (Word variations have been searched)
#15 #13 and #14

MEDLINE (OvidSP)

1. exp Brain Ischemia/
2. exp Intracranial Pressure/
3. exp Cerebrovascular Circulation/
4. exp Brain Edema/
5. exp Intracranial Hypertension/
6. exp Craniocerebral Trauma/
7. exp Brain Injuries/
8. exp Decompression, Surgical/
9. exp Monitoring, Physiologic/
10. ((Intracranial or Cerebr* or brain) adj3 Hypertens*).ab,ti.
11. (brain adj3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP)).ab,ti.
12. (cerebral adj3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP)).ab,ti.
13. or/1-12
14. lund.mp.
15. 13 and 14
16. randomi?ed.ab,ti.
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. placebo.ab.
20. clinical trials as topic.sh.
21. randomly.ab.

22. trial.ti.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. (animals not (humans and animals)).sh.
25. 23 not 24
26. (rat or rats or rodent* or mouse or mice or murine or dog or dogs or canine* or cat or cats or feline* or rabbit or rabbits or pig or pigs or porcine or swine or sheep or ovine* or guinea pig*).ti.
27. 25 not 26
28. 15 and 27

EMBASE (OvidSP)
1. exp Brain Ischemia/
2. exp Intracranial Pressure/
3. exp Cerebrovascular Circulation/
4. exp Brain Edema/
5. exp Intracranial Hypertension/
6. exp Craniocerebral Trauma/
7. exp Brain Injuries/
8. exp Decompression, Surgical/
9. exp Monitoring, Physiologic/
10. ((Intracranial or Cerebr* or brain) adj3 Hypertens*).ab,ti.
11. (brain adj3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP)).ab,ti.
12. (cerebral adj3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP)).ab,ti.
13. or/1-12
14. lund.mp.
15. 13 and 14
16. exp Randomized Controlled Trial/
17. exp controlled clinical trial/
18. exp controlled study/
19. randomi?ed.ab,ti.
20. placebo.ab.
21. *Clinical Trial/
22. exp major clinical study/
23. randomly.ab.
24. (trial or study).ti.
25. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. exp animal/ not (exp human/ and exp animal/)
27. 25 not 26
28. 15 and 27

CINAHL (EBSCO Host)
S27 S15 and S26
S26 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S25 MH quantitative studies
S24 TX random* N3 allocat*
S23 (MH "Random Assignment")
S22 TX placebo*
S21 (MH "Placebos")
S20 TX randomi?ed N3 control* N3 trial*
S19 TI ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*) or (tripl* N3 blind*)) or TI ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*)) or AB ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*)) or AB ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*))
S18 TX clinical N3 trial*
S17 PT clinical trial*
S16 (MH "Clinical Trials")
S15 S13 and S14
S14 TX lund*
S13 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12
S12 TX (cerebral N3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP))
S11 TX (brain N3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP))
S10 TX ((Intracranial or Cerebr* or brain) N3 Hypertens*)
S9 (MH "Monitoring, Physiologic+")
S8 (MH "Decompression, Surgical+")

S7 (MH "Brain Injuries+")
S6 (MH "Head Injuries+")
S5 (MH "Intracranial Hypertension+")
S4 (MH "Cerebral Edema+")
S3 (MH "Cerebrovascular Circulation")
S2 (MH "Intracranial Pressure")
S1 (MH "Cerebral Ischemia+")

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED); Conference Proceedings Citation Index - Science (CPCI-S)
1. TS=(cerebral NEAR/3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP))
2. TS=(brain NEAR/3 (isch?emia or pressure or perfusion or oedema or edema or injur* or trauma* or ICP or CCP))
3. 1 and 2
4. TS=lund*
5. 3 and 4

CONTRIBUTIONS OF AUTHORS

Both authors contributed to the development of this review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Pressure; Brain Injuries [complications] [*therapy]; Brain Ischemia [*prevention & control]; Cerebrovascular Circulation [*physiology]; Intracranial Hypertension [*prevention & control]; Microcirculation [*physiology]

MeSH check words

Humans