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[Intervention Review]

Hyperventilation therapy for acute traumatic brain injury

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ABSTRACT

Background

Because hyperventilation is often associated with a rapid fall in intracranial pressure, it has been assumed to be effective in the treatment of severe head injury. Hyperventilation reduces raised intracranial pressure by causing cerebral vasoconstriction and a reduction in cerebral blood flow. Whether or not reduced cerebral blood flow improves neurological outcome is, however, unclear.

Objectives

To quantify the effect of hyperventilation on death and neurological disability following head injury.

Search methods

We searched the following electronic databases: the Cochrane Injuries Group Specialised Register, CENTRAL (*The Cochrane Library* 2007, Issue 4), MEDLINE, PubMed, EMBASE, PsycINFO. We searched the Internet, checked reference lists of relevant studies, and contacted the first author of eligible reports to ask for assistance in identifying any further trials. The searches were updated in January 2008.

Selection criteria

All randomised trials of hyperventilation, in which study participants had a clinically defined acute traumatic head injury of any severity. There were no language restrictions.

Data collection and analysis

We collected data on the participants, the timing and duration of the intervention, duration of follow-up, neurological disability and death. Relative risks (RR) and 95% confidence intervals (CI) were calculated for each trial on an intention-to-treat basis. Timing, degree and duration of hyperventilation were identified a-priori as potential sources of heterogeneity between trials.

Main results

One trial of 113 participants was identified. Hyperventilation alone, as well as in conjunction with a buffer (THAM [tris-hydroxy-methyl-amino methane]), showed a beneficial effect on mortality at one year after injury, although the effect measure was imprecise (RR 0.73; 95% CI 0.36 to 1.49, and RR 0.89; 95% CI 0.47 to 1.72 respectively). This improvement in outcome was not supported by an improvement in neurological recovery. For hyperventilation alone, the RR for death or severe disability was 1.14 (95% CI 0.82 to 1.58). The RR for death or severe disability in the hyperventilation-plus-THAM group was 0.87 (95% CI 0.58 to 1.28).

Authors' conclusions

The data available are inadequate to assess any potential benefit or harm that might result from hyperventilation in severe head injury. Randomised controlled trials to assess the effectiveness of hyperventilation therapy following severe head injury are needed.

PLAIN LANGUAGE SUMMARY**Not enough evidence on whether hyperventilation therapy improves outcomes for people with traumatic brain injury**

Traumatic brain injury is a major cause of premature death and disability. Severe head injury can trigger brain swelling, thereby increasing pressure on the brain (raised intracranial pressure, ICP). Raised ICP increases the likelihood of brain damage or death. Treatment to lower people's ICP commonly involves hyperventilation therapy (increasing blood oxygen levels) following the brain injury. While hyperventilation therapy can reduce ICP after traumatic brain injury, the review of trials found there is no strong evidence about whether this improves outcomes. More trials are needed.

BACKGROUND

There are at least 10 million new head injuries each year, of which thousands will result in death or long term disability (Alexander 1992). Hyperventilation has been widely used in the treatment and prevention of raised intracranial pressure (ICP) following head injury. It is a simple practicable intervention in many centres. A 1995 survey of the critical care management of head injured patients in the United States showed that 83% of centres used hyperventilation in more than half of severely head injured patients with 29% of centres aiming for a target partial pressure of arterial carbon dioxide (PaCO₂) of less than 3.3kPa (Ghajar 1995). A survey in the United Kingdom showed that 100% of neurosurgical centres use hyperventilation in the treatment of raised intracranial pressure, although in contrast to the North American centres, far fewer UK units aim for very low levels of CO₂, with only 3% of units aiming for a PaCO₂ of 3.3kPa or less (Jeevaratnam 1996).

Hyperventilation to a PaCO₂ of 20 to 30mmHg during the first few days after head injury has been recommended widely (Becker 1985; Marshall 1987). The original rationale for the use of hyperventilation following head injury was first described by Bruce 1981. However, more recently, controversy has emerged as to the PaCO₂ that should be targeted in hyperventilation (Sheinberg 1992), the timing (whether within the first five days after head injury), the duration of hyperventilation, and the indications (Marion 1995; Previgliano 1995; Rosner 1995). Although hyperventilation produces a rapid reduction in ICP (intracranial pressure), and high or uncontrolled ICP is one of the most common precursors of death or neurological disability in traumatically brain injured patients, there is little evidence to suggest that reducing ICP through hyperventilation improves clinically relevant outcomes, and some pathophysiological explanations and the findings of a small randomised controlled trial have been used to suggest it may worsen outcome (Miller 1994). Recent recommendations by the task force of the United States Brain Trauma Foundation suggest that prophylactic hyperventilation (PaCO₂ < 35mmHg) during the first 24 hours after brain injury should be avoided; the use of hyperventilation at any other stage after injury was acknowledged as an area of considerable clinical uncertainty (Task force 1995).

To examine the effectiveness of hyperventilation on outcome, we conducted a systematic review of randomised controlled trials.

OBJECTIVES

To quantify the effect of hyperventilation on death and neurological disability in brain injured patients.

Timing, degree, and duration of hyperventilation and presence of raised ICP were factors identified a-priori as potential sources of heterogeneity between trials.

METHODS

Criteria for considering studies for this review

Types of studies

The review included all randomised and quasi-randomised controlled trials of hyperventilation in which hyperventilation was compared to normo-ventilation.

Types of participants

Trials in which participants had a clinically defined brain injury of any severity.

Types of interventions

The experimental intervention was hyperventilation (PaCO₂ less than or equal to 35mmHg) at any time within eight weeks following injury.

Types of outcome measures

We aimed to extract number of patients in the treatment and control groups who had died at the end of follow-up, who were in a vegetative state, severely disabled, moderately disabled or who had made a good recovery according to Glasgow Outcome Scale (GOS) criteria.

Search methods for identification of studies

The search was not restricted by language or publication status.

Electronic searches

We searched the following electronic databases;

- CENTRAL (*The Cochrane Library* 2007, Issue 4);
- MEDLINE (Ovid SP) 1950 to Nov (week 2) 2007;
- PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 7 Jan 2008: added to PubMed in the last 60 days);
- EMBASE (Ovid SP) 1980 to (week 1) Jan 2008;
- PsycINFO (Ovid SP) 1806 to April 2007;

The search strategy used for previous versions of this review can be found in [Appendix 1](#). The searches used for this update can be found in [Appendix 2](#).

Searching other resources

We also conducted a general Internet search and searched web-based trials databases.

The reference lists of all relevant articles identified were checked. A letter was sent to the first author of reports to ask for further information on the published report and asking them to assist in identifying any further trials which may have been conducted by them, or other investigators.

Data collection and analysis

Data extraction and management

Both reviewers independently extracted data and then cross-checked the extracted data. Data on the number of patients with each outcome event were extracted according to treatment allocated, regardless of whether or not the patient was subsequently deemed ineligible for follow-up or treatment, in order to allow an 'intent-to-treat' analysis.

Assessment of risk of bias in included studies

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Higgins 2008), both reviewers scored this quality on the scale used by Higgins (Higgins 2008) as shown below, assigning 'No' to poorest quality and 'Yes' to best quality:

No = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth);

Unclear = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories;

Yes = trials deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).

RESULTS

Description of studies

One study meeting the inclusion criteria was identified (reported in [Ward 1989](#); [Muizelaar 1991](#) and [Marmarou 1993](#)). This study included patients with severe closed head injury (Glasgow Coma Scale (GCS) less than or equal to 8), three years of age or older, who had already received initial resuscitation, diagnosis and treatment for mass lesions. One hundred and thirteen patients with severe head injury were stratified into two groups according to the motor score of the GCS, and then randomised to a control group (n = 41), a hyperventilation group (n = 36), and a group which received hyperventilation plus a buffer (THAM [tris-hydroxy-methyl-amino methane]) (n = 36). Approximately 70% of the participants were male and most were young adults. All patients received standard care, which included monitoring of ICP, and the introduction of various ICP-lowering agents, such as mannitol and barbiturates. All patients were intubated and artificially ventilated. Not all patients necessarily had raised ICP at entry to the study; approximately 14% in each group had elevated ICP on admission.

The intervention in the hyperventilation and in the hyperventilation-plus-THAM group comprised adjusting the respiratory rate and the volume of the ventilator to keep PaCO₂ at 24 to 28mmHg. In addition, the hyperventilation-plus-THAM group received an initial dose of THAM calculated individually according to body weight and base deficit. This was followed by a constant infusion of THAM at 1ml/kg/hr for five days. Hyperventilation was maintained for five days.

The study authors presented outcomes of death, severe disability/vegetative state and good recovery/moderate disability at 3, 6 and 12 months stratified by motor score at time of entry. Follow up was 100%.

Risk of bias in included studies

The planned method of randomisation should have been adequate to prevent foreknowledge of treatment allocation; random number

tables were used to generate randomisation, and two separate series of opaque envelopes related to the motor score were assigned to eligible patients. However the authors reported a departure from the proper method of randomisation, in that early on in the study, patients from whom informed consent could not be obtained immediately were assigned to the control group without drawing an envelope. This practice was stopped as soon as the trialist became aware of it. These patients could not be identified later.

The study was not double-blind in that the evaluator was not blind to the treatment given. Outcome was assessed by only one evaluator.

Effects of interventions

Hyperventilation alone, as well as in conjunction with the buffer THAM, showed a beneficial effect on mortality at a year after injury (RR 0.73; 95% CI 0.36 to 1.49 and RR 0.89; 95% CI 0.47 to 1.72 respectively). This improvement in outcome was not supported by an improvement in neurological recovery. For hyperventilation alone, the RR for death or severe disability was 1.14 (95% CI 0.82 to 1.58). The RR for death or severe disability for the hyperventilation-plus-THAM group was 0.87 (95% CI 0.58 to 1.28).

DISCUSSION

Owing to the small study size, all of the effect measures were imprecise. The findings of this small randomised controlled trial in severely head injured patients, not all of whom had raised ICP highlight the need for further randomised controlled trials to address the question of the appropriateness of this widely used intervention.

AUTHORS' CONCLUSIONS

Implications for practice

The data available are insufficient to assess any potential benefit or harm that might result from hyperventilation in severe head injury.

Implications for research

Further randomised controlled trials to assess the effectiveness of hyperventilation therapy following severe head injury are needed. The PaCO₂ that should be targeted in hyperventilation, the timing, duration, and whether or not the intervention has a net benefit in certain groups of patients, such as those with raised ICP, needs to be investigated.

REFERENCES

References to studies included in this review

Muizelaar 1991 {published data only}

Marmarou A, Holdaway R, Ward JD, Yoshida K, Choi SC, Muizelaar JP, et al. Traumatic brain tissue acidosis : experimental and clinical studies. *Acta neurochirurgica. Supplementum* 1993;**57**:160-4. [MEDLINE: 1993135012]

* Muizelaar JP, Marmarou A, Ward J, Kontos HA, Choi SC, Becker DP, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *Journal of Neurosurgery* 1991;**75**:731-9. [MEDLINE: 1992014242]

Ward JD, Choi A, Marmarou R, Moulton JP, Muizelaar A, DeDalle A, et al. Effect of prophylactic hyperventilation on outcome in patients with severe head injury. In: Hoff JT, Betz AL editor(s). *Intracranial Pressure*. Vol. **VII**, Berlin: Springer-Verlag, 1989.

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Kerr ME, Rudy EB, Weber BB, Stone KS, Turner BS, Orndoff PA, et al. Effect of short-duration hyperventilation during endotracheal suctioning on intracranial pressure in severe head-injured adults. *Nursing Research* 1997;**46**(4):195-201.

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Marion DW, Puccio A, Wisniewski SR, Kochanek P, Dixon CE, Bullian L, et al. Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury. *Critical Care Medicine* 2002;**30**(12):2619-25.

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Robertson 1999 {published data only}

Robertson CS, Valadka AB, Hannay J, Contant CF, Gopinath SP, Cormio M, et al. CPP/ICP Clinical Trial. www.emn-neurotrauma.de/tenerife_book/047emn99.pdf 1999.

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Becker DP, Gardner S. Intensive management of head injury. In: Wilkins RH, Rengachary SS editor(s). *Neurosurgery*. Vol. **2**, New York: McGraw-Hill, 1985:1593-9.

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Ghajar J, Hariri RJ, Narayan RK, Iacono LA, Firlik K, Patterson RH. Survey of critical care management of comatose, head-injured patients in the United States. *Critical Care Medicine* 1995;**23**(3):560-7.

Higgins 2008

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Jeevaratnam 1996

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Marion 1995

Marion DW, Darby JM. Hyperventilation and head injury [letter]. *Journal of Neurosurgery* 1995;**83**(6):1113-4; discussion 1115-7.

Marmarou 1993

Marmarou A, Holdaway R, Ward JD, Yoshida K, Choi SC, Muizelaar JP, et al. Traumatic brain tissue acidosis: experimental and clinical studies. *Acta neurochirurgica. Supplementum* 1993;**57**:160-4.

Marshall 1987

Marshall LF, Marshall S. Medical management of intracranial pressure. In: Cooper PR editor(s). *Head Injury*. 2. Baltimore: Williams & Wilkins, 1987:177-96.

Miller 1994

Miller DJ. Swelling and blood flow in the injured child's brain [commentary]. *Lancet* 1994;**44**:421-2.

Previgliano 1995

Previgliano IJ. Hyperventilation and head injury [letter]. *Journal of Neurosurgery* 1995;**83**(6):1112-3; discussion 1115-7.

Rosner 1995

Rosner MJ. Hyperventilation and head injury [letter]. *Journal of Neurosurgery* 1995;**83**(6):1113; discussion 1115-7.

Sheinberg 1992

Sheinberg M, Kanter MJ, Robertson CS, Contant CF, Narayan RK, Grossman RG. Continuous monitoring of jugular venous oxygen saturation in head injured patients. *Journal of Neurosurgery* 1992;**76**:212-71.

Task force 1995

Task force of the American Association of Neurological Surgeons and Joint Section in Neurotrauma and Critical Care.

Guidelines for the management of severe head injury. Brain Trauma Foundation, 1995.

outcome in patients with severe head injury. In: Hoff JT, Betz AL editor(s). Intracranial Pressure VII. Berlin, Heidelberg: Springer-Verlag, 1989.

Ward 1989

Ward JD, Choi A, Marmarou R, Moulton JP, Muizelaar A, DeDalles A, et al. Effect of prophylactic hyperventilation on

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Muizelaar 1991

Methods	Participants were stratified into two groups according to motor score of the GCS, and then randomised to a control group (n = 41), a hyperventilation group (n = 36) and a hyperventilation-plus-THAM group (n = 36). All patients received standard care, which included monitoring of ICP, and the introduction of various ICP lowering agents, such as mannitol and barbiturates. All patients were intubated and artificially ventilated. Not all patients necessarily had raised ICP at entry to the study; approximately 14% in each group had elevated ICP on admission. Therefore the study was testing a policy of prophylactic hyperventilation.
Participants	Participants with severe closed head injury (GCS < or equal to 8), three years of age or older, who had already received initial resuscitation, diagnosis and treatment for mass lesions. Approximately 70% of the participants were male and most were young adults.
Interventions	The intervention in the hyperventilation and in the hyperventilation-plus-THAM group comprised adjusting the respiratory rate and the volume of the ventilator to keep PaCO ₂ at 24 to 28mmHg. In addition, the hyperventilation-plus-THAM group received an initial dose of THAM calculated individually according to body weight and base deficit. This was followed by a constant infusion of THAM at 1ml/kg/hr for five days. Hyperventilation was maintained for five days. The control group received only standard care, which included monitoring of ICP, and various ICP lowering agents such as mannitol and barbiturates.
Outcomes	The authors presented outcomes of death, severe disability/vegetative state and good recovery/moderate disability at 3, 6 and 12 months stratified by motor score at time of entry. Follow up was 100%.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Kerr 1997	Intervention not eligible.
Marion 2002	Non-randomised trial.
Previgliano 2002	Hyperventilation was only used for preventing an increase in ICP during bronchoscopy.
Robertson 1999	Both study groups received hyperventilation.

DATA AND ANALYSES

Comparison 1. Hyperventilation versus Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.36, 1.49]
2 Death or severe disability	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.82, 1.58]

Analysis 1.1. Comparison 1 Hyperventilation versus Control, Outcome 1 Death.

Analysis 1.2. Comparison 1 Hyperventilation versus Control, Outcome 2 Death or severe disability.

Comparison 2. Hyperventilation plus THAM versus Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.47, 1.72]
2 Death or severe disability	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.28]

Analysis 2.1. Comparison 2 Hyperventilation plus THAM versus Control, Outcome 1 Death.

Analysis 2.2. Comparison 2 Hyperventilation plus THAM versus Control, Outcome 2 Death or severe disability.

APPENDICES

Appendix 1. Search strategy

This MEDLINE search strategy was used and adapted, as appropriate, for each of the other databases:CENTRAL (The Cochrane Library), MEDLINE, EMBASE, National Research Register and Web of Science.

```
#1explode "Craniocerebral trauma" / all SUBHEADINGS
#2 explode "Intracranial-Pressure" / all SUBHEADINGS
#3 (brain near injur*) or (head near injur*) or (brain near trauma*) or (head near trauma*)
#4 intracranial pressure
#5 #1 or #2 or #3 or #4
#6 explode "Respiration-Artificial" / all SUBHEADINGS
#7 hyperventilat*
#8 (carbon dioxide near level*) or (CO2 near level*)
#9 PaCO2
#10 #6 or #7 or #8 or #9
#11 RCT filter (Clarke 2001)
#12 #5 and #10 and #11
```

Appendix 2. Search strategies: 2008 update

CENTRAL (The Cochrane Library 2007, Issue 4)

```
#1MeSH descriptor Craniocerebral Trauma explode all trees
#2MeSH descriptor Cerebrovascular Trauma explode all trees
#3MeSH descriptor Brain Edema explode all trees
#4(brain or cerebral or intracranial) near3 (oedema or edema or swell*)
#5MeSH descriptor Glasgow Coma Scale explode all trees
```

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#6MeSH descriptor Glasgow Outcome Scale explode all trees
 #7MeSH descriptor Unconsciousness explode all trees
 #8glasgow near3 (coma or outcome) near3 (score or scale)
 #9(Unconscious* or coma* or concuss* or 'persistent vegetative state') near 3 (injur* or trauma* or damag* or wound* or fracture*)
 #10"Rancho Los Amigos Scale"
 #11(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*)
 #12Diffuse near3 axonal near3 injur*
 #13(head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) near3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)
 #14(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)

PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 7 Jan 2008 (added to PubMed in the last 60 days))

#1Craniocerebral Trauma [mh] OR Brain Edema [mh] OR Glasgow Coma Scale [mh] OR Glasgow Outcome Scale [mh] OR Unconsciousness [mh] OR Cerebrovascular Trauma [mh] OR ((head OR cranial OR cerebral OR brain* OR intra-cranial OR inter-cranial) AND (haematoma* OR hematoma* OR haemorrhag* OR hemorrhage* OR bleed* OR pressure)) OR (Glasgow AND scale) OR ("diffuse axonal injury" OR "diffuse axonal injuries") OR ("persistent vegetative state") OR ((unconscious* OR coma* OR concuss*) AND (injury* OR injuries OR trauma OR damage OR damaged OR wound* OR fracture* OR contusion* OR haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed* OR pressure))
 #2(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 [mh]) NOT ((models, animal[mh] OR Animals[mh] OR Animal Experimentation[mh] OR Disease Models, Animal[mh] OR Animals, Laboratory[mh]) NOT (Humans[mh]))
 #3Search #1 AND #2 Limits: published in the last 60 days

MEDLINE (Ovid SP) 1950 to Nov (week 2) 2007

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.((head or crani\$ 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\$)).ab,ti.
 8.((head or crani\$ or cerebr\$ or brain\$ or intra-cran\$ or inter-cran\$) adj3 (haematoma\$ or hematoma\$ or haemorrhag\$ or hemorrhag\$ or bleed\$ or pressure)).ti,ab.
 9.(Glasgow adj3 (coma or outcome) adj3 (scale\$ or score\$)).ab,ti.
 10."rancho los amigos scale".ti,ab.
 11.("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
 12.((brain or cerebral or intracranial) adj3 (oedema or edema or swell\$)).ab,ti.
 13.((unconscious\$ or coma\$ or concuss\$ or 'persistent vegetative state') adj3 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$)).ti,ab.
 14.or/1-13
 15. (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.
 16.clinical trial.pt.
 17.randomized controlled trial.pt.
 18.17 or 18 or 19
 19.exp models, animal/
 20.exp Animals/
 21.exp Animal Experimentation/
 22.exp Disease Models, Animal/
 23.exp Animals, Laboratory/
 24.or/21-25
 25.Humans/
 26.20 not 25
 27.18 not 26
 28.14 and 27
 29.2007\$.ed.
 30.28 and 29

EMBASE (Ovid SP) 1980 to (week 1) Jan 2008

1.exp Brain Injury/
 2.exp Brain Edema/

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3.exp Glasgow Coma Scale/
4.exp Glasgow Outcome Scale/
5.exp Rancho Los Amigos Scale/
6.exp Unconsciousness/
7.((brain or cerebral or intracranial) adj3 (oedema or edema or swell\$)).ab,ti.
8.((head or crani\$ 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\$)).ab,ti.
9.(Glasgow adj3 (coma or outcome) adj3 (scale\$ or score\$)).ab,ti.
10.Rancho Los Amigos Scale.ab,ti.
11.((unconscious\$ or coma\$ or concuss\$ or 'persistent vegetative state') adj3 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$)).ti,ab.
12.Diffuse axonal injur\$.ab,ti.
13.((head or crani\$ or cerebr\$ or brain\$ or intra-cran\$ or inter-cran\$) adj3 (haematoma\$ or hematoma\$ or haemorrhag\$ or hemorrhag\$ or bleed\$ or pressure)).ab,ti.
14.or/1-13
15.exp animal model/
16.Animal Experiment/
17.exp ANIMAL/
18.exp Experimental Animal/
19.1 or 2 or 3 or 4
20.Human/
21.5 not 6
22.(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.
23.exp clinical trial/
24.8 or 9
25.10 not 7
26.14 and 25
27.2007\$.em.
28.26 and 27

PsycINFO (Ovid SP) 1806 to April 2007

1.explode "Head-Injuries" in MJ,MN
2.explode "Brain-Damage" in MJ,MN
3.explode "Traumatic-Brain-Injury" in MJ,MN
4.explode "Brain-Concussion" in MJ,MN
5.explode "Coma-" in MJ,MN
6.Unconscious* or coma* or concuss* or "persistent vegetative state"
7.(head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near (injur* or trauma* or damag* or wound* or fracture* or contusion*)
8.(head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) near (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)
9.#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

WHAT'S NEW

Date	Event	Description
5 May 2009	New search has been performed	The search was updated to January 2008. No new trials were identified. The conclusions remain the same.

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 4, 1997

Date	Event	Description
9 June 2008	Amended	Converted to new review format.
8 March 2006	New search has been performed	The search was last updated in March 2006; no additional eligible studies were identified.

CONTRIBUTIONS OF AUTHORS

GS designed and ran the searches, screened the citations for eligibility, contacted authors, extracted data, entered data into RevMan and wrote the review. IR screened citations, extracted data and helped to write the review. IR updated the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHS R&D Programme: Mother and Child Health, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hyperventilation; Brain Injuries [*therapy]; Respiration, Artificial [*methods]

MeSH check words

Humans