Absence of evidence for the effectiveness of five interventions routinely used in the intensive care management of severe head injury: a systematic review

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Abstract

Objectives—To assess the effectiveness of interventions routinely used in the intensive care management of severe head injury, specifically, the effectiveness of hyperventilation, mannitol, CSF drainage, barbiturates, and corticosteroids.

Methods—Systematic review of all unfounded randomised trials, published or unpublished, that were available by August 1996.

Results—None of the interventions has been reliably shown to reduce death or disability after severe head injury. One trial of hyperventilation was identified of 77 participants. The relative risk for death was 0.73 (95% confidence interval (95% CI) 0.36–1.49), and for death or disability it was 1.14 (95% CI 0.82–1.58). One trial of mannitol was identified of 41 participants. The relative risk for death was 1.75 (95% CI 0.48–6.38), no data were available for disability. No randomised trials of CSF drainage were identified. Two randomised trials of barbiturate therapy were identified, including 126 participants. The pooled relative risk for death was 1.12 (95% CI 0.81–1.54). Disability data were available for one trial. The relative risk for death or disability was 0.96 (95% CI 0.62–1.49). Thirteen randomised trials of corticosteroids were identified, comprising 2073 participants. The pooled relative risk for death was 0.95 (0.84 to 1.07) and for death or disability it was 1.01 (95% CI 0.91 to 1.11). On the basis of the currently available randomised evidence, for every intervention studied it is impossible to refute either a moderate increase or a moderate decrease in the risk of death or disability.

Conclusion—Existing trials have been too small to support or refute the existence of a real benefit from using hyperventilation, mannitol, CSF drainage, barbiturates, or corticosteroids. Further large scale randomised trials of these interventions are required.

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year for severe head injury.¹ Of these, thousands will die and thousands will be permanently disabled. Road traffic crashes account for most serious head injuries, and the global burden of head injury can be expected to rise with the increasing use of vehicles in Asia and Africa.²

Insights from pathophysiological studies have shown that the occurrence of a severe head injury marks only the beginning of a continuing encephalopathic process.³ Secondary brain damage from ongoing cerebral hypoxia is an important cause of avoidable death and long term disability. The intensive care management of severe head injury, including the prevention, early detection, and reversal of disorders likely to cause secondary damage, such as hypoxia, hypercapnia, hypotension, and hyperthermia, may therefore be of critical importance in determining eventual outcome.

Surveys in the United States and the United Kingdom have shown that intensive care for severe head injury often involves the use of five specific interventions, aimed at the management of raised intracranial pressure: hyperventilation, mannitol, CSF drainage, barbiturates, and corticosteroids.^{4,5} A 1996 survey of therapies for raised intracranial pressure in 35 neurosurgical referral units in the United Kingdom and Ireland found that hyperventilation was used in 89% of units, osmotic diuretics (mannitol) in 100% of units, CSF drainage in 69% of units, barbiturates in 69% of units, and corticosteroids in 14% of units.⁴ Although clinical trials in head injury are increasingly focused on the evaluation of newer neuroprotective agents, the empirical basis for these widely used strategies has yet to be rigorously evaluated. The recent guidelines for the management of severe head injury assembled by the US Brain Trauma Foundation did take randomised trials into account, but the methods used would not satisfy the criteria that have been proposed for scientific overviews.^{6,7} To assess the effectiveness and safety of interventions routinely used in the intensive care management of severe head injury, we systematically reviewed the evidence from randomised controlled trials. This review draws on the work of the Cochrane Injuries Group. Systematic reviews of the effectiveness of hyperventilation, mannitol, barbiturates, and steroids are available on the Cochrane Library.^{8–11}

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World wide, several million people, mostly children and young adults, are treated each

Table 1 Included studies*

Study	Participants	Intervention	Number randomised	Allocation concealment
Hyperventilation: Muizelaar <i>et al</i> ¹²	Patients with head injuries Glasgow coma score (GCS) ≤ 8, age 3 years or older	Hyperventilation: paco ₂ 25 ± 2 mm Hg Normoventilation: paco ₂ 35 ± 2 mm Hg	77	Sealed opaque envelopes
Mannitol: Sayre <i>et al</i> ¹³	Intubated head trauma victims GCS ≤ 12, age 18 years or more before arrival in hospital	Mannitol: 5 ml/kg 20% mannitol as rapidly as possible Control: 5 ml/kg 0.9% NaCl prerandomisation inclusion criteria	44 randomised: 3 postrandomisation exclusions because did not meet all	Pharmacy prepared blinded solutions
CSF drainage: No randomised trials identified				
Barbiturates: Eisenberg <i>et al</i> ¹⁷	Severe head injury GCS ≤ 7 Aged 15–50, raised intracranial pressure (ICP) refractory to conventional management	Pentobarbitone: loading dose 10 mg/kg over 30 min 5 mg/kg every hour for three hours Maintenance 1 mg/kg/h with serum concentration monitoring Pentobarbitone: loading dose 5–10 mg/kg until burst suppression on EEG	80 randomised: 7 postrandomisation exclusions because did not meet all prerandomisation inclusion criteria	Sealed opaque envelopes
Ward <i>et al</i> ¹⁸	Consecutive head injured patients over the age of 12 years who had either an acute intradural haematoma or no mass lesion whose best motor response was abnormal flexion or extension. Treatment started after head injury regardless of ICP	Maintenance 1–3 mg/kg with serum concentration monitoring	53	Not specified

*A detailed description of randomised trials of steroids in head injury has been presented elsewhere.

Methods

IDENTIFICATION OF TRIALS

We aimed to identify all unconfounded randomised trials, published or unpublished, that were available by August 1996, in which hyperventilation, mannitol, CSF drainage, barbiturates, or corticosteroids were compared with normoventilation, no mannitol, no CSF drainage, no barbiturates, and no corticosteroids respectively. Trials were included only if they were thought to be randomised in a manner that precluded prior knowledge of the next treatment. If this could not be fully ascertained from the published report, the author was contacted for clarification. Trials in which allocation was alternate or based on odd or even record numbers were not eligible for inclusion. Trials were considered unconfounded if one treatment group differed from another only in the treatment of interest. There were no language restrictions. Trials were identified by computerised searches of the Cochrane Controlled Trials Register, Medline and Embase; by hand searching 43 international journals, conference abstracts and the proceedings of 16 neurosurgical meetings; by searching the reference lists of trials and review articles, and by contacting the authors of all identified trials asking them about any other trials they may know of whether published or unpublished.

OUTCOME MEASURES AND DATA EXTRACTION

Intervention effects were to be assessed in terms of death, disability, mean intracranial pressure and mean cerebral blood flow. Disability was assessed using the Glasgow outcome scale with death, persistent vegetative state, and severe disability comprising the poor outcome category, and moderate disability and good recovery comprising the favourable outcome category. In addition to the outcome measures, the following data were sought from each trial: strategy for allocation concealment

and the number of randomised participants. Data were extracted by two reviewers, with disagreements settled by collaborative review.

STATISTICAL METHODS

For each trial relative risks and 95% confidence intervals (95% CIs) were calculated. Pooled relative risks were estimated as an inverse variance weighted average of study specific relative risks. Heterogeneity was assessed using a χ^2 test with $p < 0.05$ taken to represent significant heterogeneity.

Results

The studies finally included are summarised in the table.

HYPERVENTILATION

One trial was identified with 77 participants.¹² Allocation concealment was by sealed opaque envelopes. There was a protocol violation early in the study, when patients for whom informed consent could not be obtained immediately were assigned to the control group without drawing an envelope. It was not possible to identify which patients were properly allocated and which were not. The relative risk for death was 0.73 (95% CI 0.36 to 1.49) (figure), and for death or disability it was 1.14 (95% CI 0.82 to 1.58). There were non-significantly fewer deaths among patients treated with hyperventilation, although the observed absolute difference in the risk of death of 9% (95% CI 29% to -11%), corresponding to 90 fewer deaths per 1000 patients treated with hyperventilation, may prove to be clinically very significant. No data were available on mean intracranial pressures. Mean cerebral blood flow was lower in the hyperventilated group. The mean difference in cerebral blood flow between the hyperventilated and normoventilated group was -9 ml/100 g/min (95% CI -15 to -3).

Summary relative risks for death at the end of the study.

MANNITOL

One trial was identified with 41 participants.¹³ Allocation concealment was by pharmacy prepared blinded solutions. The relative risk for death was 1.75 (95% CI 0.48 to 6.38). There were non-significantly more deaths among patients treated with mannitol, with an absolute increase in the risk of death of 11% (95% CI –14% to 35%). No data were available for disability, intracranial pressure, or cerebral blood flow.

CEREBROSPINAL FLUID DRAINAGE

No randomised trials of CSF drainage were identified.

BARBITURATES

Five reports of randomised controlled trials were identified.^{14–18} The trial by Saul and Ducker involving 26 randomised participants was unpublished.¹⁴ The authors were contacted, but the data were no longer available for inclusion. No information was available on the magnitude or direction of the intervention effect. Two further trials, reported as “randomised trials” were excluded after contact with the authors disclosed that allocation was quasirandom or non-random.^{15 16} The two remaining trials comprised 126

participants.^{17 18} The pooled relative risk for death was 1.12 (95% CI 0.81 to 1.54). There were non-significantly more deaths among patients treated with barbiturates, with an absolute increase in the risk of death of 6% (95% CI –11% to 24%). Disability data were available for one trial. The relative risk for death or disability was 0.96 (95% CI 0.62 to 1.49).

In the study by Eisenberger *et al*, the relative risk for uncontrolled intracranial pressure was 0.81 (95% CI 0.62 to 1.06). Similarly, in the study by Ward *et al*, mean intracranial pressure was lower in the barbiturate treated group, with a mean intracranial pressure difference of –1 mm Hg (95% CI –7.8 to 5.8). Neither study reported the effect of barbiturates on cerebral blood flow, although both reported the effect of barbiturates on the occurrence of hypotension. The pooled relative risk for hypotension was 1.80 (95% CI 1.19 to 2.70). For every four patients treated with barbiturate therapy one will develop hypotension.

CORTICOSTEROIDS

Thirteen trials were identified that reported death or disability, comprising 2073 randomised participants.¹⁹ Details of the dosage used and allocation concealment have been

presented elsewhere.¹⁹ The pooled relative risk for death was 0.95 (95% CI 0.84 to 1.07). Disability data were available for nine trials. The relative risk for death or disability was 1.01 (95% CI 0.91 to 1.11). There were non-significantly fewer deaths among patients treated with corticosteroids, with a pooled absolute risk reduction of 1.9% (95% CI 6.1% to -2.3%). No data were available to estimate pooled effects on intracranial pressure or cerebral blood flow.

Discussion

Hyperventilation, mannitol, CSF drainage, barbiturates, and corticosteroids are routinely used interventions in the intensive care management of patients with severe head injury; nevertheless, none of these interventions has been reliably shown to reduce death or disability. On the basis of the currently available randomised evidence, it is impossible to refute either a moderate increase or a moderate decrease in the absolute risk of death or disability. Although several million patients are treated for severe head injury each year, existing trials, even in aggregate, have involved only a few thousand patients, and for hyperventilation, mannitol, CSF drainage, and barbiturates, existing trials comprise only a few hundred patients. Identical results would have been obtained had the inclusion criteria been broadened to include trials using quasirandom allocation. One quasirandomised trial of barbiturate therapy was identified, with 82 participants, in which the relative risk for death was 1.0 (95% CI 0.49 to 2.04),¹⁵ and one quasirandomised trial of corticosteroids was identified with 25 participants, in which there were no deaths in the intervention or control groups.²⁰

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.²¹ This reasoning is supported by the results of the only randomised trial of hyperventilation, in which mean cerebral blood flow was lower in the hyperventilated group. Whether reduced cerebral blood flow improves neurological outcome however, is unclear, and this question cannot be resolved on the basis of the existing randomised evidence.

Mannitol is sometimes dramatically effective in reversing the signs of transtentorial herniation, but in the absence of reliable evidence from randomised trials its effectiveness in the on-going management of severe head injury remains open to question. There is evidence that in prolonged dosage mannitol may pass from the blood into the brain, where it might cause reverse osmotic shifts that increase intracranial pressure.²²

The intracranial pressure lowering effect of barbiturates is thought to be due to the coupling of cerebral blood flow to regional metabolic demands.⁶ By suppressing cerebral metabolism, barbiturates reduce cerebral metabolic demands, thus reducing cerebral blood volume and intracranial pressure. Re-

sults from randomised trials show that barbiturate therapy does reduce raised intracranial pressure, but there is no evidence that this is associated with reductions in mortality or disability. Barbiturate therapy results in a significant increase in the occurrence of hypotension in patients with severe head injury. For every four patients treated with barbiturates one will develop hypotension. There is a correlation between raised intracranial pressure and adverse neurological outcome, but cerebral perfusion pressure depends on both intracranial pressure and mean arterial blood pressure (cerebral perfusion pressure = mean arterial blood pressure - mean intracranial pressure) and the hypotensive effect of barbiturates may offset any beneficial effect of a barbiturate related reduction in intracranial pressure.

The guidelines for the management of severe head injury assembled by the US Brain Trauma Foundation recommend that corticosteroids should not be used.⁶ When all previous randomised trials of corticosteroids in head injury are taken into account, the difference in the risk of death between the steroid and control groups is 2%. This is statistically compatible with there being no real benefit, but is also easily compatible with there being a benefit of up to 6%. Existing trials, even in aggregate, are too small to support or refute the existence of a clinically important benefit from using corticosteroids.

Recent reviews of the management of severe head injury emphasise the need to evaluate the effectiveness and safety of the newer neuroprotective agents.²³ The results of this systematic review, however, underscore the importance of evaluating the effectiveness of the interventions that are currently used in the management of severe head injury. World wide some millions of people are treated each year for severe head injury, of whom over a million die, and a similar number are permanently disabled. If a treatment as widely practicable as corticosteroid therapy reduced the risk of death by "only" 2%, and reduced the risk of permanent disability by a similar amount, then treatment of 100 000 patients would avoid 2000 deaths and prevent 2000 permanent disabilities. However, such a benefit would be impossible to show reliably without large scale randomised evidence.^{24 25} Heterogeneity of the types of patients entering large randomised trials is a scientific strength, not a weakness. If a wide range of patients are randomised then it may be possible for the trial to help determine which (if any) particular types of patient are most likely to benefit from treatment.

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The use of the tuning fork to clinically test vibration sense is generally credited to Heinrich Rumpf, professor and director of the poliklinik in the University of Marburg, who published his findings¹² in 1889*. A controversy surrounded its significance. Tomson, Treitel, Rydel, and Seiffer argued that it was a discrete sensation, sometimes impaired when touch and pressure sensation were preserved, in tabes and polyneuritis. Egger¹³ in Dejerine's clinic, and Schwane, thought that the receptors lay in the periosteum but the sensation (pallaesthesiae) was conducted by bone. However, vibration sense was not generally accepted as a valid clinical test for another 10 years.¹⁴

The idea of bony sensibility—ignoring the sense of vibration when a fork was applied to soft tissues—dominated neurological concepts for many years. In the presence of posterior column and peripheral nerve lesions physicians discovered vibration sense to be impaired, although it is evident that vibration perception is a physician's tool stimulating rapidly adapting mechanoreceptors conveyed both in posterior columns and corticospinal pathways in the cord. Transmission of several proprioceptive modalities, not limited to the posterior columns, ascend and are integrated and perceived at a higher level. There is no known corresponding physiological function.

The empirical use of vibration sense tests has, however, not been superseded. In modern times physicians employ many refinements for measuring vibration thresholds that include the

Rydel-Seiffer graduated tuning fork,¹⁵ biothesiometer, vibrometer, and the Optacon tactile tester, which provide quick and fairly reliable assessments.

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