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A systematic review of the use of hyperbaric oxygen therapy in the treatment of acute traumatic brain injury

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Key words
Cochrane library, brain injury, hyperbaric oxygen, reprinted from

Abstract
(Bennett MH, Trytko BE, Jonker B. A systematic review of the use of hyperbaric oxygen therapy in the treatment of acute traumatic brain injury. The Cochrane Database of Systematic Reviews 2004, Issue 4, Art. No. CD004609.)
Introduction: We aimed to assess the randomised clinical evidence for the benefits and harms of adjunctive hyperbaric oxygen therapy (HBOT) for acutely brain-injured patients. HBOT can improve oxygen supply to the injured brain and reduce both cerebral oedema and cerebrospinal fluid pressure and might therefore result in a reduction in patient death and disability.
Methods: We performed a systematic search of the literature for randomised controlled trials and made pooled analyses of pre-determined clinical outcomes where possible using Cochrane Collaboration methodology. We included adults with serious closed head injury requiring admission to an intensive care environment and included trials must have compared a standard therapy with adjunctive HBOT to standard therapy alone following randomised allocation. We pre-determined important clinical outcomes and assessed them when reported in the primary studies.
Results: Four trials contributed to this review (382 participants, 199 receiving HBOT and 183 control). Pooled analysis suggested a significant reduction in the risk of dying when HBOT was added (RR 0.69, 95% CI 0.54 to 0.88, NNT = 7, P = 0.003), but no statistically significant increase in the chance of a favourable clinical outcome (RR 1.94, 95% CI 0.92 to 4.08, P = 0.08).
Conclusions: HBOT reduced the risk of death but did not clearly increase the chance of favourable clinical outcome. Routine application of HBOT to these patients should not be justified from this review. More research of high methodological rigour is needed in order to confirm or refute the findings of this review.

Introduction

Traumatic brain injury (TBI) is a significant cause of premature death and disability. There are at least 10 million new head injuries worldwide annually and these account for a high proportion of deaths in young adults.[1,2] In the US, 2% of the population (5.3 million citizens) are living with disability as a result of TBI[1] and this places considerable medical, social and financial burden on both families and health systems.[3] Any intervention that may improve the chance of a good functional outcome is therefore worthy of study.

Hyperbaric oxygen therapy (HBOT) is one such intervention. HBOT is the administration of 100% oxygen at environmental pressures greater than 1 atmosphere absolute (ATA), an absolute pressure of 101.3 kPa. This involves placing the patient in an airtight vessel and increasing the pressure within that vessel while administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased partial pressure of oxygen to the tissues. At 2 ATA (202.6 kPa) for example, patients with reasonable cardiopulmonary function will have an arterial oxygen tension of over 1000 mmHg, and a muscle oxygen tension around 221 mmHg.[4,5] Administration of HBOT is therefore based on the potential for reversing tissue hypoxia and modifying secondary neurological effects.

Following primary injury, there is ongoing injury to the brain through a variety of mechanisms including hypoxia, reduced cerebral blood flow (ischaemia), release of toxic levels of excitatory neurotransmitters, impaired calcium homeostasis and elevated levels of cytokines (secondary injury).[6,7] In addition oxygen extraction is increased in the hours following injury.[8]

Hypoxic neurons performing anaerobic metabolism result in acidosis, unsustainable reduction in cellular metabolic reserve,[9] loss of the ability to maintain ionic homeostasis, free oxygen radical accumulation, degradation of cell membranes and eventual secondary cell death.[10,11] When hypoxia is severe enough, these changes occur rapidly, but there is some evidence that these effects can sometimes occur over a period of days.[12]

A therapy able to increase oxygen availability in the early period following TBI may therefore improve long-term outcome. HBOT is also thought to reduce tissue oedema by an osmotic effect,[13] and any agent that has a positive effect on brain swelling following trauma might also contribute

to improved outcomes. On the other hand, oxygen in high doses is potentially toxic to normally perfused tissue, and the brain is particularly at risk.[14] HBOT may therefore do more harm than good in some patients.

Since the 1960s, there have been scattered reports that HBOT improves the outcome following brain trauma.[15] HBOT has been shown to reduce intracranial pressure (ICP) in brain-injured patients,[16,17] improve grey matter metabolic activity on SPECT scan,[18] and improve glucose metabolism.[19] Some studies suggest that any effect of HBOT may not be uniform across all brain-injured patients. For example, Hayakawa demonstrated that CSFP rebounded to higher levels following HBOT than at pre-treatment estimation in some patients, while others showed persistent reductions.[17] It is possible that HBOT has a positive effect in a sub-group of patients with moderate injury, but not in those with extensive cerebral injury. Furthermore, repeated exposure to hyperbaric oxygen may be required to attain consistent changes.[20]

Clinical reports have attributed a wide range of improvements to HBOT including cognitive and motor skills, improved attention span and increased verbalisation.[16,18] These improvements are, however, difficult to ascribe to any single treatment modality because HBOT was most often applied in conjunction with intensive supportive and rehabilitative therapies.

The purpose of this review is to assess the randomised clinical evidence for the benefit or harm of adjunctive HBOT in the treatment of acute TBI. This paper is based on a Cochrane review first published in The Cochrane Library 2004, Issue 4. Chichester, UK: John Wiley & Sons, Ltd (www.thecochranelibrary.com). Copywrite Cochrane Library, reproduced with permission. Cochrane reviews are regularly updated as new evidence emerges and in response to comments and criticisms. The Cochrane Library should be consulted for the most recent version of the review.

Methods

It was our intention to identify and review all randomised controlled trials (RCTs) concerning the treatment with HBOT of any patient with TBI in the first days following injury. We included all trials using hyperbaric oxygen administered in a compression chamber above 1.5 ATA (152 kPa) and for treatment times between 30 and 120 minutes on at least one occasion. For the comparator therapy, we accepted any standard treatment regimen designed to maximise brain protection and promote recovery from TBI. We did not include studies where comparator interventions were not undertaken in a specialised acute care setting.

Specific search strategies were developed to identify eligible reports from database inception to August 2004 in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Randomised Controlled Trials in Hyperbaric Medicine (DORCTIHM). The latter is a specifically targeted database of clinical evidence in the field (<http://www.hboevidence.com>).

Medical subject headings (MeSH) and main key words used were 'hyperbaric oxygenation', 'head injuries, closed', 'head injuries, penetrating', 'craniocerebral trauma' and 'coma- post head injury', with variants of the main key words and free text terms also applied. No restrictions to language were made. Relevant hyperbaric textbooks, journals and conference proceedings were hand searched. Experts in the field were contacted for published, unpublished and ongoing RCTs. Additional trials were identified from the citations within obtained papers.

We pre-determined the following clinically important outcomes for assessment, and all included studies must have reported at least one of these: functional outcome measures (e.g. Glasgow Outcome Scale, GOS), death, activities of daily living (ADL) or quality of life (QALY) measures. In

Table 1
Summary of Jadad score from[21]
(each criteria scores or deducts one point if satisfied, giving a quality score from zero to five)

Criteria	Description
Randomisation	**The study is described as randomised, including using words such as 'random', 'randomised' or 'randomly'**
Additional	The method of randomisation is described and appropriate (e.g. use of random number table)
Deduction	The method of randomisation is described and is inappropriate (e.g. use birth date)
Double blinding	**The study is described as double-blind**
Additional	The method of double-blinding is described and appropriate (e.g. use of placebo or sham therapy)
Deduction	The method of double-blinding is described and is inappropriate (e.g. use observably different placebo)
Description of withdrawals	**There is a description of any dropouts or withdrawals during the course of the study**

addition we recorded the following indirect outcomes: intracranial pressure (ICP), magnetic resonance image (MRI) findings, computed tomography (CT) findings and cost-effectiveness. Any reported adverse events of HBOT were also recorded.

Each reviewer independently assessed the electronic search results and selected potentially relevant studies. Disagreements were settled by examination of the full paper and consensus. To assess methodological quality and detect potential sources of bias we applied the quality scale of Jadad (Table 1).[21] We also recorded the adequacy of allocation concealment. If any relevant data were missing from trial reports, we attempted to contact the authors. To allow an intention to treat analysis we extracted the data reflecting the original allocation group where possible. Disagreements were again settled by consensus.

STATISTICAL ANALYSIS

Following agreement, the data were entered into Review Manager® 4.2.1. (Cochrane Collaboration, Oxford, UK). For dichotomous outcomes such as the proportion of participants who died, we calculated Relative Risks (RR) with 95% confidence interval (CI). A statistically significant difference from control was assumed when the 95% CI of the RR did not include the value 1.0. For continuous outcomes such as the mean change in ICP for each group, we calculated the mean difference (MD) between groups with 95% CI. We used a fixed-effects model where problematic heterogeneity between the studies was not likely and a random-effects model where such heterogeneity was likely. Heterogeneity was deemed problematic if the I^2 analysis suggested more than 30% of the variability in an analysis was due to systematic differences between trials rather than chance alone.[22] Consideration was then given

Table 2
Characteristics of included studies (GOS - Glasgow outcome score)

Study	Methods	Participants	Interventions	Outcomes
Artru 1976[28]	Method of randomisation not stated. No blinding reported. Jadad score 2.	60 participants, 31 HBOT and 29 control. Inclusion depended on availability of chamber. Stratified into nine categories of severity and pathology.	Control: 'Standard care' included hyperventilation and frusemide. HBOT: above plus 2.5 ATA oxygen for 1 hour daily for 10 days, followed by 4 days rest and repeat if not responding.	Death Unfavourable outcome Adverse effects
Holbach 1974[29]	Quasi-random, no blinding. Jadad score 1.	99 participants, 49 HBOT and 50 control. Included: history of closed head injury and comatose with 'acute midbrain syndrome'.	Control: 'Usual intensive care regimen'. HBOT: above plus 1.5 ATA oxygen for 60 mins daily. Total dose not stated.	Death Complete recovery
Ren 2001[26]	Method of randomisation not stated. No blinding. Jadad score 1.	55 participants, 35 HBOT and 20 control. Included: closed head injury with GCS < 9. Randomised on day 3 post admission after condition stabilised.	Control: Standard care plus dehydration, steroids and antibiotics. HBOT: above plus 2.5 ATA for a total of 400 to 600 minutes every 4 days, repeated 3 or 4 times.	Favourable GOS Change in GCS
Rockswold 1992[27]	Method of randomisation not clear, medical assessors blind. Jadad score 2.	168 participants, 84 HBOT and 84 control. Included: closed head injury with GCS < 10 for > 6 hrs, < 24 hrs.	Control: 'Intensive neurosurgical care according to a comprehensive protocol'. HBOT: above plus 1.5 ATA oxygen for 1 hour every 8 hours for 2 weeks or until waking or death (ave 21 treatments).	Death Favourable outcome (GOS 1 or 2) ICP Adverse events

Table 3
Summary of pooled outcomes

Outcome	Studies	N HBOT/Control	Efficacy data[a] with 95% CI, P-value and NNT
Good functional outcome at four weeks	Holbach 1974[29] Artru 1976[28]	80/79	RR 2.66, 95% CI 0.73 to 9.69
Good functional outcome at final follow-up	Holbach 1974[29] Artru 1976[28] Rockswold 1992[27] Ren 2001[26]	199/183	RR 1.94, 95% CI 0.92 to 4.08
Death at any time after enrolment	Holbach 1974[29] Artru 1976[28] Rockswold 1992[27] Ren 2001[26]	199/183	[b]RR 1.46, 95% CI 1.13 to 1.87 NNT 7, 95% CI 4 to 22
Development of any significant respiratory symptoms	Artru 1976[28] Rockswold 1992[27]	115/113	[b]RR 0.06, 95% CI 0.01 to 0.47 NNH 8, 95% CI 5 to 15

[a]RR: Relative Risk, NNT: number needed to treat, NNH: number needed to harm
[b]Significant outcomes (statistical difference is assumed if the 95%CI does not include the value 1.0)

to the appropriateness of pooling and meta-analysis. Number-needed-to-treat (NNT) with 95% CI was calculated when the relative risk estimates were statistically significant.

We planned sensitivity analyses for missing data and study quality. We also considered subgroup analysis based on age, oxygen dose, comparator therapy used, and the nature and severity of injury.

Results

THE INCLUDED STUDIES

The search in August 2004 yielded 23 articles of which seven were considered to be possible randomised human trials dealing with the treatment of TBI with HBOT. Two were excluded because they were incomplete reports of included trials,[23,24] and one because it enrolled only participants with non-acute injuries.[25] Four publications therefore met our inclusion criteria.[26-29] One trial[29] used a sequential system for allocation that may not have been truly random. The total number of participants enrolled was 382, 199 receiving HBOT and 183 control.

All four trials enrolled participants with closed head injury, but inclusion criteria varied. Rockswold[27] accepted those with a Glasgow Coma Score (GCS) of less than 10 for between six and 24 hours, Ren[26] accepted participants with a GCS of less than nine for up to three days after trauma. The other two older trials did not specify inclusion criteria, other than 'closed head injury and comatose'.[28,29] Treatment pressures (1.5 to 2.5ATA, or 152 to 253.3 kPa), time schedule (60 to 90 min), and number of sessions (10 to 40) of HBOT differed between studies. Similarly, there was some variation in comparator therapies and the time to final assessment. Individual study characteristics are given in Table 2.

No study described the method of randomisation, clearly concealed allocation from the individual responsible for randomisation or employed a sham therapy. Study quality was generally assessed as low and was not used as a basis for sensitivity analysis.

CLINICAL OUTCOMES

Statistical pooling was not possible for many of the pre-planned outcome measures due to lack of suitable data. Problems included the small number of studies, modest number of patients, and the variability in outcome measures employed. The data are summarised in Table 3.

PRIMARY OUTCOMES

Good functional outcome

Good functional outcome was defined in these studies as any one of the following: GOS < three,[26] 'return of consciousness',[28] 'complete recovery'[29] or classified as 'independent'.[27] Two trials reported this outcome early (0 to 4 weeks) following the course of therapy[28,29] and involved 159 participants. 29 (36%) were described as having a good outcome in the HBOT group versus 11 (14%) in the control group. Pooled analysis suggests however, that there is no significant difference between groups (RR with HBOT: 2.66,

95% CI 0.73 to 9.69, P = 0.06). There was evidence of significant heterogeneity between these studies (I^2 = 72%) and this result is performed using a random effects model (Figure 1).

Ren reported a significant improvement in the chance of a good outcome at six months' review[26] (RR 2.8, 95% CI 1.4 to 5.5, P = 0.004), while at one year, Rockswold did not[27] (RR 0.98, 95% CI 0.73 to 1.3, P = 0.87). When combining all trials at final outcome, 109 participants (51%) in the HBOT group had a good outcome versus 61 (34%) of controls, however this difference was not statistically significant (RR 1.94, 95% CI 0.92 to 4.08, P = 0.08). This result is very likely to be subject to important heterogeneity between trials (I^2 = 81%) and should be interpreted very cautiously.

Subgroup analysis by treatment pressure suggested the application of a high treatment pressure (2.5 ATA or 253.3 kPa) was associated with a better outcome than the application of a low treatment pressure (1.5 ATA or 152 kPa) (high pressure RR 2.07, 95% CI 1.15 to 3.72, P = 0.003, low pressure RR 2.12, 95% CI 0.35 to 12.78, P = 0.11). This result is unconvincing given the high probability of important heterogeneity remaining between the two low pressure trials (I^2 = 89%) and the similar estimate of RR in these two groups.

Mortality

Three trials reported this data at some time (Holbach at 12 days, Artru and Rockswold 1992 at 12 months) involving 327 participants. There was significantly increased mortality with control therapy (RR 1.46, 95% CI 1.13 to 1.87, P = 0.003). Heterogeneity between studies was low (I^2 = 0%). The NNT to avoid one death by applying HBOT was 7, 95% CI 4 to 22 (Figure 2).

No trials reported on activities of daily living, quality of life measures, CT or MRI findings, progress of GCS or cost-effectiveness.

SECONDARY OUTCOMES

Intracranial pressure

Only Rockswold reported the effects of therapy on ICP.[27] The effect of HBOT was complicated by a change in the experimental protocol during the period of recruitment. While overall there was no difference in the mean maximum ICP between the two groups (MD 3.1 mmHg lower with HBOT, 95% CI -9.6 mmHg to +3.4 mmHg), the authors noted higher than expected ICP in the early HBOT participants. As this was likely to represent pain from middle ear barotrauma (MEBT), the last 46 participants recruited to

Figure 1
Forest plot for risk of good outcome at final follow-up

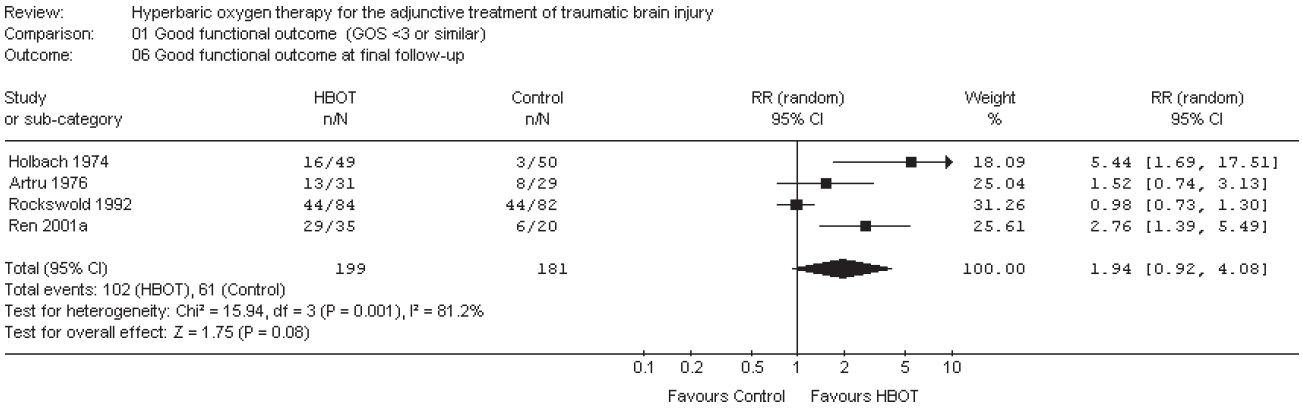
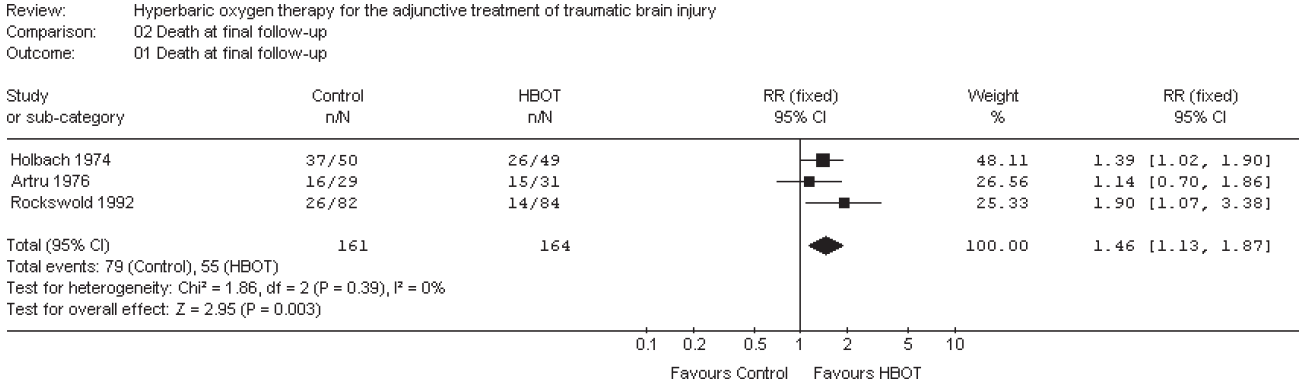


Figure 2
Forest plot for risk of death at any time after enrolment



HBOT had pre-compression myringotomy tubes inserted to allow free equalisation of middle ear pressures. Comparing the standard care group with the HBOT subjects with and without myringotomy, there is a significant lowering of ICP with HBOT plus myringotomy, but no difference without myringotomy (MD with myringotomy -8.2 mmHg, 95% CI -14.7 mmHg to -1.7 mmHg, P = 0.01; without myringotomy MD +2.7 mmHg, 95% CI -5.9 mmHg to +11.3 mmHg, P = 0.54).

Adverse effects

Rockswold reported generalised seizures in two participants in the HBOT group versus none in the control group (RR 0.2, P = 0.3) and a further two with haemotympanum from MEBT (RR 0.2, P = 0.03).

Two trials reported participants with significant pulmonary effects.[27,28] Rockswold reported ten individuals with rising oxygen requirements and infiltrates on chest x-ray, while Artru reported five patients with respiratory symptoms including cyanosis and hyperpnoea so severe as to imply 'impending hyperoxic pneumonia'. Overall, therefore, 15 patients (13% of those receiving HBOT) had severe pulmonary complications while no such complications were reported in the standard therapy arm. This difference is statistically significant (RR 0.06, 95% CI 0.01 to 0.47, P = 0.007). There was no indication of heterogeneity between trials (I^2 = 0%) and this analysis suggests we might expect to treat eight patients with HBOT in order to cause this adverse effect in one individual (NNH 8, 95% CI 5 to 15).

Discussion

This review has included data from four trials and we believe these represent all randomised human trials in this area, both published and unpublished, at the time of searching the databases. We found some evidence that HBOT reduces mortality following closed head injury, but cannot be confident that the addition of HBOT to standard therapy increases the chance of recovery to independence. The single trial looking at ICP as a proxy for beneficial effects did suggest that ICP was lower immediately following HBOT when patients had received middle ear ventilation tubes. These tubes avoid MEBT on compression – a highly painful and stimulating condition that might be expected to raise ICP, regardless of the underlying brain injury. Any clinical benefit may come at the cost of significant pulmonary complications. These complications are rare in general hyperbaric practice[30] and may be related specifically to the head injuries suffered by these patients.

Only 382 participants were available for evaluation using our planned comparisons, and meta-analysis was not appropriate or possible for a number of these. Other problems for this review were the poor methodological quality of these trials, variability and poor reporting of entry criteria, the variable nature and timing of outcomes, poor reporting of both outcomes and methodology and the long time period spanned by the four trials (27 years). In particular, there is a possibility of bias due to different times to entry in these small trials, as well as from non-blinded management decisions in all trials.

We had planned to perform subgroup analyses with respect to age, oxygen dose, nature of comparative therapies and the severity of injury. The paucity of eligible trials and poor reporting suggested the majority of these analyses would not be informative, and we only performed subgroup analysis with respect to treatment pressure for the proportion of individuals achieving a good outcome. No standard severity index was employed uniformly across these trials, no standard injury pattern was established, and only Rockswold and Ren described the time at which the inclusion criteria were applied.

While 13% of participants in two of these trials suffered significant pulmonary complications, this is unusual, and HBOT is generally regarded as a relatively benign intervention. There are few major adverse effects (pulmonary barotrauma, drug reactions, injuries or death related to chamber fire), and a number of more minor complications that may occur commonly. Visual disturbance, usually reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported – perhaps as many as 50% of those having a course of 30 treatments.[31] While the great majority of patients recover spontaneously over a period of days to weeks, a small proportion of patients continue to require correction to restore sight to pre-treatment levels. The second most common adverse effect associated with HBOT is barotrauma, usually MEBT, although other sites include the respiratory sinuses and dental cavities. Most episodes of barotrauma do not require the therapy to be abandoned. Less commonly, perhaps once every 5,000 treatments, HBOT may be associated with acute neurological toxicity manifesting as seizure.[30]

While we have made every effort to locate further unpublished data, it remains possible that this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. With regard to long-term outcomes following HBOT and any effect on the quality of life for these patients, we have located no relevant data.

Conclusions

We conclude there is limited evidence that HBOT reduces mortality in patients with acute TBI, but no clear evidence of improved functional outcome. The small number of studies, the modest numbers of patients, and the methodological and reporting inadequacies of the primary studies included in this review demand a cautious interpretation. We do not believe routine use of HBOT for these patients is justified by this review.

There is a case for large randomised trials of high methodological rigour in order to define the true extent of benefit (if any) from the administration of HBOT. Specifically, more information is required on the subset of disease severity or classification most likely to benefit from this therapy and the oxygen dose most appropriate. Any future trials would also need to consider appropriate sample sizes with power to detect expected differences, appropriate and carefully defined comparator therapy, use of an effective sham therapy, effective and explicit blinding of outcome assessors, appropriate outcome measures including all those listed in this review, careful elucidation of any adverse effects and the cost-utility of the therapy.

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The results of a Cochrane review can be interpreted differently, depending on people's perspectives and circumstances. Please consider the conclusions presented carefully. They are the opinions of review authors, and are not necessarily shared by The Cochrane Collaboration.

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ANZCA Citations

ANZCA Citations have been awarded to:
Dr Carl Edmonds
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Dr John Williamson
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The poetry doctor

Beware below blues

The sea is full of danger.
For me it is a fact
For whenever I go diving
I always get attacked.

The lion fish is lurking
Looking oh so tame
As I guide it with my hand
To fit my photo frame.

The jelly fish drifts passively,
Its tentacles so slim,
Yet as I swim through their mass
They wrap around my limbs.

The octopus just ogles me,
So serene and calm
As I admire its blue rings
Whilst it nestles in my palm.

The cone shell waits so patiently.
It shows no fire or fear
As I pick and pocket it
As a souvenir.

The stone fish sits so stoically
With camouflage so neat
As I walk the shallow reef
With unprotected feet.

The hydroid seems so innocent
So soft and fine and thin
As I gently fin past it
And brush my ankle skin.

As the sharks patrol the reef
I watch them with alarm
As they speed at me bare teethed
My speared fish underarm.

I am so scared to dive below.
It's full of dangerous things.
Please tell me how I can avoid
These bites and spines and stings?

I wrote this after brushing my ankle on a stinging hydroid. These stings always give me grief and afterwards I thought how stupid I am not to wear bootees every dive. A few days later I was bitten by a red back spider as I put my boot on in my shed. I was immensely grateful for the four ampoules of antivenene used to ease this particular reminder of how important it is to be cautious both in and out of the water.

John Parker
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